IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

State of Missouri, *et al.*,

Intervenor-Plaintiffs, and

State of Florida, State of Texas,

Proposed Intervenor-Plaintiffs,

and

Rosalie Markezich and **State of Louisiana**, by and through its Attorney General, **Liz Murrill**,

Proposed Intervenor-Plaintiffs,

v.

United States Food and Drug Administration, *et al.,*

Defendants, and

Danco Laboratories, LLC,

Intervenor-Defendant, and

GenBioPro, Inc.,

Intervenor-Defendant.

Civ. No. 2:22-cv-00223-Z

APPENDIX IN SUPPORT OF PROPOSED INTERVENOR-PLAINTIFFS ROSALIE MARKEZICH AND THE STATE OF LOUISIANA'S MOTION TO INTERVENE

VOLUME A

INDEX

VOLUME A	
Ex. 1: Society of Family Planning, #WeCount Report April 2022 to June 2024 (Oct. 22, 2024)	App. 1-57
Ex. 2: Society of Family Planning, #WeCount Report April 2022 to December 2024 (Jun. 23, 2025)	App. 58-125
Ex. 3: 2021 FDA Letter to ACOG and SMFM About Mifepristone REMS (Apr. 12, 2021)	App. 126-128
Ex. 4: Dr. Margaret Carpenter indictment	App. 129-131
Ex. 5: Center for Drug Evaluation and Research, Application Number: 20-687 Medical Review(s) (Jan. 27, 2000	App. 132-175
Ex. 6: Blake M. Autry & Roopma Wadhwa, *Mifepristone*, StatPearls (Feb. 28, 2024)	App. 176-184
Ex. 7: *The Facts on Mifepristone,* Planned Parenthood	App. 185-188
Ex. 8: *Medication Abortion: Your Questions Answered*, Yale Med. (Sept. 11, 2023	App. 189-194
Ex. 9: FDA-Approved Label for Mifepristone (Mifeprex) (Jan. 2023) ("Mifeprex 2023 Label")	App. 195-214
Ex. 10: 2021 FDA Letter to AAPLOG and Am. Coll. of Pediatricians denying in part and granting in part 2016 Citizen Petition, Docket No. FDA-2019-P-1534 (Dec. 16, 2021)	App. 215-255
Ex. 11: Center for Drug Evaluation and Research, Application Number: 020687Orig1s020 Summary Review (Mar. 29, 2016) ("FDA 2016 Summary Review")	App. 256-284
Ex. 12: Maarit Niinimaki et al., *Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study*, BMJ (April 20, 2011)	App. 285-292
Ex. 13: Jamie Bryan Hall & Ryan T. Anderson, *The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Patients Experiences a Serious Adverse Event,* Ethics & Pub. Pol'y Ctr. (Apr. 28, 2025)	App. 293-299
Ex. 14: James Studnicki et al., *Comparative Acuity of Emergency Department Visits Following Pregnancy Outcomes Among Medicaid Eligible Women, 2004–2015*, Int'l J. Epidemiology & Pub. Health Rsch., Apr. 2024	App. 300-304
Ex. 15: *Will a doctor be able to tell if you've taken abortion pills?* Women Help Women (Sept. 23, 2019)	App. 305-307
Ex. 16: *How do you know if you have complications and what should you do?* Aid Access	App. 308-310

Ex. 17: *Am. Coll. of Obstetricians and Gynecologists Practice Bulletin No. 181: Prevention of Rh D Alloimmunization*, 130 Obstetrics & Gynecology 481 (Aug. 2017)	App. 311-325
Ex. 18: Katherine A. Rafferty & Tessa Longbons, *#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives*, 36 Health Commc'n 1485 (2021	App. 326-336
Ex. 19: Population Council	App. 337-351
Ex. 20: 2002 Citizen Petition of AAPLOG to FDA (Aug. 8, 2002) ("2002 Citizen Petition")	App. 352-444
Ex. 21: Robert O'Harrow Jr., *Drug's U.S. Marketer Remains Elusive*, Wash. Post (Oct. 11, 2000)	App. 445-448
Ex. 22: Hannah Levintova, *The Abortion Pill's Secret Money Men*, Mother Jones (March–April 2023)	App. 449-459
Ex. 23: Letter from Center for Drug Evaluation and Research to Ann Robbins, Ph.D. (Sept. 18, 1996)	App. 460-470
Ex. 24: 2000 FDA Approval Letter for Mifeprex (mifepristone) Tablets (Sept. 28, 2000)	App. 471-474
Ex. 25: 2019 FDA ANDA Approval Letter to GenBioPro, Inc. (Apr. 11, 2019)	App. 475-481
Ex. 26: FDA Center for Drug Evaluation & Research Letter to Population Council re: NDA (Feb. 18, 2000)	App. 482-489
Ex. 27: 2000 FDA Approval Memo. to Population Council re: NDA 20-687 Mifeprex (mifepristone) (Sept. 28, 2000)	App. 490-498
Ex. 28: Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16313, 16314 (Mar. 27, 2008)	App. 499-501
Ex. 29: 2011 FDA Supplemental Approval Letter to Danco Laboratories, LLC (June 8, 2011) ("2011 Approval Letter")	App. 502-506
Ex. 30: 2011 REMS for NDA 20-687 Mifeprex (mifepristone) Tablets, 200mg (June 8, 2011) ("2011 REMS")	App. 507-517
VOLUME B	
Ex. 31: 2016 FDA Letter to AAPLOG, Christian Medical & Dental Associations, and Concerned Women for America denying 2002 Citizen Petition, Docket No. FDA2002-P-0364 (Mar. 29, 2016) ("2016 Petition Denial")	App. 518-551
Ex. 32: 2020 Letter from ACOG & SMFM to FDA about Mifepristone REMS (Apr. 20, 2020) ("2020 ACOG-SMFM Letter")	App. 552-555
Ex. 33: Students for Life of America, Citizen Petition to FDA (Dec. 13, 2022)	App. 556-623

Ex. 34: 2023 FDA Letter to Students for Life of Am. denying 2022 SFLA Petition, Docket No. FDA-2022-P-3209 (Jan. 3, 2023)	App. 624-626
Ex. 35: 2021 FDA Center for Drug Evaluation & Research Director Patrizia Cavazzoni Letter to Dr. Graham Chelius (Dec. 16, 2021)	App. 627-628
Ex. 36: Oral History Interview with Ruth B. Merkatz (Oct. 16, 2019)	App. 629-727
Ex. 37: White House, Readout of White House Roundtable Meeting with Women's Rights and Reproductive Health Leaders (Sept. 3, 2021)	App. 728-731
Ex. 38: White House, Press Briefing by Press Secretary Jen Psaki and Deputy National Security Advisor for Cyber and Emerging Technologies Anne Neuberger, September 2, 2021 (Sept. 2, 2021)	App. 732-769
Ex. 39: Ian Millhiser, *It sure sounds like Roe v. Wade is doomed*, Vox (Dec. 1, 2021)	App. 770-778
Ex. 40: White House, Remarks by President Biden Before Meeting with His Task Force on Reproductive Healthcare Access (Jan. 22, 2024)	App. 779-786
Ex. 41: White House, Remarks by President Biden on the Supreme Court's Decision on Affirmative Action (June 29, 2023)	App. 787-794
Ex. 42: White House, FACT SHEET: President Biden to Sign Executive Order Protecting Access to Reproductive Health Care Services (July 8, 2022)	App. 795-802
Ex. 43: White House, Remarks by President Biden on the Supreme Court Decision to Overturn *Roe v. Wade* (June 24, 2022)	App. 803-809
Ex. 44: Exec. Order No. 14076, Protecting Access to Reproductive Healthcare Services, 87 Fed. Reg. 42053 (July 8, 2022)	App. 810-813
Ex. 45: Exec. Order No. 14079, Securing Access to Reproductive and Other Healthcare Services, 87 Fed. Reg. 49505 (Aug. 3, 2022)	App. 814-817
Ex. 46: Presidential Memorandum, Further Efforts To Protect Access to Reproductive Healthcare Services, 88 Fed. Reg. 4895 (Jan. 22, 2023)	App. 818-821
Ex. 47: White House, FACT SHEET: President Biden Announces Actions In Light of Today's Supreme Court Decision on *Dobbs v. Jackson Women's Health Organization* (June 24, 2022)	App. 822-824
Ex. 48: Press Release, HHS, HHS Secretary Becerra's Statement on Supreme Court Ruling in *Dobbs v. Jackson Women's Health Organization* (June 24, 2022)	App. 825-826
Ex. 49: Press Release, HHS, Remarks by Secretary Xavier Becerra at the Press Conference in Response to President Biden's Directive following Overturning of Roe v. Wade (June 28, 2022)	App. 827-830
Ex. 50: Center for Drug Evaluation and Research, Application Number: 020687Orig1s025 Summary Review (Jan. 3, 2023) ("FDA 2023 Summary Review")	App. 831-920

Ex. 51: Center for Drug Evaluation and Research, Application Numbers: 020687 and 91178 Rationale Review (Dec. 16, 2021) ("FDA 2021 Rationale Review")	App. 921-971
Ex. 52: FDA Adverse Events Reporting System (FAERS) Public Dashboard	App. 972-989
Ex. 53: Kathi A. Aultman et al., *Deaths and Severe Adverse Events After the Use of Mifepristone as an Abortifacient from September 2000 to February 2019,* 26 Issues in L. & Med., no. 1, Nov. 1, 2021	App. 990-1015
Ex. 54: *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* (Apr. 2021)	App. 1016-1064
VOLUME C	
Ex. 55: Christiana A. Cirucci et al., *Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act*, 8 Health Servs. Rsch & Managerial Epidemiology 1, 1 (2021)	App. 1065-1070
Ex. 56: Pam Belluck, *CVS and Walgreens Will Begin Selling Abortion Pills this Month*, N.Y. Times (Mar. 1, 2024)	App. 1071-1076
Ex. 57: 2019 REMS Single Shared System for Mifepristone 200MG (Apr. 2019)	App. 1077-1085
Ex. 58: HHS, Marking the 50th Anniversary of Roe: Biden-Harris Administration Efforts to Protect Reproductive Health Care (Jan. 19, 2023)	App. 1086-1092
Ex. 59: Press Release, HHS, HHS Releases Report Detailing Biden-Harris Administration Efforts to Protect Reproductive Health Care Since Dobbs (Jan. 19, 2023)	App. 1093-1096
Ex. 60: White House, FACT SHEET: The Biden-Harris Administration's Record on Protecting Access to Medication Abortion (Apr. 12, 2023)	App. 1097-1099
Ex. 61: HHS, Secretary's Report, Health Care Under Attack: An Action Plan to Protect and Strengthen Reproductive Care (Aug. 2022)	App. 1100-1123
Ex. 62: Abuzz, *Abortion Pill Access in Louisiana*	App. 1124-1126
Ex. 63: Abuzz, *Need abortion care at home?*	App. 1127-1133
Ex. 64: A Safe Choice, *Home*	App. 1134-1140
Ex. 65: A Safe Choice, *Online Consultation Form*	App. 1141-1143
Ex. 66: Choices Rising, *Abortion Pill*	App. 1144-1148

Ex. 67: MAP, *Frequently asked questions*	App. 1149-1152
Ex. 68: Scott Calvert, *The Parties Where Volunteers Pack Abortion Pills for Red-State Women*, Wall St. J. (Aug. 12, 2024)	App. 1153-1160
Ex. 69: Rachel Roubein, *'Shield' Laws Make it Easier to Send Abortion Pills to Banned States*, Wash. Post. (July 20, 2023)	App. 1161-1166
Ex. 70: Rebecca Grant, *Group Using 'Shield Laws' to Provide Abortion Care in States That Ban It*, The Guardian (July 23, 2023)	App. 1167-1170
Ex. 71: Aid Access, *Get Abortion Pill Online in Louisiana*	App. 1171-1175
Ex. 72: Elissa Nadworny, I*nside a medical practice sending abortion pills to states where they're banned,* NPR (Aug. 7, 2024)	App. 1176-1183
Ex. 73: Abigail Brooks & Dasha Burns, *How a network of abortion pill providers works together in the wake of new threats*, NBC News (April 7, 2024)	App. 1184-1191
Ex. 74: Pam Belluck, *Abortion Shield Laws: A New War Between the States*, N.Y. Times (Feb. 22, 2024)	App. 1192-1209
Ex. 75: Caroline Kitchener, *Alone in a bathroom: The fear and uncertainty of a post-Roe medication abortion*, Wash. Post (April 11, 2024)	App. 1210-1244
Ex. 76: Her Safe Harbor, *Abortion Pills Online*	App. 1245-1250
Ex. 77: Pam Belluck, *A day with one abortion pill prescriber*, N.Y. Times (Jun. 9, 2025)	App. 1251-1264
VOLUME D	
Ex. 78: Abuzz, *FAQs*	App. 1265-1278
Ex. 79: ACT, *Who We Are*	App. 1279-1283
Ex. 80: ACT, *What We Do*	App. 1284-1288
Ex. 81: ACT, *FAQs*	App. 1289-1293
Ex. 82: ACT, *Resources*	App. 1294-1297
Ex. 83: Alaa Elassar, *New York Doctor Indicted in Louisiana Abortion Case Recognized as a Leader in Women's Reproductive Health*, CNN (Feb. 23, 2025)	App. 1298-1311
Ex. 84: Rosemary Westwood, *After Historic Indictment, Doctors Will Keep Mailing Abortion Pills Over State Lines*, NPR (Mar. 19, 2025)	App. 1312-1322

Ex. 85: Katherine Donlevy, *Louisiana DA warns there's trove of evidence against NY doctor who allegedly mailed abortion pills to teen – who was planning gender reveal party: report*, New York Post (Feb. 15, 2025)	App. 1323-1328
Ex. 86: Lorena O'Neil, *Louisiana Mother Pleads Not Guilty Following Abortion Pill Indictment*, La. Illuminator (Mar. 11, 2025)	App. 1329-1332
Ex. 87: Press Release, ACT, Statement on Governor Hochul's Response to Louisiana Extradition Order (Feb. 13, 2025)	App. 1333-1334
Ex. 88: Press Release, Protecting Reproductive Freedom: Governor Hochul Signs Legislation Affirming New York's Status as a Safe Haven for Reproductive Health Care (Feb. 3, 2025)	App. 1335-1345
Ex. 89: Rosemary Westwood, *Louisiana Investigates Second Case Against New York Doctor Over Mailing Abortion Pills*, La. Illuminator (May 13, 2025)	App. 1346-1348
Ex. 90: Governor Kathy Hochul (GovKathyHochul), X (May 13, 2025, 4:28 PM)	App. 1349-1350
Ex. 91: Society of Family Planning, #WeCount Report April 2022 to December 2024 (Jun. 23, 2025)	App. 1351-1368
Ex. 92: Rosalie Markezich Declaration	App. 1369-1374
Ex. 93: *Exhibit 5: Medicaid as a Share of States' Total Budgets and State-Funded Budgets, SFY 2021,* Medicaid and CHIP Payment and Access Commission (MACPAC) (2023)	App. 1375-1378
Ex. 94: Julie O'Donoghue, *Louisiana Medicaid Set to Grow Under Landry, Even as D.C. May Force Cuts,* La. Illuminator, (Mar. 26, 2025)	App. 1379-1384
Ex. 95: Louisiana Department of Health, Medicaid Annual Report 2022/2023	App. 1385-1510
Ex. 96: Marc Roemer, HHS, Agency for Healthcare Research and Quality, *Costs of Treat-and-Release Emergency Department Visits in the United States, 2021* (September 2024)	App. 1511-1524
Ex. 97: Hospital Services Provider Manual: Chapter Twenty-Five of the Medicaid Services Manual, State of Louisiana Bureau of Health Services Financing, § 25.2 (July 1, 2011)	App. 1525-1623
Ex. 98: Louisiana Medicaid Hospital Ambulatory Surgery Fee Schedule: State Hospitals (Effective Jan. 1, 2025)	App.1624-1692
Ex. 99: Louisiana Medicaid Hospital Ambulatory Surgery Fee Schedule: Rural Hospitals (Effective Jan. 1, 2025)	App. 1693-1760
Ex. 100: Louisiana Medicaid Hospital Ambulatory Surgery Fee Schedule: Non-Rural and Non-State Hospitals (Effective Jan. 1, 2025)	App. 1761-1829

Ex. 101: Medicaid Services, Louisiana Department of Health	App. 1830-1839
Ex. 102: State Hospitals Outpatient Services Fee Schedule (Effective Jan. 1, 2025)	App. 1840-1935
Ex. 103: Small Rural Hospital Outpatient Services Fee Schedule (Effective Jan. 1, 2025)	App. 1936-2031
Ex. 104: Louisiana Medicaid Hospital Provider Inpatient Per Diem Rates (Effective 7/1/2024)	App. 2032-2038
Ex. 105: Pam Belluck, *California Passes Bill Allowing Omission of Patients' Names from Abortion Pill Bottles*, N.Y. Times (Sept. 11, 2025)	App. 2039-2043
Ex. 106: The Associated Press, *Texas Has a New Abortion Pill Law. But At Least One Provider Plans to Keep Shipping Them There,* Newsday (Sept. 18, 2025)	App. 2044-2047
Ex. 107: Caroline Kitchener, *Blue-state doctors launch abortion pill pipeline into states with bans*, Wash. Post (July 19, 2023)	App. 2048-2061

EXHIBIT 1

Society of Family Planning, #WeCount
Report April 2022 to June 2024
(Oct. 22, 2024)

#WeCount Report
April 2022 to June 2024
Released: October 22, 2024

This is the eighth in a series of reports. Please see www.SocietyFP.org/WeCount for past and future reports. Cite this report using the following DOI: 10.46621/728122kflzwf

Introduction

Abortion is a fundamental component of reproductive health care and an essential health service.[1] Access to abortion not only allows individuals to make critical decisions regarding their bodies and life circumstances, but also enables people to receive lifesaving and stabilizing pregnancy care when an unexpected problem arises. Access to safe and legal abortion services ensures that people can manage unplanned pregnancies, protect their health, and maintain autonomy over their reproductive choices. When individuals are denied an abortion, by way of abortion restrictions, they may face a range of serious consequences, including physical and mental health risks, financial strain, and disruptions to their education or career goals.[2–5] Being denied an abortion impacts not only the individual but also their families and communities. Ensuring access to abortion is essential for promoting overall health and well-being.

#WeCount is a national effort that aims to report the monthly number of abortions in the United States, by state and month starting in April 2022. #WeCount data include clinician-provided abortions, defined in this report as medication or procedural abortions completed by a licensed clinician within the US in a clinic, private medical office, hospital, or virtual-only clinic (ie, clinics that only provide telehealth abortions). This report does not reflect any self-managed abortions, defined as ending a pregnancy outside the formal healthcare system, including using medications, herbs, or something else, or obtaining pills from friends or online without clinician assistance. These data reflect the status of abortion provision in the US and can be used by healthcare systems, public health practitioners, and policymakers so that their decisions can be informed by evidence.

This is the 8th in the series of #WeCount reports. Since our first report we have seen significant changes in the abortion care landscape, some of which were driven by the growth of telehealth abortion care that first began during the COVID-pandemic in 2020 and some of which were driven by the *Dobbs v Jackson's Women's Health Organization* US Supreme Court decision in 2022. Following the *Dobbs* decision, some states have

banned abortion except in rare exceptions, other states have expanded access—either through state legislatures or through referendums and judicial decisions.

Aside from the first #WeCount report, each subsequent report has found a small increase in the national monthly number of abortions. While several factors may be driving this increase, one important factor visible in the #WeCount data is the expansion of telehealth models of abortion care. In the context of this report, we define a telehealth abortion as medication abortion offered by a clinician through a remote consultation with the patient (via video, phone, or messaging) that results in medications dispensed via mail.[1] All telehealth abortions are counted according to the state to which the medications are mailed. Since the start of #WeCount in April 2022, we have been reporting telehealth abortions provided by virtual-only clinics. Starting in July 2023, #WeCount began to enumerate telehealth abortion numbers provided by brick-and-mortar abortion facilities (which were previously included as part of the state and national totals) separately to provide a more comprehensive picture of the total number of telehealth abortions.

Also starting in July 2023, we began to include abortions provided by licensed clinicians in states with shield laws in place. Shield laws give some legal protections to clinicians who offer abortion care via telehealth to people living in states with total abortion bans, with 6-week bans, or with laws that explicitly or implicitly preclude a component of telehealth abortion, such as requiring in-person ultrasounds. In this report, for the first time, we provide data on the number of abortions provided under shield laws by state, including for states with abortion bans and restrictions.

National findings

- The monthly average national abortion volume in the first six months of 2024 was nearly 98,000 abortions, which is higher than the national monthly averages for 2022 or 2023 (Figures 1 and 2). Monthly totals across the reporting period of April 2022 to June 2024 vary modestly month-to-month. In the three most recent months of data collection, we observed between 91,510 abortions (in June 2024) and 98,920 abortions (in April 2024) (Table 1).
- Nationally, abortions increased from 260,730 in the second quarter of 2023 to 289,270 in the second quarter of 2024. This national increase of 11% is due in part to increases in telehealth abortion.
    - When we examine all abortions provided via telehealth, we observe a 155% increase (from 22,430 in the second quarter of 2023 to 57,150 in the second quarter of 2024). When we exclude abortions provided under shield laws from the counts in the second quarter of 2024, we still observe a 25% increase in telehealth abortions between these two periods.

[1] Although sometimes used interchangeably, the terms telehealth and telemedicine have different meanings. Briefly, telehealth is a broad term that encompasses administrative, clinical, and (patient and clinician) educational services provided remotely, while telemedicine refers specifically to the delivery of clinical services remotely.

  - In the same period, the numbers of in-person abortions have stayed relatively consistent across years (over 238,000 in the second quarter of 2023 and over 232,000 in the second quarter of 2024), representing a 3% decrease.
- In comparing monthly totals across years, we note the increases in abortion provision in the US throughout 2023 and 2024. Part of the increase in 2023 is due to our inclusion of abortions that were provided under shield laws for the first time in July 2023. While some of abortion provision under shield laws represents new services, at least one large service had offered care previously, supported by clinicians outside the US.[6] Thus, while abortions provided by these services were newly counted by #WeCount as of July 2023, a significant number of abortions were obtained via this service in months prior that are not reflected in our data.
- We also note the seasonality of abortion provision (that is, abortion incidence is higher in some months and lower in others every year). For example, we see drops in February and November and peaks in January and August every year (Figure 2).

Figure 1. Abortions in the US from April 2022 to June 2024

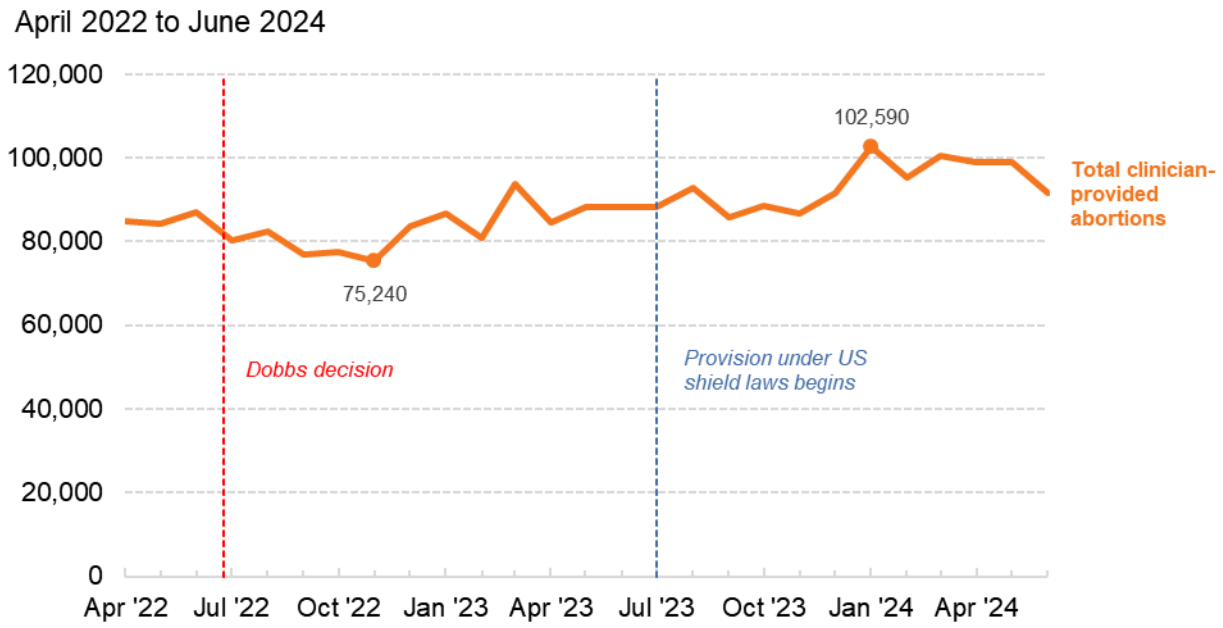
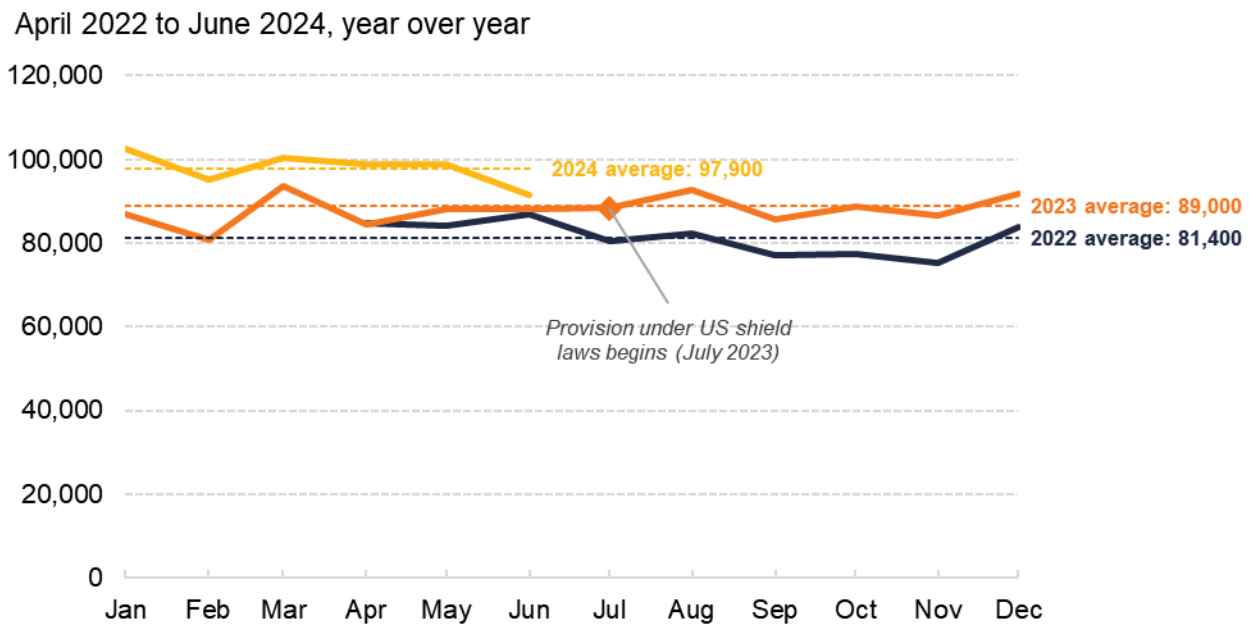


Figure 2. Abortions in the US from April 2022 to June 2024, year over year



Telehealth findings

- In April-June 2024, we observed an average of over 19,000 telehealth abortions per month (Table 2).
- In April-June 2024, we observed an average of over 7,700 monthly telehealth abortions provided under shield laws to people in states with total abortion bans or 6-week bans, and nearly 2,000 monthly telehealth abortions provided under shield laws to people in states with restrictions that explicitly ban telehealth abortion or implicitly preclude telehealth due to in-person visit requirements. (Figure 3). This amounts to an average monthly number of telehealth abortions provided under shield laws in April-June 2024 of over 9,700.
- In April-June 2024, we observed a national average of nearly 1,800 brick-and-mortar telehealth abortions per month (Figure 4).
- The number of telehealth abortions provided by all categories of providers (for example, virtual-only, brick-and-mortar) appear to be increasing (Figure 4).
- As the number of abortions has been increasing nationally, so too has the proportion of abortions that are provided through telehealth (Figures 5 and 6).
- Telehealth represented 19% of all abortions in April 2024, 20% in May, and 20% in June. The average was 20% for the quarter. (Figures 6 and 7)
- Nationally, telehealth abortions grew from 4% of all abortions in April 2022 to 20% in June 2024 (Table 2).
- During April-June 2024, the proportion of abortions provided by telehealth (in states where permitted) ranged from 8% in New York to 55% in Wyoming. (Figure 8).

Figure 3. Abortions provided under shield laws in the US from July 2023 to June 2024

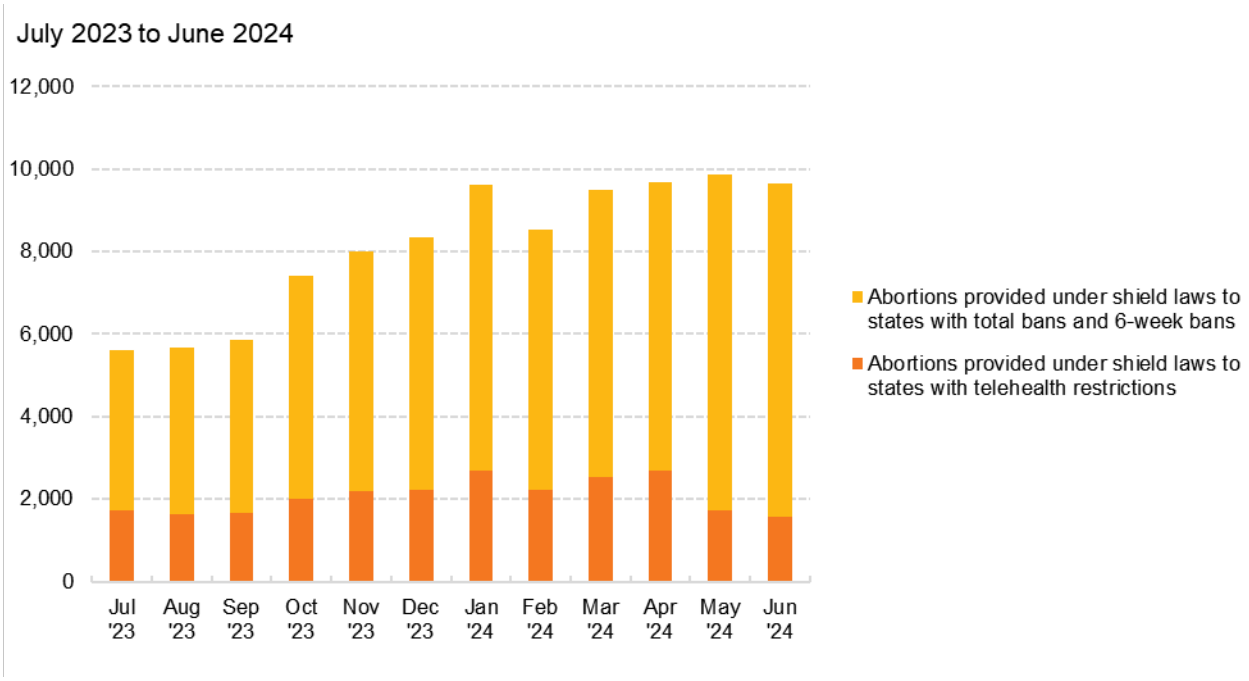
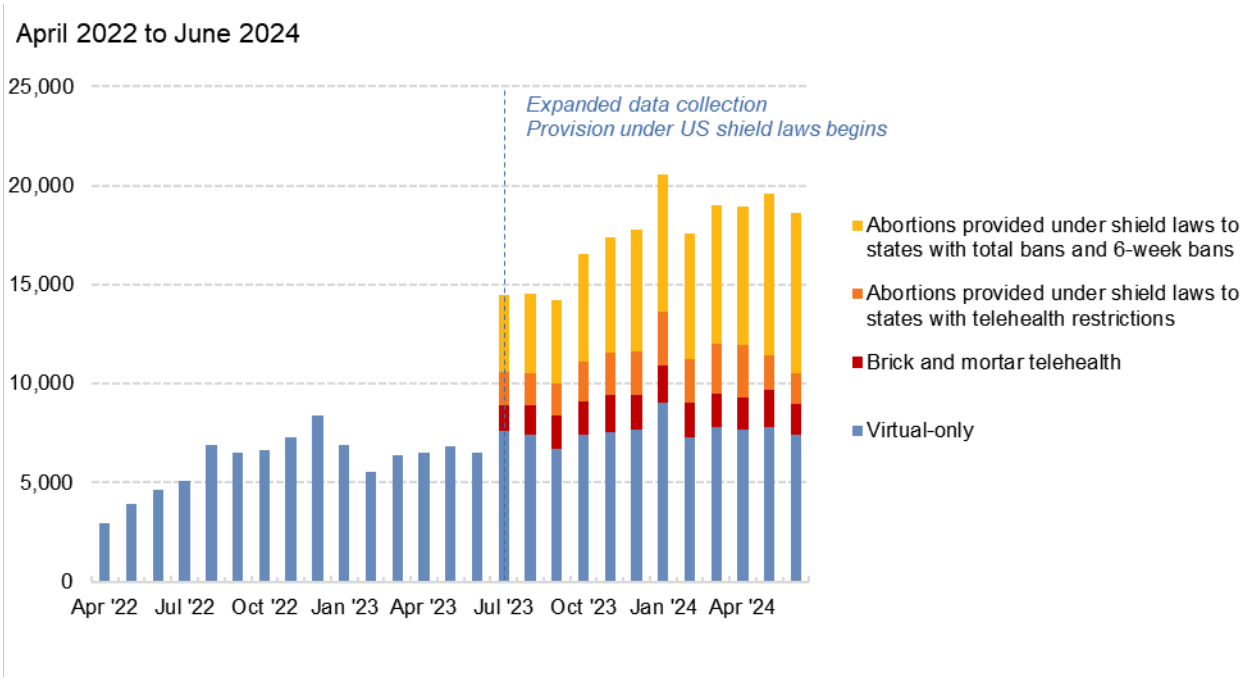
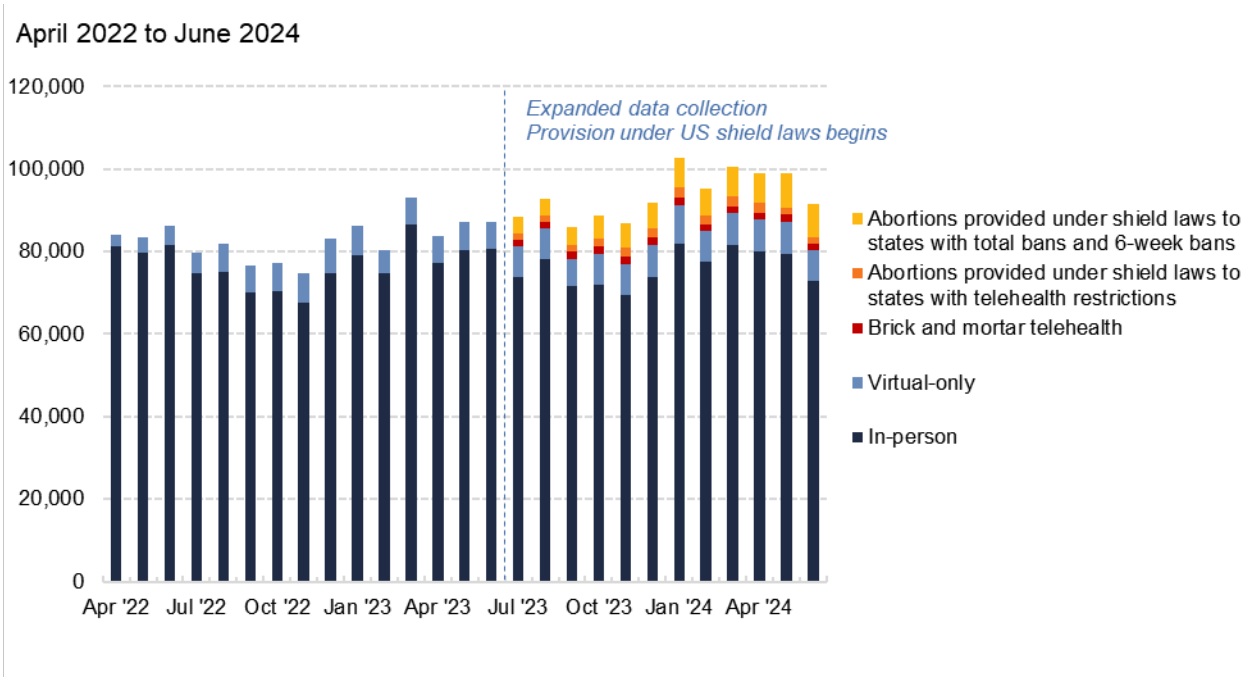


Figure 4. Telehealth abortions in the US from April 2022 to June 2024 (includes abortions provided under shield laws, July 2023 to June 2024)



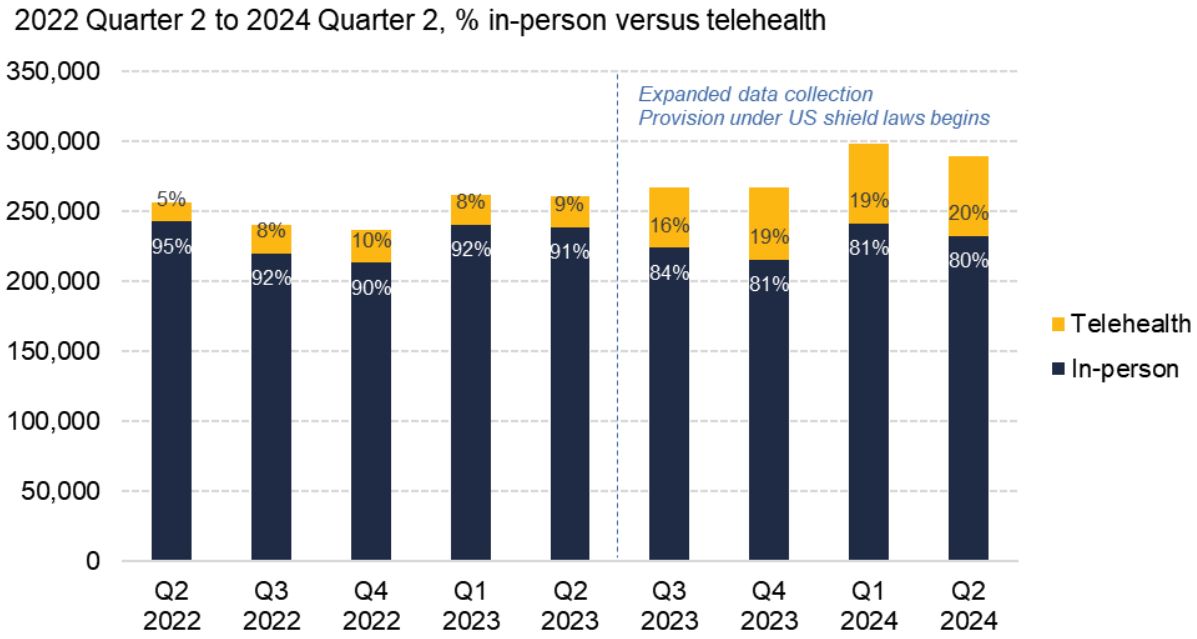
Note: Prior to July 2023, brick and mortar telehealth abortions were categorized as in-person.

Figure 5. Abortions in the US from April 2022 to June 2024



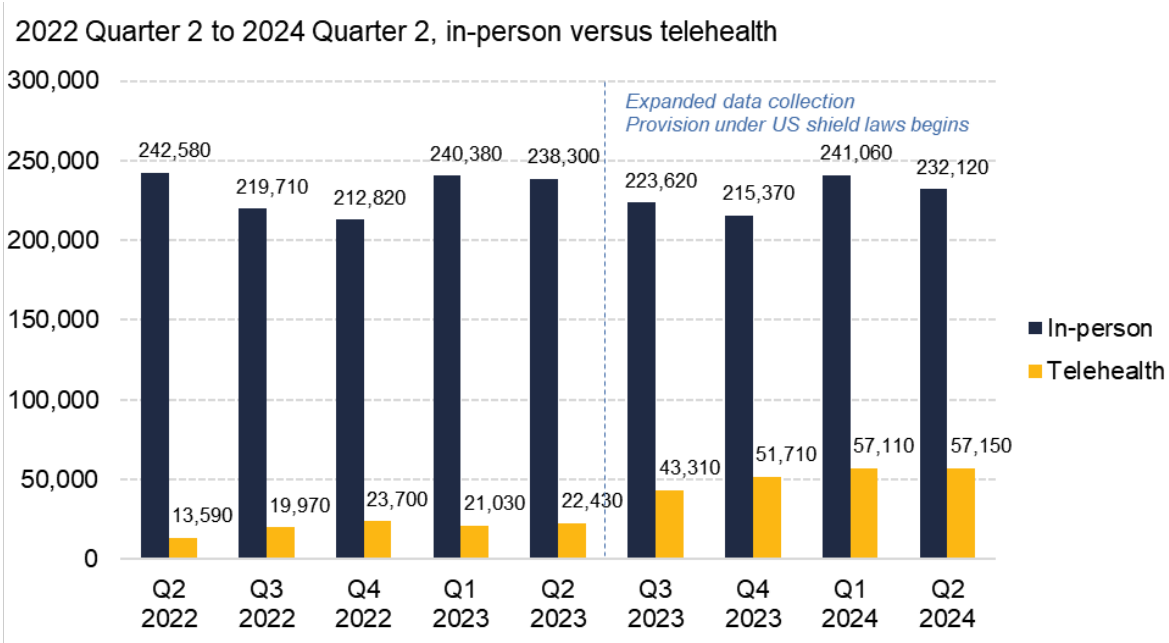
Notes: Includes abortions provided under shield laws, July 2023 to June 2024.
Prior to July 2023, brick and mortar telehealth abortions were categorized as in-person.

Figure 6. Abortions in the US, 2022-2024 quarterly totals and distribution between in-person versus telehealth



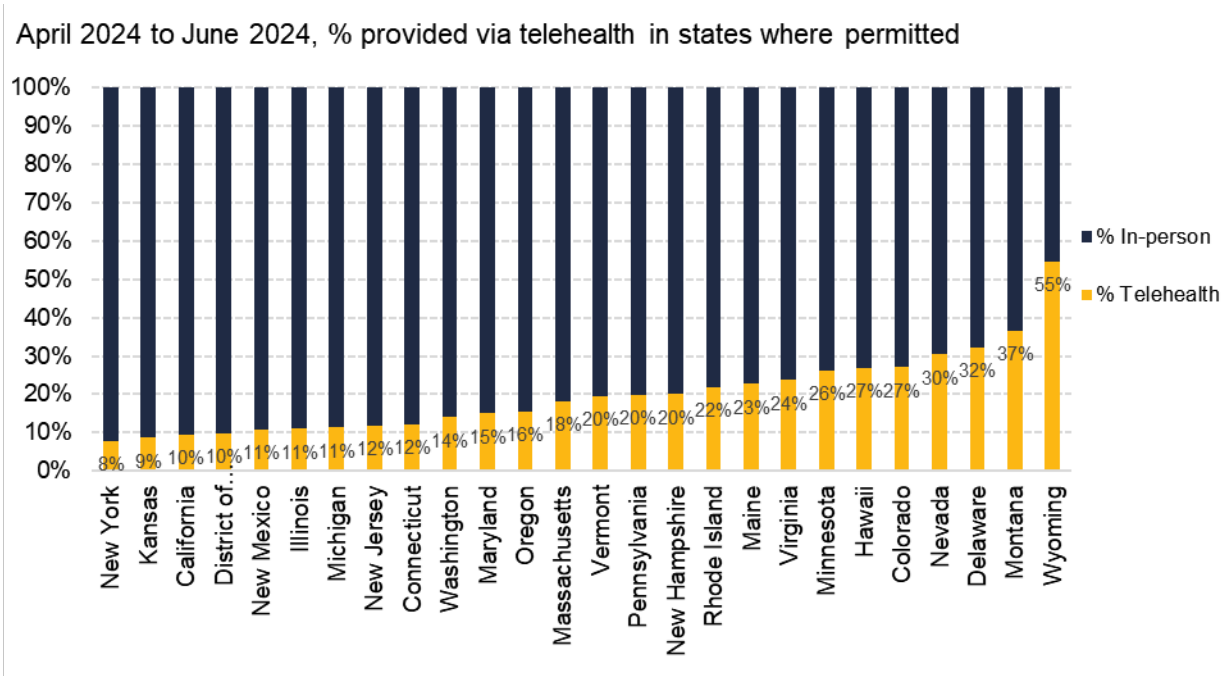
Note: 2023 Q3 reflects the first period in which telehealth abortions provided by brick-and-mortar facilities were disaggregated from total abortions and reported to #WeCount; additionally, 2023 Q3 reflects the start of abortion provision under shield laws.

Figure 7. Abortions in the US, 2022-2024 in-person and telehealth quarterly totals



Note: 2023 Q3 reflects the first period in which telehealth abortions provided by brick-and-mortar facilities were disaggregated from total abortions and reported to #WeCount; additionally, 2023 Q3 reflects the start of abortion provision under shield laws.

Figure 8. Proportion of abortions provided by telehealth versus in-person in states where abortion is permitted from April to June 2024



States where abortion remained legal but access was limited

In April-June 2024, Florida, Georgia, and South Carolina were the three states where abortion was banned after detection of embryonic cardiac activity, also referred to as a "6-week ban," because detection of such activity usually occurs around that point in pregnancy. Florida's 6-week ban went into effect on May 1, 2024. These states also explicitly ban telehealth abortion (Florida, Georgia) or implicitly preclude telehealth due to in-person visit requirements (Iowa).

- Florida saw a large increase in abortions just before the state enacted its 6-week ban. We observed about 8,400 abortions in January, 7,900 in February, and 8,300 in March, and then the number rose to over 10,100 abortions in April 2024. In subsequent months, the monthly abortion counts declined to about 6,200 in May and further down to 5,600 in June. Between March and May, Florida saw a decline of about 2,500 in-person abortions, but an increase of only about 400 abortions provided under shield laws.
- In Georgia, in April, May, and June there was an average of nearly 2,200 in-person abortions per month, and about 750 telehealth abortions per month.

- In South Carolina, in April, May, and June 2024, there were about as many abortions provided by telehealth (average 270) as there were provided in-person (average 260).

States where abortion via telehealth is restricted

In April-June 2024, in Arizona, Iowa, Nebraska, South Carolina, and Wisconsin, abortion was legal beyond 6-weeks but laws either banned telehealth abortion explicitly or restrictions implicitly precluded a component of telehealth. Some of these states have severely restricted access, as described above. However, these states are being served by abortion providers operating under shield laws.

- In Arizona between April to June 2024, we observed an average of nearly 1,100 in-person abortions per month, with another 300 provided through telehealth.
- In Iowa, we observed an average of about 260 in-person abortions per month, with another 130 abortions provided through telehealth.
- In Nebraska, we observed an average of about 220 in-person abortions per month, with another 70 provided through telehealth.
- In Ohio, we observed an average of about 2,100 in-person abortions per month, with another 500 provided through telehealth.
- In Wisconsin, we observed an average of 410 in-person abortions per month, with another 150 provided through telehealth.

States with abortion bans

In total, 14 states (Alabama, Arkansas, Idaho, Kentucky, Louisiana, Mississippi, Missouri, North Dakota, Oklahoma, South Dakota, Tennessee, Texas, West Virginia, and Wisconsin) have had total abortion bans for the majority of the 24 months since the *Dobbs* decision. In this report, we include the number of abortions provided under shield laws to states with abortion bans, as these represent abortions provided to residents of these states without travel to another state (Table 1). These numbers reflect location of receipt, not the state from which the medications were sent.

- In Alabama, between July 2023 to June 2024, we observed a range from 220 to 440 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 433 abortions per month.
- In Arkansas, between July 2023 to June 2024, we observed a range from 130 to 260 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 240 abortions per month.

- In Idaho, between July 2023 to June 2024, we observed a range from 30 to 70 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 57 abortions per month.
- In Kentucky, between July 2023 to June 2024, we observed a range from 120 to 230 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 210 abortions per month.
- In Louisiana, between July 2023 to June 2024, we observed a range from 310 to 620 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 617 abortions per month.
- In Mississippi, between July 2023 to June 2024, we observed a range from 200 to 420 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 390 abortions per month.
- In Missouri, between July 2023 to June 2024, we observed a range from 100 to 180 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 167 abortions per month.
- In North Dakota, between July 2023 to June 2024, we observed a range from 10 to 30 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 20 abortions per month.
- In Oklahoma, between July 2023 to June 2024, we observed a range from 120 to 260 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 250 abortions per month.
- In South Dakota, between July 2023 to June 2024, we observed a range from 10 to 30 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 27 abortions per month.
- In Tennessee, between July 2023 to June 2024, we observed a range from 230 to 470 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 460 abortions per month.
- In Texas, between July 2023 to June 2024, we observed a range from 1,680 to 2,910 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 2,800 abortions per month.
- In West Virginia, between July 2023 to June 2024, we observed a range from 30 to 60 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 53 abortions per month.

- In Wisconsin, between July 2023 to June 2024, we observed a range from 100 to 160 in the number of abortions delivered via telehealth. In the most recent quarter (April to June 2024), the average number of telehealth abortions provided under shield laws was 147 abortions per month.

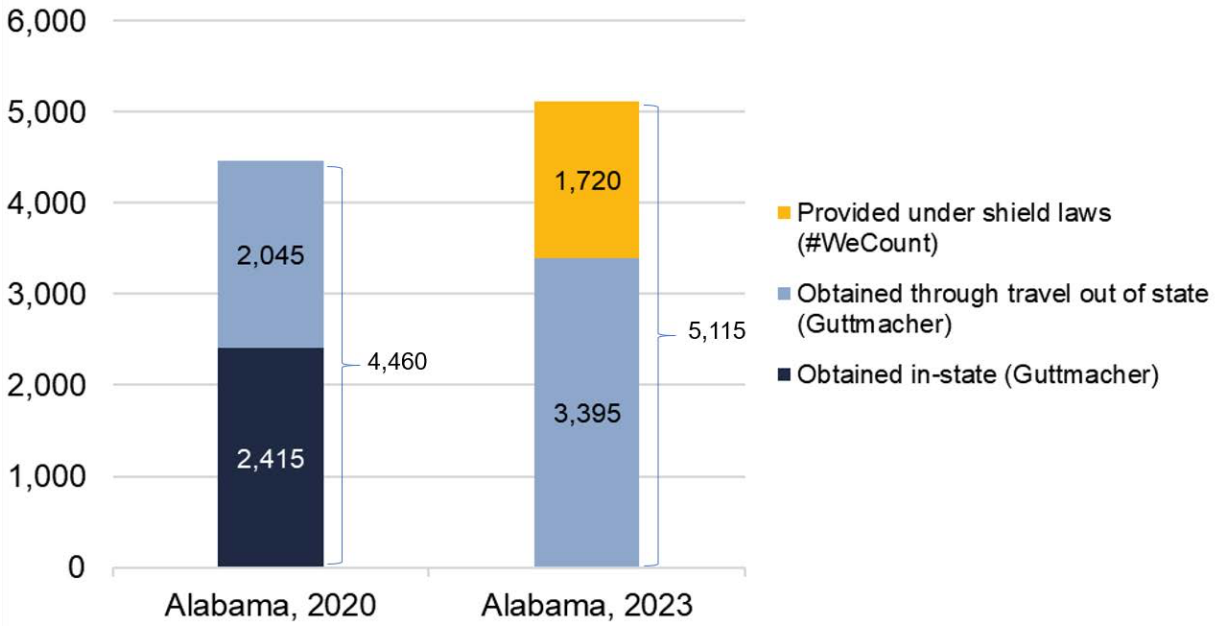
Abortions provided to state residents in-state, out-of-state, and via telehealth

This report makes available for the first time monthly counts of clinician-provided medication abortion delivered via telehealth to specific states. These numbers are actual counts collected by #WeCount of all known provider groups offering this telehealth service. We combine the numbers of medication abortions provided under shield laws with data reflecting 12-month totals from the Guttmacher Institute's Monthly Abortion Provision Study. We present a combination of #WeCount data about abortions provided under shield laws with state-of-residence data for: states with total abortion bans, states with 6-week bans, and states with restrictions that preclude a component of telehealth abortion July to December 2023. We do not provide combined data for Indiana, South Carolina, and Wisconsin because instability in the legal status of abortion in these states prevent us from dividing the 12-month abortion totals into a 6-month period.

States with abortion bans

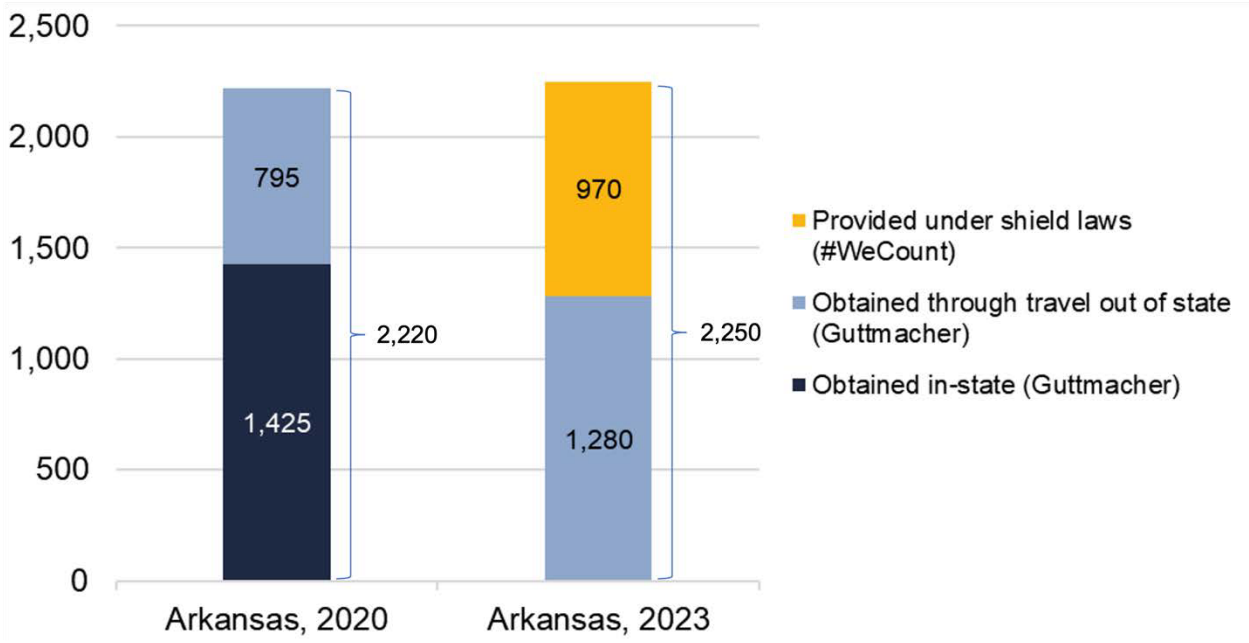
In one half of 2020, we estimate Alabama residents obtained approximately 4,460 abortions; 2,415 were obtained at facilities in state and 2,045 were to Alabama residents who traveled to another state for care (Figure 9). By 2023, Alabama had implemented an abortion ban. In the second half of 2023 an estimated 3,395 residents traveled out of state for care and 1,720 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 5,115 abortions among Alabama residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 9. Alabama, six months of 2020 and 2023, respectively



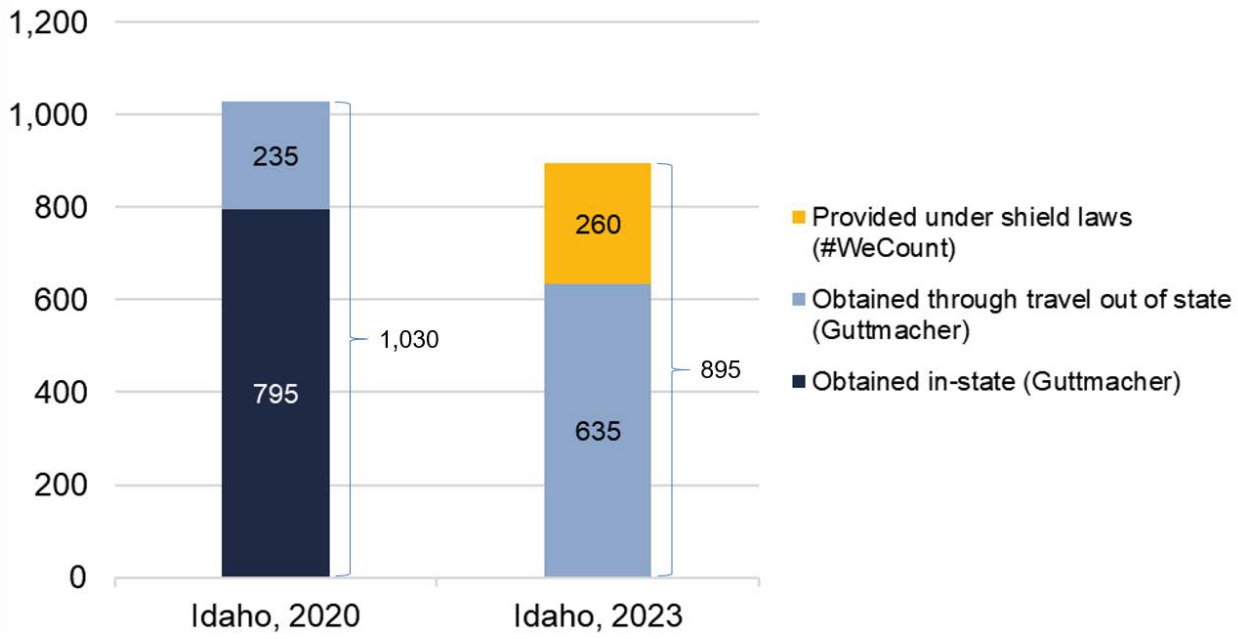
In one half of 2020, we estimate Arkansas residents obtained approximately 2,220 abortions; 1,425 were obtained at facilities in state and 795 were to Arkansas residents who traveled out of state for care (Figure 10). By 2023, Arkansas had implemented an abortion ban. In the second half of 2023, an estimated 1,280 residents travelled out of state for care and 970 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 2,250 abortions among Arkansas residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 10. Arkansas, six months of 2020 and 2023, respectively



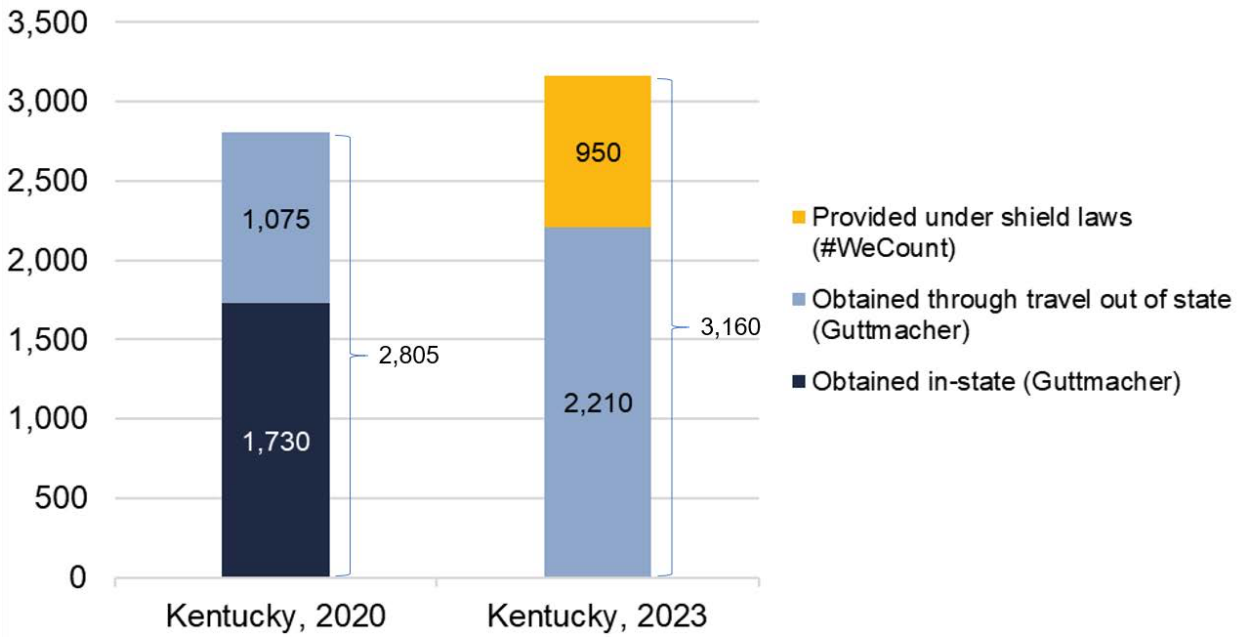
In one half of 2020, we estimate Idaho residents obtained approximately 1,030 abortions; 705 were obtained at facilities in state and 235 were to Idaho residents who traveled to another state for care (Figure 11). By 2023, Idaho had implemented an abortion ban. In the second half of 2023, an estimated 635 residents travelled out of state for care and 280 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 895 abortions among Idaho residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 11. Idaho, six months of 2020 and 2023, respectively



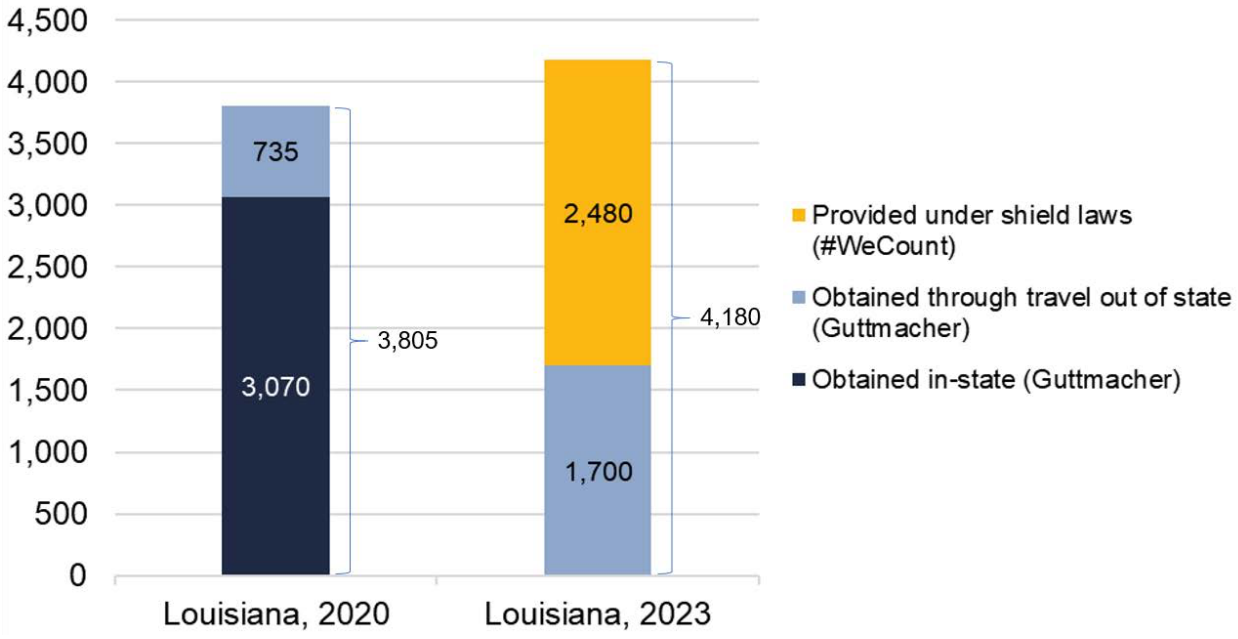
In one half of 2020, we estimate Kentucky residents obtained approximately 2,805 abortions; 1,730 were obtained at facilities in the state and 1,075 were to Kentucky residents who traveled to another state for care (Figure 12). By 2023, Kentucky had implemented an abortion ban. In the second half of 2023, an estimated 2,210 residents travelled out of state for care and 950 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 3,160 abortions among Kentucky residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 12. Kentucky



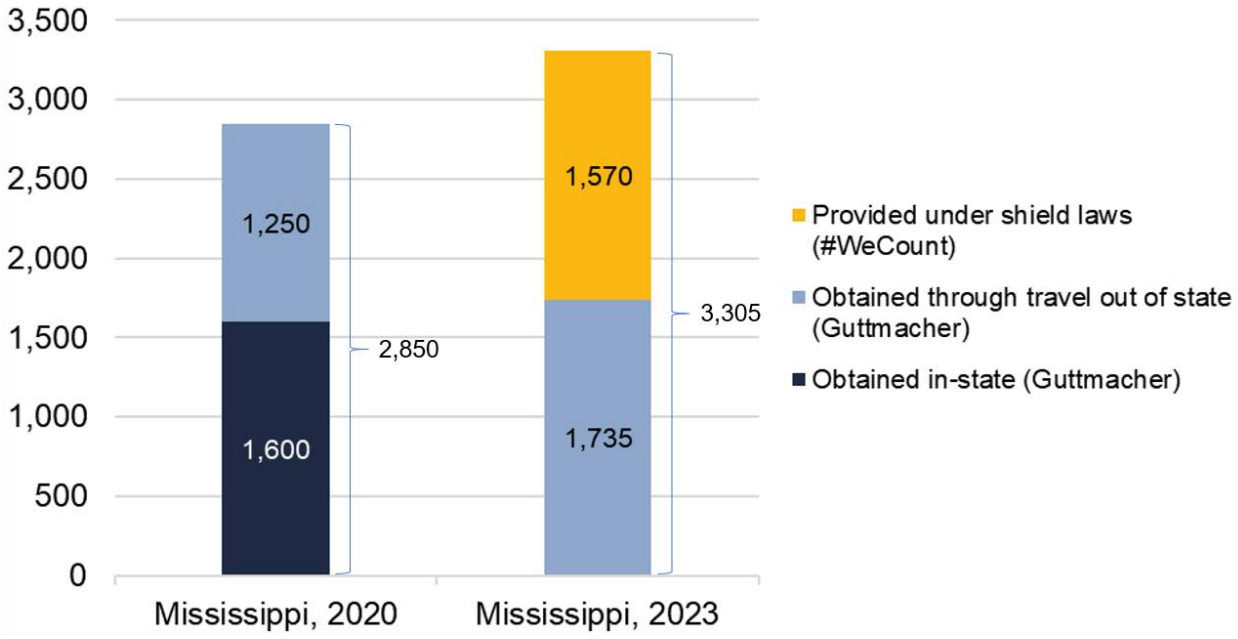
In one half of 2020, we estimate Louisiana residents obtained approximately 3,805 abortions; 3,070 were obtained at facilities in the state and 735 were to Louisiana residents who traveled to another state for care (Figure 13). By 2023, Louisiana had implemented an abortion ban. In the second half of 2023, an estimated 1,700 residents travelled out of state for care and 2,480 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 4,180 abortions among Louisiana residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 13. Louisiana, six months of 2020 and 2023, respectively



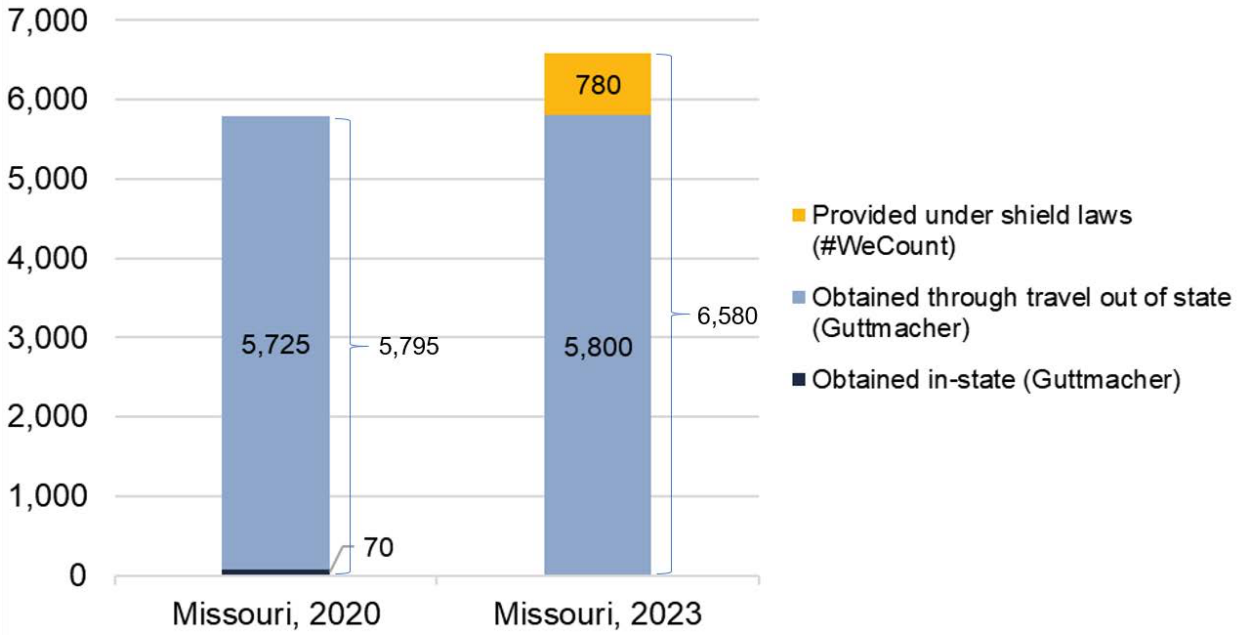
In one half of 2020, we estimate Mississippi residents obtained approximately 2,850 abortions; 1,600 were obtained at facilities in state and 1,250 were to Mississippi residents who traveled to another state for care (Figure 14). By 2023, Mississippi had implemented an abortion ban. In the second half of 2023, an estimated 1,735 residents travelled out of state for care and 1,570 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 3,305 abortions among Mississippi residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 14. Mississippi, six months of 2020 and 2023, respectively



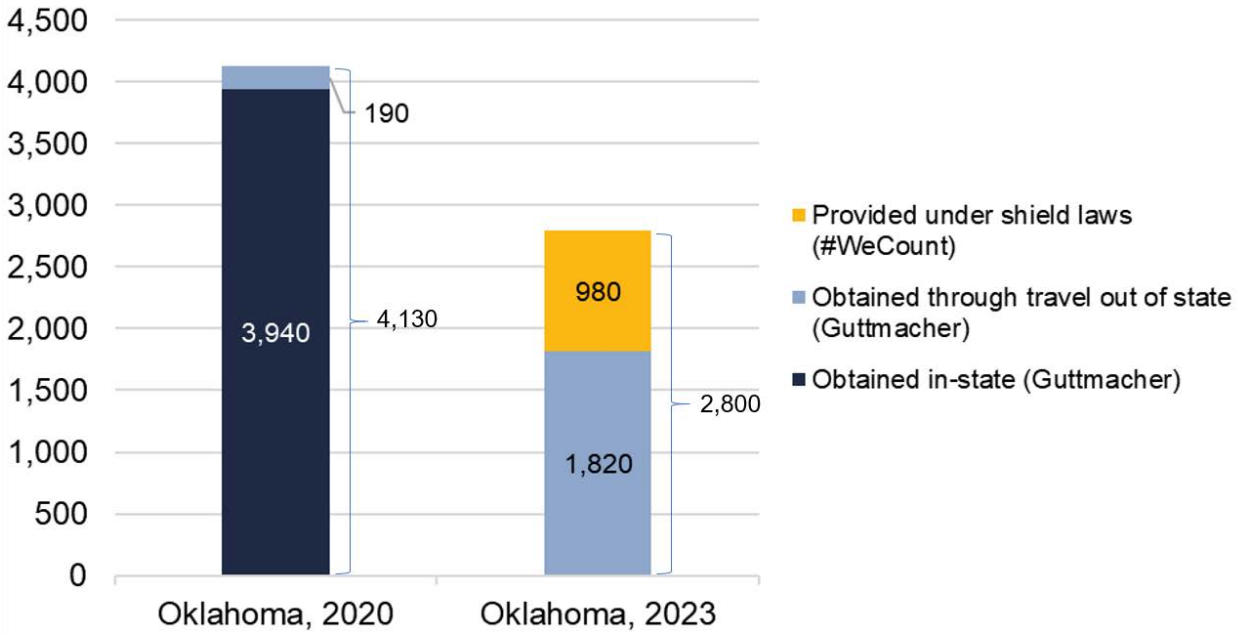
In one half of 2020, we estimate Missouri residents obtained approximately 5,795 abortions; 70 were obtained at facilities in state and 5,725 were to Missouri residents who traveled to another state for care (Figure 15). By 2023, Missouri had implemented an abortion ban. In the second half of 2023, an estimated 5,800 residents were able travel out of state for care and 780 obtained abortion medications from health care providers operating under of shield laws. We calculate a possible total of 6,580 abortions among Missouri residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 15. Missouri, six months of 2020 and 2023, respectively



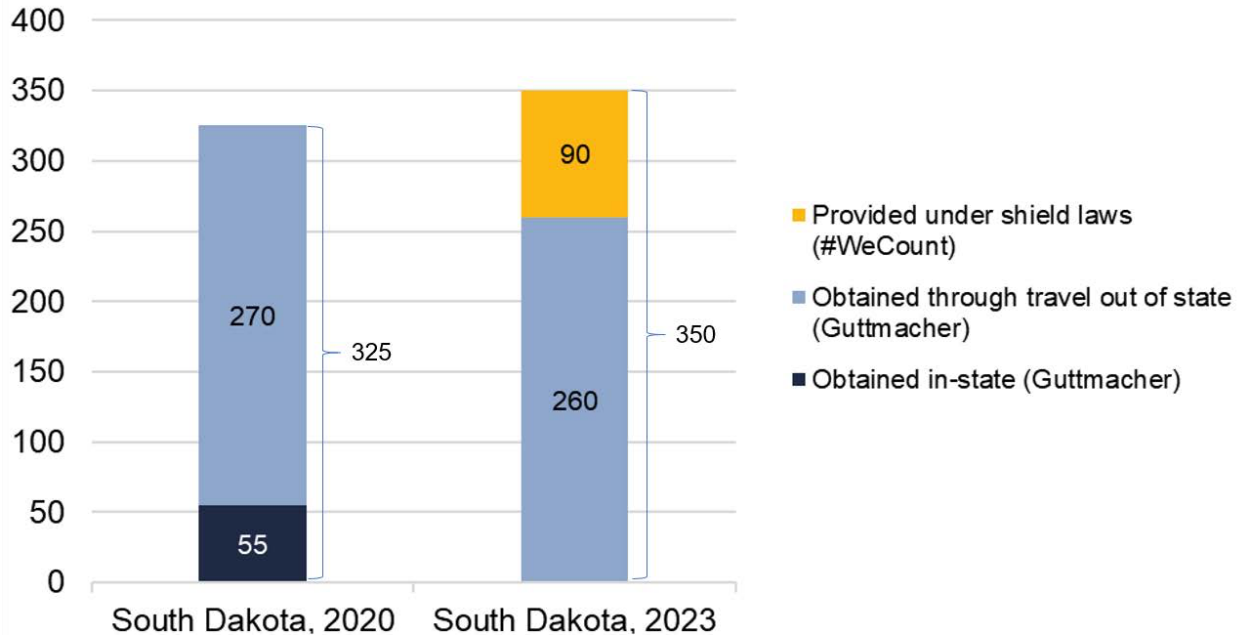
In one half of 2020, we estimate Oklahoma residents obtained approximately 4,130 abortions; 3,940 were obtained at facilities in state and 190 were to Oklahoma residents who traveled to another state for care (Figure 16). It is important to note that t the Guttmacher Institute's Abortion Provider Census shows that 2020 and 2019 were unusual years, with the study showing a substantially large increase in the number of abortions in Oklahoma since its data collection in 2017. Concretely, these numbers reflect an increase in the number of abortions in Oklahoma of 103% between 2017 and 2022, compared to 8% nationally.[7,8] By 2023, Oklahoma had implemented an abortion ban. In the second half of 2023, an estimated 1,820 residents travelled out of state for care and 980 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 2,800 abortions among Oklahoma residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 16. Oklahoma, six months of 2020 and 2023, respectively



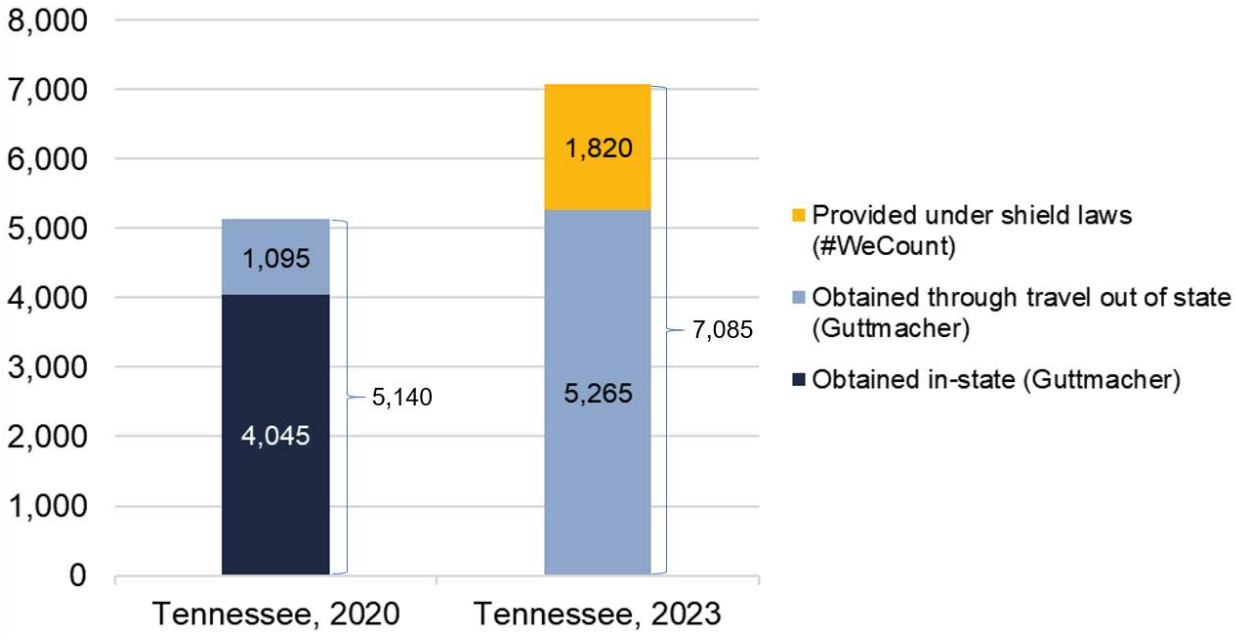
In one half of 2020, we estimate South Dakota residents obtained approximately 325 abortions; 55 were obtained at facilities in state and 270 were to South Dakota residents who traveled to another state for care (Figure 17). By 2023, South Dakota had implemented an abortion ban. In the second half of 2023, an estimated 280 residents travelled out of state for care and 90 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 350 abortions among South Dakota residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 17. South Dakota, six months of 2020 and 2023, respectively



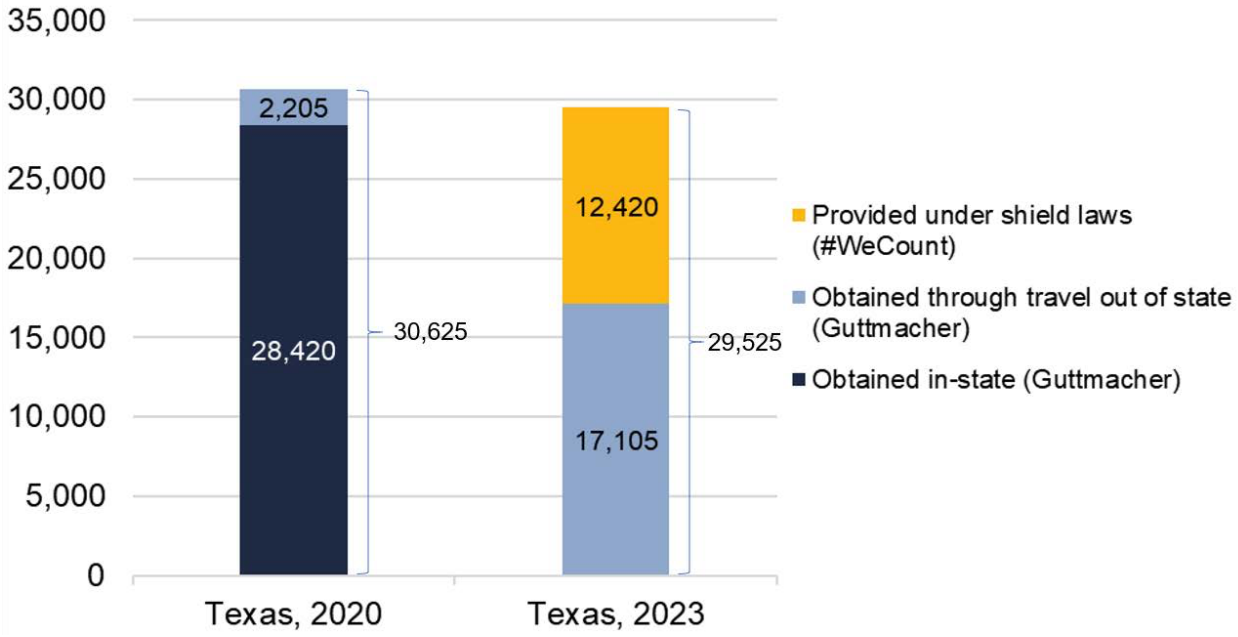
In one half of 2020, we estimate Tennessee residents obtained approximately 5,140 abortions; 4,045 were obtained at facilities in state and 1,095 were to Tennessee residents who traveled to another state for care (Figure 18). By 2023, Tennessee had implemented an abortion ban. In the second half of 2023, an estimated 5,265 residents travelled out of state for care and 1,820 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 7,085 abortions among Tennessee residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 18. Tennessee, six months of 2020 and 2023, respectively



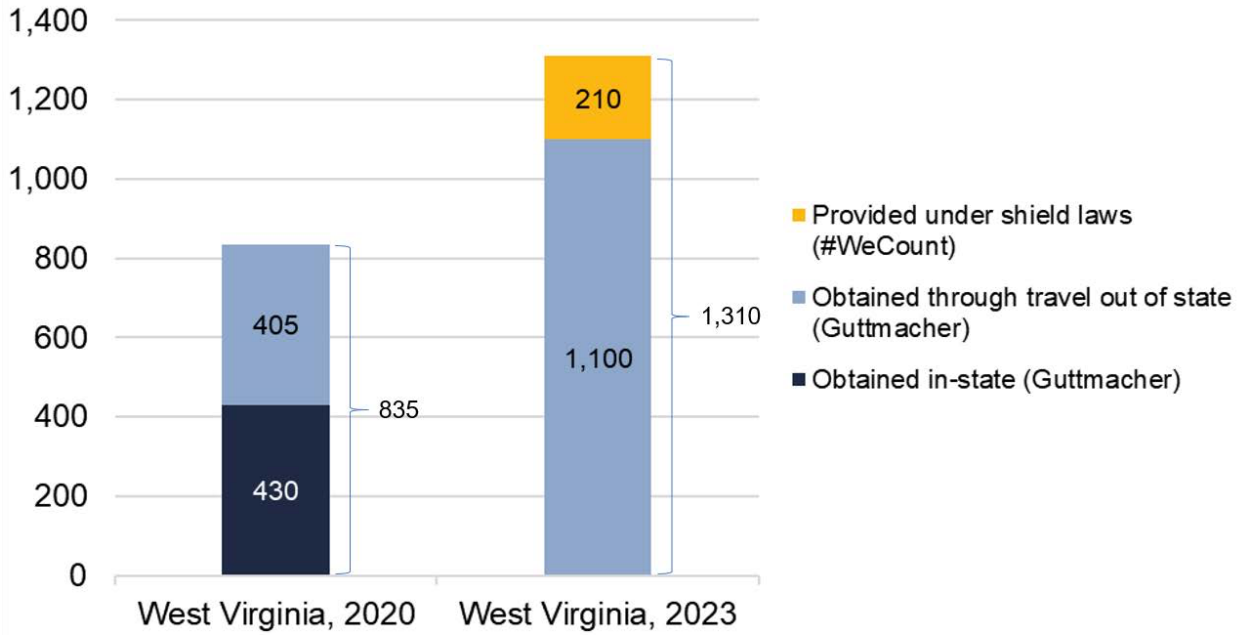
In one half of 2020, we estimate Texas residents obtained approximately 30,625 abortions; 28,420 were obtained at facilities in state and 2,205 were to Texas residents who traveled to another state for care (Figure 19). By 2023, Texas had implemented an abortion ban. In the second half of 2023, an estimated 17,105 residents were able to travel out of state for care and 12,420 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 29,525 abortions among Texas residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 19. Texas, six months of 2020 and 2023, respectively



In one half of 2020, we estimate West Virginia residents obtained approximately 835 abortions; 430 were obtained at facilities in state and 405 were to West Virginia residents who traveled to another state for care (Figure 20). By 2023, West Virginia had implemented an abortion ban. In the second half of 2023, an estimated 1,110 residents travelled out of state for care and 210 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 1,310 abortions among West Virginia residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

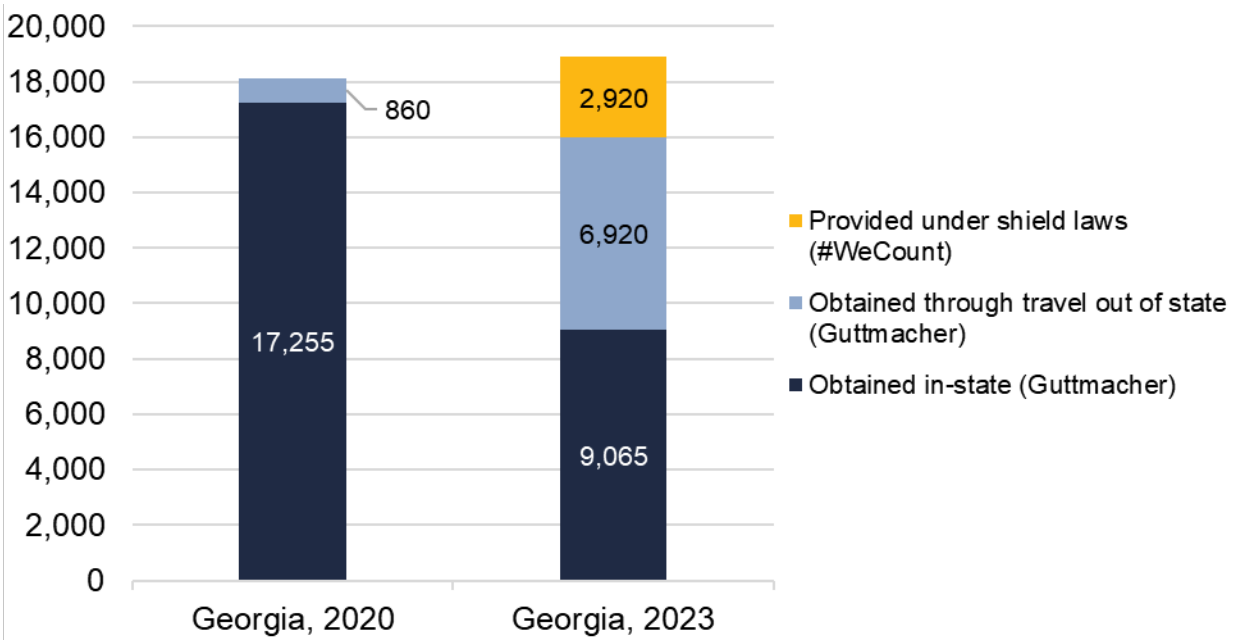
Figure 20. West Virginia, six months of 2020 and 2023, respectively



States with 6-week abortion bans

While several states have now have 6-week abortion bans, during the July to December 2023 period, only Georgia falls in this category. In one half of 2020, we estimate Georgia residents obtained approximately 18,115 abortions; 17,255 were obtained at facilities in state and 860 were to Georgia residents who traveled to another state for care (Figure 21). By 2023, Georgia had implemented a 6-week abortion ban. In the second half of 2023, an estimated 11,985 residents obtained abortion care in state, 6,920 travelled out of state for care, and 2,920 obtained abortion medications from health care providers operating under shield laws. We calculate a possible total of 21,825 abortions among Georgia residents in July to December 2023. Not included are an unspecified number of clinician-supported abortions provided from outside the US in 2020 and those sourced from online pharmacies or community networks without clinician support in both 2020 and 2023.

Figure 21. Georgia, six months of 2020 and 2023, respectively



Methods

In early 2022, #WeCount developed a database of all clinics, private medical offices, hospitals, and virtual clinic providers in the US known to offer abortion care. We started with the Abortion Facility Database from Advancing New Standards in Reproductive Health (ANSIRH) at University of California, San Francisco. We also included providers who were participating in the Ryan Training program and the Complex Family Planning

Fellowship, as well as others identified through outreach from AbortionFinder.com, the Society of Family Planning, and the Society for Maternal-Fetal Medicine. Throughout the study period, we added new providers to our database as we became aware of them. In both January and August 2024, we conducted searches within all 50 states and Washington, DC using AbortionFinder.com and INeedanA.com to confirm that our database was updated. We added new clinics that had opened and noted clinics that had closed. This report includes abortions provided under shield laws by US-based licensed providers who are following their own state law.

The data in this report includes the monthly counts reported by providers for April 2022 through June 2024. We continued to recruit abortion providers and request reporting throughout the study period, incorporating and updating their numbers into each data release. The Society provided compensation to participating facilities for each monthly submission.

In total, 81% of the abortions we counted across the study period were based on data obtained from providers or health departments, while the remaining 19% of the data were imputed. The magnitude of imputation in each state is noted with symbols in the data tables. In 12 states, we had complete reporting from all abortion providers known to #WeCount. In four states (Idaho, Indiana, Texas, and West Virginia) we used state health department data and thus we imputed very little data for those states. In an additional five states (Alabama, Florida, Kentucky, Oklahoma, and South Dakota), we used department of health public data to inform our imputations. In some cases, we divided yearly or quarterly counts into months based on the distribution of abortion volume from sites that did report monthly numbers in that state. In 32 states, we had at least one clinic or hospital known to provide abortions that did not submit any data to #WeCount. In those states, we imputed the number of missing abortions for those clinics or hospitals. We used information from news articles, contacts known to the non-reporting clinics, knowledge of the abortion volumes by state, or the median #WeCount number for the clinic or hospital type. To compute medians, we categorized reporters to #WeCount into five types of facilities and calculated the median for April and May 2022 for each category: 1) small abortion clinics, 2) large abortion clinics, 3) primary care clinics, 4) low volume hospitals, and 5) high volume hospitals. In 39 states, we used clinic-level imputations for at least one clinic in the state that submitted most but not all 27 months of data. For these, we calculated the average percent change in abortion volume in the state and imputed values for clinics with missing months. We also developed imputations for virtual clinics that did not submit data to us, using the median number of abortions that were provided by other virtual clinics in the state

We estimated the number of abortions by state restrictiveness level using three categories: states that banned abortion, states that restricted abortion to before detection of embryonic cardiac activity, also referred to as a “6-week bans”, because detection of such activity usually occurs around that point, and states that permitted abortion. These categories were based on the abortion policy in each state on the 15th of each month as reported by the New York Times. For a legal analysis of restrictions

that prevent explicitly ban telehealth or implicitly preclude telehealth abortion, we rely on the RHITES map.

#WeCount estimates the number of abortions in all 50 states. While #WeCount is the only effort that reports the total number of abortions provided via telehealth by state and by month, complementary data collection efforts are critical to the understanding of abortion volume in the years since the *Dobbs* ruling. One such effort is the Guttmacher Institute's Monthly Abortion Provision Study which estimates the number of clinician-provided abortions that take place each month in each US state without a total ban. While #WeCount aims to survey all clinicians providing abortions in the US, the Monthly Abortion Provision Study is based on data from samples of providers, which is combined with extensive historical facility-level data on variations in caseloads over time. In addition to the number of abortions in states without a total ban, the Monthly Abortion Provision Study also systematically collects additional data beyond abortion counts, including state of residence, gestational duration, and a rotating topic relevant to the current policy landscape.

This report uses previously released state-of-residence data reflecting 12-month totals from the Guttmacher Institute's Monthly Abortion Provision Study, accessed on September 11, 2024. As previously discussed, state-of-residence data are reported for 12 months; we have presented half of the 12-month total in order to estimate the 6-month period from July to December 2023. To provide historical context, we also present publicly available data from the Guttmacher Institute's 2020 Abortion Provider Census effort, similarly transforming data from a 12-month period into an estimate of the 6-month period from July to December 2020.

#WeCount was deemed exempt by Advarra IRB. All major decisions were guided by a Research Steering Committee listed here. This research was sponsored by the Society of Family Planning. In the tables, total abortions are presented per month by state, for the US, and by state policy category (banned, 6-week bans, or permitted) for April 2022 to June 2024. Monthly state totals were rounded to the nearest 10. Data that are suppressed are represented by a dash (—) in the table. If the number of abortions for a given state was 0 to 9 for a single month, it was either rounded up to 10 or represented as a dash. Thus, any cell with a dash could represent 0 abortions provided. For states where we did not collect data for a particular time period, geographic region, or service type, we indicate this with an ellipsis (...). In all states telehealth abortions were counted as part of the total for the state to where the medications were mailed.

Data limitations

First, and most importantly, research has never accurately captured the underlying need for abortion. For that reason, we advise against inferring a story of access from the number of abortions alone. We are unable to estimate the number of people who were unable to access abortion care and had to carry their unwanted pregnancy to term. The

inability to access abortion was a reality for many people before total abortion bans came into place,[11,12] and remains a reality for many, even in states that permit abortion. We are documenting the number of abortions that occur, and cannot estimate the number of people who wanted and were unable to obtain abortion care. Still, these counts, alone and in conversation with other data, offer an important signal about the present reality of abortion in the US.

Measuring abortion access and use is fraught with challenges.[9] Our findings are all reported at the national or state level, so we cannot describe how smaller geographic regions or individual facilities experienced increases or decreases. Observing the raw data, it is clear that the trends we report at the state level are not universally experienced in smaller regions or by each facility. In addition, we imputed, or estimated, a large number of abortions in California, Florida, New Jersey, and New York, contributing to some uncertainty in those estimates.

In addition, providers in the healthcare system, including those protected by shield laws, are not the only source of abortion medications. We are unable to estimate the number of abortions that occurred outside clinician-provided care, including those provided by online stores that sell abortion medications, volunteer accompaniment networks, and other types of self-managed abortion.

Regarding abortion provided via telehealth, we started measuring telehealth provided by brick-and-mortar clinics in July 2023, so cannot compare to past months. Finally, while we have an accurate count of how many telehealth abortions were mailed to patients, #WeCount cannot confirm how many patients did not take the pills that were sent to them.

Telehealth provision under shield laws started in June 2023, which triggered their inclusion in #WeCount in July 2023. Clinicians were mailing medications to residents of states with abortion bans, states with 6-week bans, and states with restrictions on a component of telehealth abortion prior to June 2023, but these occurred outside the US healthcare system and were not measured by #WeCount. At this time, there is no comparison possible to previous months.[10]

Regarding the findings about abortions provided to state residents in-state, out-of-state, and via telehealth, there are important limitations to this combination of data from multiple sources. First, there is emerging evidence that not every remotely dispensed package of medication results in medications taken. As is the case with any medication compared to any medical procedure, whether the person receiving this care ultimately uses the medication is more difficult to measure as compared to a procedure completed in a medical office. There is evidence that some people seeking medication abortion in all states, including those in states with bans or severe restrictions, may order medications from multiple sources to ensure they ultimately get the care they need (there is a similar trend observed informally around in-person care, with people making

multiple appointments). Second, the Guttmacher Institute's Monthly Abortion Provision Study state-of-residence data are reported for 12 months; we have presented half of the 12-month total in order to estimate the 6-month period from July to December 2023. This approach allows us to combine the data, but representing 6 months by dividing 12 months in half does not account for specific changes during a discrete period within that year. We are using this calculation as a proxy and it may overestimate the number of abortions for the 6-month period of July to December 2023.

Additionally, we caution against making direct inferences that compare 2020 and 2023 data over time for two reasons. First, the 2020 data also divides in half underlying data that reflect 12 months, prone to the same potential lack of sensitivity to month-to-month fluctuations, and thus potentially overestimating the 2020 numbers. Second, there is an unspecified number of clinician-supported abortions provided in the US during this period, under a model of care that relied on clinicians from outside the US. As of July 2023, these services shifted to rely on US clinicians in states with shield law protections for telehealth. We are mindful that the numbers of abortions provided under shield laws are quantifiable by #WeCount from July 2023, but there was also abortion care being provided for many years prior to our counting effort that was uncounted by #WeCount because it was outside the inclusion criteria for our effort.

Implications

Despite the dramatic declines in access in states that have enacted total abortion bans and 6-week bans, overall the national monthly abortion volume has increased, with the 2024 monthly average greater than the 2023 and 2022 monthly averages.

Increased numbers of abortions in states that permit abortion likely represent a combination of two main factors: people traveling from states where they cannot access care, and increased abortions among residents of states where abortion remains legal.[13,14] Such volume increases are likely influenced by reductions of barriers to abortion care, including reduced burden of cost[15,16] and travel by use of telehealth, increased financial support for low-income abortion seekers, and improved access via care navigation from practical support groups and public health departments.

Over the study period, monthly fluctuations can be seen at state and national levels. These changes are due to dynamic combinations of state-level changes in access (decreases and increases) and seasonal variation in the need for abortion.

The provision of medication abortion via telehealth increased across the study period and continues to increase. Telehealth, as a service-delivery model for many types of healthcare, has increased in the past few years, in part due to the COVID-19 pandemic.[17,18] The use of shield laws has brought access to telehealth abortions to residents of states where it was previously not available. While the majority of abortions occur within an in-person model of care, abortions provided via telehealth are an

important and complementary model of care. Yet many states ban the use of telehealth for abortion care even while in-person abortion care remains legal.

Nevertheless, counts do not tell the whole story. People in states with abortion bans or severe restrictions were forced to delay their abortions, travel to another state, obtain care from a provider in a shield law state and negotiate legal risk, or self-manage their abortions when they would have wanted clinical support, or continue a pregnancy, when any of these outcomes do not align with an individual preference.[19] Regardless of their outcome, lack of access to safe, legal, and local care has grave consequences for people who need abortions.

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Table 1-2022. Estimated number of abortions by state and month, April 2022 to December 2022

	Jan '22	Feb '22	Mar '22	Apr '22	May '22	Jun '22	Jul '22	Aug '22	Sep '22	Oct '22	Nov '22	Dec '22
All US state totals	…	…	…	**84,900**	**84,250**	**87,020**	**80,400**	**82,290**	**76,990**	**77,550**	**75,240**	**83,730**
Alabama*	…	…	…	650	620	520	–	–	–	–	–	–
Alaska‡	…	…	…	120	130	140	110	150	160	140	140	160
Arizona*	…	…	…	1,320	1,470	1,170	210	720	610	420	790	820
Arkansas	…	…	…	290	340	260	–	–	–	–	–	–
California‡	…	…	…	13,930	13,910	14,540	14,180	14,690	12,970	13,000	13,210	15,380
Colorado†	…	…	…	1,620	1,700	1,810	1,980	2,230	2,010	1,970	1,980	2,140
Connecticut†	…	…	…	920	950	970	1,000	960	880	880	900	990
Delaware‡	…	…	…	220	230	270	250	270	300	300	310	350
District of Columbia‖	…	…	…	920	880	870	870	940	830	890	810	830
Florida¶	…	…	…	6,160	6,230	6,750	6,690	7,150	6,830	7,430	6,760	7,940
Georgia‡	…	…	…	4,540	4,230	4,450	4,430	1,970	2,270	2,380	2,690	2,420
Hawaii‡	…	…	…	270	230	280	240	330	310	280	310	300
Idaho§	…	…	…	220	220	230	190	180	–	10	–	–
Illinois‡	…	…	…	5,590	5,550	6,170	6,780	7,250	6,640	6,620	6,320	7,190
Indiana	…	…	…	920	850	860	1,100	1,060	710	480	670	550
Iowa	…	…	…	380	370	390	360	280	320	310	350	370
Kansas‡	…	…	…	970	950	930	930	1,280	1,150	1,260	1,130	1,310
Kentucky	…	…	…	310	380	300	280	–	–	–	–	–
Louisiana	…	…	…	760	810	540	310	–	–	–	–	–
Maine†	…	…	…	200	230	240	240	240	220	210	190	200
Maryland§	…	…	…	2,880	2,860	2,890	2,770	2,930	2,990	3,070	3,080	3,560
Massachusetts§	…	…	…	1,790	1,650	1,760	1,790	1,790	1,750	1,700	1,650	1,840
Michigan‡	…	…	…	2,610	2,570	2,910	3,030	3,130	2,960	2,970	2,850	3,000
Minnesota†	…	…	…	950	930	1,040	1,180	1,230	1,240	1,280	1,310	1,250
Mississippi	…	…	…	350	350	470	–	–	–	–	–	–
Missouri	…	…	…	10	10	10	–	–	–	–	–	–
Montana*	…	…	…	170	180	170	160	220	170	200	190	170
Nebraska	…	…	…	200	190	210	210	260	230	240	200	170
Nevada§	…	…	…	1,140	1,090	1,320	1,220	1,510	1,360	1,430	1,380	1,520
New Hampshire‡	…	…	…	230	200	220	210	230	220	200	200	240
New Jersey‖	…	…	…	3,890	3,830	3,910	3,950	4,270	3,680	3,730	3,910	4,140
New Mexico‡	…	…	…	1,230	1,200	1,430	1,460	1,530	1,690	1,730	1,820	1,930
New York‖	…	…	…	8,770	9,190	9,780	9,400	10,140	9,250	9,300	7,520	8,900
North Carolina‡	…	…	…	3,280	3,270	3,230	3,930	4,400	4,090	3,870	3,770	4,070
North Dakota†	…	…	…	90	110	130	100	20	–	–	–	–
Ohio†	…	…	…	2,040	1,990	1,830	810	780	1,070	1,500	1,510	1,860
Oklahoma	…	…	…	480	140	–	–	–	–	–	–	–
Oregon†	…	…	…	850	800	920	880	1,080	970	970	960	1,010
Pennsylvania*	…	…	…	2,950	2,690	2,970	3,350	3,140	3,080	2,760	2,570	3,170
Rhode Island†	…	…	…	330	300	280	290	310	300	320	210	240
South Carolina*	…	…	…	690	630	490	180	360	790	830	830	850
South Dakota	…	…	…	20	40	30	–	–	–	–	–	–
Tennessee*	…	…	…	1,190	1,220	1,040	280	250	–	–	–	–
Texas	…	…	…	3,190	2,990	2,600	70	–	–	–	10	–
Utah*	…	…	…	320	400	360	270	310	320	280	320	340
Vermont§	…	…	…	120	140	140	130	150	130	120	140	130
Virginia§	…	…	…	2,230	2,280	2,480	2,700	2,370	2,380	2,410	2,360	2,380
Washington‡	…	…	…	1,790	1,740	1,960	1,760	1,970	2,020	2,010	1,840	1,950
West Virginia	…	…	…	170	230	220	60	160	20	–	–	–
Wisconsin§	…	…	…	580	700	470	–	–	–	–	–	–
Wyoming§	…	…	…	50	50	60	60	50	70	50	50	60

	Jan '22	Feb '22	Mar '22	Apr '22	May '22	Jun '22	Jul '22	Aug '22	Sep '22	Oct '22	Nov '22	Dec '22
Restrictiveness level												
Banned	…	…	…	–	–	–	130	–	710	10	10	–
6-week ban	…	…	…	3,190	2,990	2,600	990	3,110	2,270	2,380	2,690	2,420
Permitted	…	…	…	81,710	81,260	84,420	79,280	79,180	74,010	75,160	72,540	81,310
Abortions provided under shield laws to states with telehealth restrictions				…	…	…	…	…	…	…	…	…
Abortions provided under shield laws to states with total bans and 6-week bans				…	…	…	…	…	…	…	…	…

National and state totals include telehealth abortions, including those provided under shield laws.

All numbers have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

*For states marked * there is less than 1% imputation, † 1-4% imputation, ‡ 5-14% imputation, § 15-29% imputation, ‖ 30-44% imputation, ¶ >45% imputation. States with no notation by their name have no imputation for missingness. In Florida, Indiana, Texas, and West Virginia, we used state health department data and thus we did not have to impute any data for those states.*

Legal status is time varying, and we use the status for each state as reported by the New York Times on the 15th of each month.

Table 1-2023. Estimated number of abortions by state and month, January 2023 to December 2023

	Jan '23	Feb '23	Mar '23	Apr '23	May '23	Jun '23	Jul '23	Aug '23	Sep '23	Oct '23	Nov '23	Dec '23
All US state totals	**86,770**	**80,910**	**93,730**	**84,460**	**88,130**	**88,140**	**88,310**	**92,810**	**85,810**	**88,610**	**86,760**	**91,710**
Alabama*	–	–	–	–	–	–	220	250	250	300	340	360
Alaska‡	140	130	140	110	160	140	160	170	150	180	150	140
Arizona*	1,120	990	1,260	1,000	1,150	1,090	1,280	1,350	1,410	1,310	1,230	1,270
Arkansas	–	–	–	–	–	–	130	140	140	180	200	180
California‡	15,910	14,180	16,270	15,010	15,720	15,390	14,290	15,590	14,120	14,350	13,710	14,950
Colorado†	2,340	2,080	2,400	2,200	2,400	2,280	2,230	2,310	1,990	2,130	2,140	2,060
Connecticut†	1,120	1,000	1,230	1,250	1,320	1,290	1,400	1,240	1,130	1,260	1,140	1,260
Delaware‡	270	240	300	260	270	310	310	280	270	300	320	300
District of Columbia‖	900	870	1,080	920	1,000	730	770	740	610	630	610	590
Florida¶	7,170	7,050	8,040	7,080	7,110	7,040	7,540	7,510	7,450	7,360	6,910	7,240
Georgia‡	2,640	2,390	2,980	2,590	2,440	2,470	2,770	2,740	2,670	2,690	2,870	3,050
Hawaii‡	330	290	310	340	330	290	310	330	300	310	310	280
Idaho§	–	–	–	–	–	–	30	30	40	60	50	50
Illinois‡	7,840	7,310	8,460	7,640	7,850	7,930	7,640	8,320	7,510	7,520	7,650	7,810
Indiana	510	690	730	610	640	700	880	180	170	220	220	240
Iowa	370	300	390	240	260	290	310	370	330	390	350	360
Kansas‡	1,660	1,560	1,700	1,740	1,810	2,020	1,710	1,820	1,620	1,720	1,880	1,830
Kentucky	–	–	–	–	–	–	140	130	150	180	190	180
Louisiana	–	–	–	–	–	–	310	380	320	480	470	520
Maine†	240	220	260	210	220	250	230	230	230	210	220	220
Maryland§	3,580	3,590	3,570	3,480	3,810	3,820	3,780	3,660	3,190	3,320	3,590	3,410
Massachusetts§	1,880	1,620	2,070	1,700	1,850	1,900	1,760	1,940	1,720	1,800	1,880	2,110
Michigan‡	2,990	2,910	3,370	3,070	3,000	2,940	2,990	3,150	2,970	3,000	2,950	3,060
Minnesota†	1,240	1,110	1,430	1,210	1,400	1,360	1,320	1,410	1,270	1,250	1,240	1,180
Mississippi	–	–	–	–	–	–	200	210	220	280	300	360
Missouri	–	–	–	10	–	–	110	120	110	150	150	160
Montana*	210	170	190	180	190	200	210	250	210	220	230	220
Nebraska	320	280	250	280	180	240	180	270	210	190	210	290
Nevada§	1,540	1,430	1,630	1,380	1,370	1,390	1,260	1,420	1,300	1,360	1,330	1,420
New Hampshire‡	210	220	270	250	250	230	240	280	250	230	280	290
New Jersey‖	4,170	4,020	4,640	4,220	4,790	4,640	4,320	4,630	3,940	3,880	3,730	4,420
New Mexico‡	2,070	1,850	2,150	1,890	1,870	1,980	1,770	1,820	1,820	1,670	1,680	1,790
New York‖	8,600	8,010	9,970	8,980	9,360	9,520	9,140	10,060	9,100	9,610	8,910	9,710
North Carolina‡	4,510	4,120	4,730	4,210	4,560	4,730	3,390	3,570	4,190	4,130	3,540	3,960
North Dakota†	–	–	–	–	–	–	10	10	30	20	20	10
Ohio†	1,950	1,920	2,110	1,860	1,970	1,970	1,970	2,220	1,970	2,290	2,180	2,280
Oklahoma	–	–	–	–	–	–	120	150	140	190	180	200
Oregon†	1,050	880	1,140	930	1,060	1,080	1,020	1,130	970	1,030	970	990
Pennsylvania*	2,940	3,050	3,530	3,100	3,130	3,300	3,260	3,420	3,210	3,110	3,090	3,340
Rhode Island†	280	240	320	220	240	250	220	240	250	260	300	270
South Carolina*	990	1,000	1,090	950	890	930	1,060	960	350	440	440	480
South Dakota	–	–	–	–	–	–	10	10	10	20	20	20
Tennessee*	–	–	–	–	–	–	230	270	260	310	390	360
Texas	10	–	10	–	10	–	1,780	1,690	1,780	2,260	2,410	2,540
Utah*	360	340	400	340	310	330	410	390	400	380	440	380
Vermont§	150	120	150	140	200	140	120	160	130	140	140	150
Virginia§	3,040	2,770	3,010	2,930	2,910	2,880	2,650	2,980	2,860	2,770	2,680	2,950
Washington‡	2,060	1,910	2,090	1,870	2,020	2,010	1,920	2,050	1,840	2,030	1,940	1,950
West Virginia	–	–	–	–	–	–	40	30	30	40	40	40
Wisconsin§	–	–	–	–	–	–	100	110	150	370	460	400
Wyoming§	60	50	60	60	80	80	60	90	70	80	80	80

	Jan '23	Feb '23	Mar '23	Apr '23	May '23	Jun '23	Jul '23	Aug '23	Sep '23	Oct '23	Nov '23	Dec '23
Restrictiveness level												
Banned	10	–	10	10	10	–	3,430	3,710	3,650	4,690	4,980	5,220
6-week ban	2,640	2,390	2,980	2,590	2,440	2,470	3,080	2,740	3,020	3,130	3,310	3,530
Permitted	84,120	78,520	90,740	81,860	85,680	85,670	81,800	86,360	79,140	80,790	78,470	82,960
Abortions provided under shield laws to states with telehealth restrictions	…	…	…	…	…	…	1,720	1,640	1,650	2,000	2,180	2,220
Abortions provided under shield laws to states with total bans and 6-week bans	…	…	…	…	…	…	3,900	4,040	4,220	5,420	5,820	6,120

National and state totals include telehealth abortions, including those provided under shield laws.

All numbers have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

*For states marked * there is less than 1% imputation, † 1-4% imputation, ‡ 5-14% imputation, § 15-29% imputation, ‖ 30-44% imputation, ¶ >45% imputation. States with no notation by their name have no imputation for missingness. In Florida, Indiana, Texas, and West Virginia, we used state health department data and thus we did not have to impute any data for those states.*

Legal status is time varying, and we use the status for each state as reported by the New York Times on the 15th of each month.

Table 1-2024. Estimated number of abortions by state and month, January 2024 to March 2024

	Jan '24	Feb '24	Mar '24	Apr '24	May '24	Jun '24	Jul '24	Aug '24	Sep '24	Oct '24	Nov '24	Dec '24
All US state totals	**102,590**	**95,150**	**100,430**	**98,920**	**98,840**	**91,510**	…	…	…	…	…	…
							…	…	…	…	…	…
Alabama*	390	410	420	420	440	440	…	…	…	…	…	…
Alaska‡	130	140	140	160	160	170	…	…	…	…	…	…
Arizona*	1,570	1,480	1,580	1,480	1,430	1,310	…	…	…	…	…	…
Arkansas	230	230	260	220	240	260	…	…	…	…	…	…
California‡	17,510	15,590	16,170	15,620	16,040	14,560	…	…	…	…	…	…
Colorado†	2,320	2,080	2,150	2,110	2,110	2,000	…	…	…	…	…	…
Connecticut†	1,310	1,100	1,280	1,160	1,220	1,120	…	…	…	…	…	…
Delaware‡	360	330	310	300	340	290	…	…	…	…	…	…
District of Columbia‖	710	740	810	750	820	760	…	…	…	…	…	…
Florida¶	8,410	7,920	8,290	10,120	6,170	5,560	…	…	…	…	…	…
Georgia‡	3,060	2,700	3,220	2,990	3,010	2,780	…	…	…	…	…	…
Hawaii‡	340	290	330	330	280	280	…	…	…	…	…	…
Idaho§	70	50	40	60	60	50	…	…	…	…	…	…
Illinois‡	8,120	8,100	8,350	8,090	8,530	8,110	…	…	…	…	…	…
Indiana	290	240	290	240	250	230	…	…	…	…	…	…
Iowa	360	350	410	380	420	370	…	…	…	…	…	…
Kansas‡	2,130	2,050	2,250	1,920	2,130	1,720	…	…	…	…	…	…
Kentucky	230	180	220	220	220	210	…	…	…	…	…	…
Louisiana	560	540	600	610	620	620	…	…	…	…	…	…
Maine†	280	240	250	250	270	230	…	…	…	…	…	…
Maryland§	3,860	3,450	3,560	3,460	3,590	3,270	…	…	…	…	…	…
Massachusetts§	2,100	2,000	2,050	1,830	2,010	1,730	…	…	…	…	…	…
Michigan‡	3,520	3,260	3,350	3,130	3,240	2,990	…	…	…	…	…	…
Minnesota†	1,340	1,270	1,310	1,350	1,360	1,340	…	…	…	…	…	…
Mississippi	390	380	420	390	400	380	…	…	…	…	…	…
Missouri	160	140	160	180	160	160	…	…	…	…	…	…
Montana*	230	200	210	200	230	200	…	…	…	…	…	…
Nebraska	270	260	270	280	300	310	…	…	…	…	…	…
Nevada§	1,690	1,530	1,670	1,420	1,510	1,470	…	…	…	…	…	…
New Hampshire‡	290	300	310	310	320	270	…	…	…	…	…	…
New Jersey‖	4,580	3,970	4,460	4,270	4,720	4,650	…	…	…	…	…	…
New Mexico‡	2,080	1,820	1,970	1,810	1,800	1,710	…	…	…	…	…	…
New York‖	10,780	9,930	10,200	10,310	11,000	9,820	…	…	…	…	…	…
North Carolina‡	4,310	4,190	4,400	4,720	4,510	4,590	…	…	…	…	…	…
North Dakota†	20	20	10	20	20	20	…	…	…	…	…	…
Ohio†	2,340	2,300	2,610	2,470	2,800	2,660	…	…	…	…	…	…
Oklahoma	220	190	220	260	240	250	…	…	…	…	…	…
Oregon†	1,060	1,100	1,030	1,050	1,010	960	…	…	…	…	…	…
Pennsylvania*	3,550	3,640	3,640	3,180	3,480	3,080	…	…	…	…	…	…
Rhode Island†	300	270	290	300	300	310	…	…	…	…	…	…
South Carolina*	580	520	590	510	570	510	…	…	…	…	…	…
South Dakota	30	20	20	20	30	30	…	…	…	…	…	…
Tennessee*	420	380	440	460	470	450	…	…	…	…	…	…
Texas	2,920	2,650	2,850	2,880	2,730	2,830	…	…	…	…	…	…
Utah*	450	420	420	440	460	400	…	…	…	…	…	…
Vermont§	150	160	160	160	160	140	…	…	…	…	…	…
Virginia§	3,620	3,370	3,660	3,280	3,810	3,500	…	…	…	…	…	…
Washington‡	2,250	2,050	2,040	2,060	2,120	1,830	…	…	…	…	…	…
West Virginia	60	50	50	60	50	50	…	…	…	…	…	…
Wisconsin§	550	480	590	600	610	460	…	…	…	…	…	…
Wyoming§	90	70	100	80	70	70	…	…	…	…	…	…

	Jan '24	Feb '24	Mar '24	Apr '24	May '24	Jun '24	Jul '24	Aug '24	Sep '24	Oct '24	Nov '24	Dec '24
Restrictiveness level												
Banned	5,990	5,480	6,000	6,040	5,930	5,980	…	…	…	…	…	…
6-week ban	3,640	3,220	3,810	3,500	9,750	8,850	…	…	…	…	…	…
Permitted	92,960	86,450	90,620	89,380	83,160	76,680	…	…	…	…	…	…
Abortions provided under shield laws to states with telehealth restrictions	2,700	2,220	2,540	2,700	1,730	1,580						
Abortions provided under shield laws to states with total bans and 6-week bans	6,930	6,310	6,960	6,990	8,150	8,070						

National and state totals include telehealth abortions, including those provided under shield laws.

All numbers have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

*For states marked * there is less than 1% imputation, † 1-4% imputation, ‡ 5-14% imputation, § 15-29% imputation, ‖ 30-44% imputation, ¶ >45% imputation. States with no notation by their name have no imputation for missingness. In Florida, Indiana, Texas, and West Virginia, we used state health department data and thus we did not have to impute any data for those states.*

Legal status is time varying, and we use the status for each state as reported by the New York Times on the 15th of each month.

Table 2-2022a. Estimated number of in-person and telehealth abortions by state and month, April 2022 to June 2022

	Jan '22		Feb '22		Mar '22		Apr '22		May '22		Jun '22	
	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health
All US state totals	…	…	…	…	…	…	**81,250**	**3,650**	**79,670**	**4,580**	**81,660**	**5,360**
Alabama*	…	…	…	…	…	…	650	–	620	–	520	–
Alaska‡	…	…	…	…	…	…	110	10	120	10	120	20
Arizona*	…	…	…	…	…	…	1,320	–	1,470	–	1,170	–
Arkansas	…	…	…	…	…	…	290	–	340	–	260	–
California‡	…	…	…	…	…	…	13,240	690	13,040	870	13,510	1,030
Colorado†	…	…	…	…	…	…	1,400	220	1,380	320	1,440	370
Connecticut†	…	…	…	…	…	…	870	50	890	60	910	60
Delaware‡	…	…	…	…	…	…	200	20	190	40	230	40
District of Columbia‖	…	…	…	…	…	…	890	30	850	30	830	40
Florida¶	…	…	…	…	…	…	6,160	–	6,230	–	6,750	–
Georgia‡	…	…	…	…	…	…	3,990	550	3,710	520	3,960	490
Hawaii‡	…	…	…	…	…	…	260	10	220	10	260	20
Idaho§	…	…	…	…	…	…	200	20	190	30	190	40
Illinois‡	…	…	…	…	…	…	5,260	330	5,100	450	5,610	560
Indiana	…	…	…	…	…	…	920	–	850	–	860	–
Iowa	…	…	…	…	…	…	360	20	360	10	380	10
Kansas‡	…	…	…	…	…	…	970	–	950	–	930	–
Kentucky	…	…	…	…	…	…	310	–	380	–	300	–
Louisiana	…	…	…	…	…	…	760	–	810	–	540	–
Maine†	…	…	…	…	…	…	190	10	220	10	220	20
Maryland§	…	…	…	…	…	…	2,740	140	2,720	140	2,710	180
Massachusetts§	…	…	…	…	…	…	1,720	70	1,550	100	1,640	120
Michigan‡	…	…	…	…	…	…	2,610	–	2,450	120	2,720	190
Minnesota†	…	…	…	…	…	…	730	220	670	260	770	270
Mississippi	…	…	…	…	…	…	350	–	350	–	470	–
Missouri	…	…	…	…	…	…	10	–	10	–	10	–
Montana*	…	…	…	…	…	…	130	40	150	30	130	40
Nebraska	…	…	…	…	…	…	200	–	190	–	210	–
Nevada§	…	…	…	…	…	…	1,020	120	940	150	1,140	180
New Hampshire‡	…	…	…	…	…	…	230	–	200	–	220	–
New Jersey‖	…	…	…	…	…	…	3,750	140	3,640	190	3,730	180
New Mexico‡	…	…	…	…	…	…	1,130	100	1,080	120	1,250	180
New York‖	…	…	…	…	…	…	8,400	370	8,690	500	9,240	540
North Carolina‡	…	…	…	…	…	…	3,280	–	3,270	–	3,230	–
North Dakota†	…	…	…	…	…	…	90	–	110	–	130	–
Ohio†	…	…	…	…	…	…	2,040	–	1,990	–	1,830	–
Oklahoma	…	…	…	…	…	…	480	–	140	–	–	–
Oregon†	…	…	…	…	…	…	820	30	740	60	840	80
Pennsylvania*	…	…	…	…	…	…	2,950	–	2,690	–	2,960	10
Rhode Island†	…	…	…	…	…	…	310	20	270	30	250	30
South Carolina*	…	…	…	…	…	…	690	–	630	–	490	–
South Dakota	…	…	…	…	…	…	20	–	40	–	30	–
Tennessee*	…	…	…	…	…	…	1,190	–	1,220	–	1,040	–
Texas	…	…	…	…	…	…	3,190	–	2,990	–	2,600	–
Utah*	…	…	…	…	…	…	320	–	400	–	360	–
Vermont§	…	…	…	…	…	…	100	20	120	20	120	20
Virginia§	…	…	…	…	…	…	1,990	240	2,010	270	2,160	320
Washington‡	…	…	…	…	…	…	1,650	140	1,550	190	1,680	280
West Virginia	…	…	…	…	…	…	170	–	230	–	220	–
Wisconsin§	…	…	…	…	…	…	580	–	700	–	470	–
Wyoming§	…	…	…	…	…	…	10	40	10	40	20	40

	Jan '22		Feb '22		Mar '22		Apr '22		May '22		Jun '22	
	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health
Restrictiveness level							–	–	–	–	–	–
Banned	…	…	…	…	…	…	–	–	–	–	–	–
6-week ban	…	…	…	…	…	…	3,190	–	2,990	–	2,600	–
Permitted	…	…	…	…	…	…	78,060	3,650	76,680	4,580	79,060	5,360
Abortions provided under shield laws to states with telehealth restrictions							…	…	…	…	…	…
Abortions provided under shield laws to states with total bans and 6-week bans							…	…	…	…	…	…

National and state totals of telehealth abortions include those provided under shield laws.

All numbers have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

Table 2-2022b. Estimated number of in-person and telehealth abortions by state and month, July 2022 to December 2022

	Jul '22		Aug '22		Sep '22		Oct '22		Nov '22		Dec '22	
	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health
All US state totals	**74,680**	**5,720**	**74,930**	**7,360**	**70,100**	**6,890**	**70,490**	**7,060**	**67,460**	**7,780**	**74,870**	**8,860**
Alabama*	–	–	–	–	–	–	–	–	–	–	–	–
Alaska‡	90	20	110	40	120	40	110	30	100	40	120	40
Arizona*	210	–	720	–	610	–	420	–	790	–	820	–
Arkansas	–	–	–	–	–	–	–	–	–	–	–	–
California‡	13,050	1,130	13,210	1,480	11,610	1,360	11,630	1,370	11,750	1,460	13,680	1,700
Colorado†	1,470	510	1,610	620	1,440	570	1,380	590	1,400	580	1,530	610
Connecticut†	940	60	850	110	760	120	780	100	770	130	830	160
Delaware‡	210	40	200	70	240	60	240	60	250	60	290	60
District of Columbia‖	810	60	860	80	780	50	860	30	780	30	790	40
Florida¶	6,690	–	7,150	–	6,830	–	7,430	–	6,760	–	7,940	–
Georgia‡	4,110	320	1,970	–	2,270	–	2,380	–	2,690	–	2,420	–
Hawaii‡	220	20	270	60	270	40	250	30	280	30	250	50
Idaho§	140	50	100	80	–	–	10	–	–	–	–	–
Illinois‡	6,220	560	6,530	720	5,970	670	5,990	630	5,600	720	6,380	810
Indiana	1,100	–	1,060	–	710	–	480	–	670	–	550	–
Iowa	340	20	260	20	300	20	280	30	310	40	330	40
Kansas‡	930	–	1,280	–	1,150	–	1,260	–	1,130	–	1,300	10
Kentucky	280	–	–	–	–	–	–	–	–	–	–	–
Louisiana	310	–	–	–	–	–	–	–	–	–	–	–
Maine†	220	20	210	30	190	30	170	40	130	60	150	50
Maryland§	2,600	170	2,630	300	2,680	310	2,740	330	2,670	410	3,090	470
Massachusetts§	1,650	140	1,610	180	1,590	160	1,490	210	1,370	280	1,570	270
Michigan‡	2,830	200	2,720	410	2,550	410	2,540	430	2,390	460	2,430	570
Minnesota†	870	310	940	290	940	300	970	310	1,020	290	960	290
Mississippi	–	–	–	–	–	–	–	–	–	–	–	–
Missouri	–	–	–	–	–	–	–	–	–	–	–	–
Montana*	120	40	180	40	130	40	160	40	160	30	140	30
Nebraska	210	–	260	–	230	–	240	–	200	–	170	–
Nevada§	1,030	190	1,220	290	1,040	320	1,110	320	1,060	320	1,150	370
New Hampshire‡	200	10	200	30	200	20	170	30	150	50	190	50
New Jersey‖	3,700	250	3,880	390	3,310	370	3,330	400	3,450	460	3,590	550
New Mexico‡	1,250	210	1,310	220	1,480	210	1,500	230	1,580	240	1,670	260
New York‖	8,860	540	9,310	830	8,540	710	8,550	750	6,690	830	7,840	1,060
North Carolina‡	3,930	–	4,400	–	4,090	–	3,870	–	3,770	–	4,070	–
North Dakota†	100	–	20	–	–	–	–	–	–	–	–	–
Ohio†	810	–	780	–	1,070	–	1,500	–	1,510	–	1,860	–
Oklahoma	–	–	–	–	–	–	–	–	–	–	–	–
Oregon†	800	80	950	130	840	130	850	120	810	150	850	160
Pennsylvania*	3,310	40	3,090	50	3,030	50	2,700	60	2,520	50	3,100	70
Rhode Island†	260	30	280	30	270	30	290	30	170	40	210	30
South Carolina*	180	–	360	–	790	–	830	–	830	–	850	–
South Dakota	–	–	–	–	–	–	–	–	–	–	–	–
Tennessee*	280	–	250	–	–	–	–	–	–	–	–	–
Texas	70	–	–	–	–	–	–	–	10	–	–	–
Utah*	270	–	310	–	320	–	280	–	320	–	340	–
Vermont§	110	20	130	20	110	20	100	20	100	40	90	40
Virginia§	2,310	390	1,870	500	1,870	510	1,880	530	1,740	620	1,740	640
Washington‡	1,510	250	1,660	310	1,730	290	1,710	300	1,510	330	1,560	390
West Virginia	60	–	160	–	20	–	–	–	–	–	–	–
Wisconsin§	–	–	–	–	–	–	–	–	–	–	–	–
Wyoming§	20	40	20	30	20	50	10	40	20	30	20	40

	Jul '22		Aug '22		Sep '22		Oct '22		Nov '22		Dec '22	
	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health
Restrictiveness level												
Banned	130	–	–	–	710	–	10	–	10	–	–	–
6-week ban	990	–	3,110	–	2,270	–	2,380	–	2,690	–	2,420	–
Permitted	73,560	5,720	71,820	7,360	67,120	6,890	68,100	7,060	64,760	7,780	72,450	8,860
Abortions provided under shield laws to states with telehealth restrictions	…	…	…	…	…	…	…	…	…	…	…	…
Abortions provided under shield laws to states with total bans and 6-week bans	…	…	…	…	…	…	…	…	…	…	…	…

Table 3 national totals include telehealth abortions provided under shield laws. Abortions provided under shield laws are reported in aggregate only and thus are not included in the state totals.

All numbers in Table 3 have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

Table 2-2023a. Estimated number of in-person and telehealth abortions by state and month, January 2023 to June 2023

	Jan '23		Feb '23		Mar '23		Apr '23		May '23		Jun '23	
	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health
All US state totals	**79,230**	**7,540**	**74,630**	**6,280**	**86,520**	**7,210**	**77,210**	**7,250**	**80,350**	**7,780**	**80,740**	**7,400**
Alabama*	–	–	–	–	–	–	–	–	–	–	–	–
Alaska‡	110	30	110	20	120	20	90	20	130	30	120	20
Arizona*	1,120	–	990	–	1,260	–	1,000	–	1,150	–	1,090	–
Arkansas	–	–	–	–	–	–	–	–	–	–	–	–
California‡	14,480	1,430	13,020	1,160	15,000	1,270	13,770	1,240	14,350	1,370	14,170	1,220
Colorado†	1,830	510	1,620	460	1,920	480	1,700	500	1,910	490	1,770	510
Connecticut†	970	150	890	110	1,100	130	1,100	150	1,180	140	1,150	140
Delaware‡	200	70	180	60	240	60	180	80	210	60	230	80
District of Columbia‖	860	40	840	30	1,030	50	870	50	940	60	680	50
Florida¶	7,170	–	7,050	–	8,040	–	7,080	–	7,110	–	7,040	–
Georgia‡	2,640	–	2,390	–	2,980	–	2,590	–	2,440	–	2,470	–
Hawaii‡	290	40	270	20	270	40	310	30	290	40	260	30
Idaho§	–	–	–	–	–	–	–	–	–	–	–	–
Illinois‡	7,040	800	6,670	640	7,670	790	6,880	760	6,980	870	7,080	850
Indiana	510	–	690	–	730	–	610	–	640	–	700	–
Iowa	340	30	270	30	330	60	150	90	160	100	230	60
Kansas‡	1,580	80	1,460	100	1,560	140	1,600	140	1,680	130	1,890	130
Kentucky	–	–	–	–	–	–	–	–	–	–	–	–
Louisiana	–	–	–	–	–	–	–	–	–	–	–	–
Maine†	180	60	180	40	220	40	170	40	180	40	210	40
Maryland§	3,180	400	3,190	400	3,120	450	3,060	420	3,240	570	3,350	470
Massachusetts§	1,670	210	1,470	150	1,840	230	1,530	170	1,650	200	1,680	220
Michigan‡	2,700	290	2,680	230	3,120	250	2,820	250	2,760	240	2,770	170
Minnesota†	940	300	850	260	1,080	350	960	250	1,070	330	1,050	310
Mississippi	–	–	–	–	–	–	–	–	–	–	–	–
Missouri	–	–	–	–	–	–	10	–	–	–	–	–
Montana*	170	40	140	30	150	40	150	30	150	40	170	30
Nebraska	320	–	280	–	250	–	280	–	180	–	240	–
Nevada§	1,230	310	1,130	300	1,320	310	1,100	280	1,060	310	1,150	240
New Hampshire‡	170	40	200	20	230	40	210	40	210	40	210	20
New Jersey‖	3,640	530	3,590	430	4,170	470	3,730	490	4,280	510	4,140	500
New Mexico‡	1,850	220	1,650	200	1,970	180	1,710	180	1,670	200	1,790	190
New York‖	7,760	840	7,350	660	9,160	810	8,090	890	8,550	810	8,740	780
North Carolina‡	4,510	–	4,120	–	4,730	–	4,210	–	4,560	–	4,730	–
North Dakota†	–	–	–	–	–	–	–	–	–	–	–	–
Ohio†	1,950	–	1,920	–	2,110	–	1,860	–	1,970	–	1,970	–
Oklahoma	–	–	–	–	–	–	–	–	–	–	–	–
Oregon†	940	110	790	90	1,060	80	840	90	960	100	990	90
Pennsylvania*	2,940	–	3,050	–	3,530	–	2,980	120	3,020	110	3,130	170
Rhode Island†	250	30	210	30	280	40	190	30	190	50	200	50
South Carolina*	990	–	1,000	–	1,090	–	950	–	890	–	930	–
South Dakota	–	–	–	–	–	–	–	–	–	–	–	–
Tennessee*	–	–	–	–	–	–	–	–	–	–	–	–
Texas	10	–	–	–	10	–	–	–	10	–	–	–
Utah*	360	–	340	–	400	–	340	–	310	–	330	–
Vermont§	120	30	100	20	110	40	120	20	170	30	120	20
Virginia§	2,460	580	2,250	520	2,460	550	2,390	540	2,350	560	2,200	680
Washington‡	1,730	330	1,670	240	1,840	250	1,560	310	1,710	310	1,720	290
West Virginia	–	–	–	–	–	–	–	–	–	–	–	–
Wisconsin§	–	–	–	–	–	–	–	–	–	–	–	–
Wyoming§	20	40	20	30	20	40	20	40	40	40	40	40

	Jan '23		Feb '23		Mar '23		Apr '23		May '23		Jun '23	
	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health
Restrictiveness level												
Banned	10	–	–	–	10	–	10	–	10	–	–	–
6-week ban	2,640	–	2,390	–	2,980	–	2,590	–	2,440	–	2,470	–
Permitted	76,580	7,540	72,240	6,280	83,530	7,210	74,610	7,250	77,900	7,780	78,270	7,400
Abortions provided under shield laws to states with telehealth restrictions	…	…	…	…	…	…	…	…	…	…	…	…
Abortions provided under shield laws to states with total bans and 6-week bans	…	…	…	…	…	…	…	…	…	…	…	…

National and state totals of telehealth abortions include those provided under shield laws.

All numbers have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

Table 2-2023b. Estimated number of in-person and telehealth abortions by state and month, July 2023 to December 2023

	Jul '23		Aug '23		Sep '23		Oct '23		Nov '23		Dec '23	
	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health
All US state totals	**73,810**	**14,500**	**78,240**	**14,570**	**71,570**	**14,240**	**72,060**	**16,550**	**69,360**	**17,400**	**73,950**	**17,760**
Alabama*	–	220	–	250	–	250	–	300	–	340	–	360
Alaska‡	130	30	140	30	120	30	140	40	120	30	100	40
Arizona*	1,030	250	1,120	230	1,120	290	1,020	290	950	280	1,020	250
Arkansas	–	130	–	140	–	140	–	180	–	200	–	180
California‡	12,790	1,500	14,030	1,560	12,800	1,320	12,780	1,570	12,150	1,560	13,370	1,580
Colorado†	1,690	540	1,740	570	1,440	550	1,610	520	1,580	560	1,510	550
Connecticut†	1,250	150	1,100	140	1,000	130	1,120	140	970	170	1,090	170
Delaware‡	220	90	180	100	190	80	200	100	220	100	190	110
District of Columbia‖	720	50	690	50	570	40	560	70	530	80	520	70
Florida¶	7,050	490	7,060	450	6,930	520	6,740	620	6,260	650	6,530	710
Georgia‡	2,400	370	2,370	370	2,250	420	2,190	500	2,250	620	2,410	640
Hawaii‡	240	70	270	60	230	70	240	70	220	90	200	80
Idaho§	–	30	–	30	–	40	–	60	–	50	–	50
Illinois‡	6,670	970	7,320	1,000	6,630	880	6,590	930	6,690	960	6,840	970
Indiana	720	160	20	160	20	150	10	210	20	200	20	220
Iowa	190	120	270	100	240	90	270	120	190	160	190	170
Kansas‡	1,540	170	1,680	140	1,510	110	1,570	150	1,720	160	1,670	160
Kentucky	–	140	10	120	–	150	–	180	10	180	–	180
Louisiana	–	310	–	380	–	320	–	480	–	470	–	520
Maine†	170	60	150	80	130	100	130	80	140	80	140	80
Maryland§	3,270	510	3,130	530	2,660	530	2,780	540	3,040	550	2,870	540
Massachusetts§	1,480	280	1,660	280	1,450	270	1,510	290	1,540	340	1,790	320
Michigan‡	2,690	300	2,830	320	2,640	330	2,680	320	2,590	360	2,760	300
Minnesota†	970	350	1,070	340	1,010	260	960	290	940	300	840	340
Mississippi	–	200	–	210	–	220	–	280	–	300	–	360
Missouri	–	110	–	120	10	100	–	150	10	140	–	160
Montana*	140	70	180	70	130	80	140	80	140	90	140	80
Nebraska	130	50	230	40	170	40	140	50	150	60	220	70
Nevada§	970	290	1,110	310	900	400	960	400	950	380	1,000	420
New Hampshire‡	180	60	220	60	210	40	190	40	230	50	240	50
New Jersey‖	3,810	510	4,120	510	3,500	440	3,330	550	3,210	520	3,860	560
New Mexico‡	1,600	170	1,690	130	1,660	160	1,510	160	1,540	140	1,630	160
New York‖	8,270	870	9,220	840	8,380	720	8,840	770	8,130	780	8,890	820
North Carolina‡	3,140	250	3,340	230	3,950	240	3,790	340	3,190	350	3,600	360
North Dakota†	–	10	–	10	–	30	–	20	–	20	–	10
Ohio†	1,720	250	1,920	300	1,680	290	1,940	350	1,750	430	1,880	400
Oklahoma	–	120	–	150	–	140	–	190	–	180	–	200
Oregon†	890	130	1,000	130	860	110	880	150	830	140	860	130
Pennsylvania*	2,800	460	3,060	360	2,640	570	2,510	600	2,420	670	2,760	580
Rhode Island†	150	70	180	60	200	50	210	50	240	60	210	60
South Carolina*	870	190	760	200	160	190	200	240	170	270	200	280
South Dakota	–	10	–	10	–	10	–	20	–	20	–	20
Tennessee*	–	230	–	270	–	260	–	310	–	390	–	360
Texas	10	1,770	10	1,680	10	1,770	–	2,260	10	2,400	–	2,540
Utah*	360	50	330	60	350	50	310	70	350	90	300	80
Vermont§	90	30	130	30	100	30	120	20	110	30	120	30
Virginia§	1,900	750	2,190	790	2,110	750	1,940	830	1,850	830	2,060	890
Washington‡	1,520	400	1,660	390	1,520	320	1,650	380	1,580	360	1,610	340
West Virginia	10	30	–	30	–	30	–	40	–	40	–	40
Wisconsin§	–	100	–	110	50	100	250	120	330	130	260	140
Wyoming§	30	30	50	40	40	30	50	30	40	40	50	30

	Jul '23		Aug '23		Sep '23		Oct '23		Nov '23		Dec '23	
	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health
Restrictiveness level												
Banned	20	3,410	40	3,670	40	3,610	10	4,680	50	4,930	20	5,200
6-week ban	2,590	490	2,370	370	2,410	610	2,390	740	2,420	890	2,610	920
Permitted	71,200	10,600	75,830	10,530	69,120	10,020	69,660	11,130	66,890	11,580	71,320	11,640
Abortions provided under shield laws to states with telehealth restrictions	…	1,720	…	1,640	…	1,650	…	2,000	…	2,180	…	2,220
Abortions provided under shield laws to states with total bans and 6-week bans	…	3,900	…	4,040	…	4,220	…	5,420	…	5,820	…	6,120

National and state totals of telehealth abortions include those provided under shield laws.

All numbers have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

Table 2-2024a. Estimated number of in-person and telehealth abortions by state and month, January 2023 to June 2023

	Jan '24		Feb '24		Mar '24		Apr '24		May '24		Jun '24	
	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health
All US state totals	**82,020**	**20,570**	**77,600**	**17,550**	**81,440**	**18,990**	**79,960**	**18,960**	**79,270**	**19,570**	**72,890**	**18,620**
Alabama*	–	390	–	410	–	420	–	420	–	440	–	440
Alaska‡	110	20	120	20	110	30	130	30	130	30	130	40
Arizona*	1,250	320	1,190	290	1,230	350	1,120	360	1,120	310	1,050	260
Arkansas	–	230	–	230	–	260	–	220	–	240	–	260
California‡	15,670	1,840	14,080	1,510	14,650	1,520	14,110	1,510	14,540	1,500	13,160	1,400
Colorado†	1,750	570	1,560	520	1,610	540	1,540	570	1,540	570	1,460	540
Connecticut†	1,150	160	980	120	1,120	160	1,010	150	1,060	160	1,000	120
Delaware‡	230	130	230	100	190	120	200	100	230	110	200	90
District of Columbia‖	610	100	670	70	720	90	670	80	740	80	690	70
Florida¶	7,640	770	7,270	650	7,510	780	9,230	890	4,980	1,190	4,470	1,090
Georgia‡	2,370	690	2,090	610	2,510	710	2,260	730	2,220	790	2,040	740
Hawaii‡	250	90	200	90	250	80	240	90	210	70	200	80
Idaho§	–	70	–	50	–	40	–	60	–	60	–	50
Illinois‡	7,150	970	7,210	890	7,410	940	7,200	890	7,570	960	7,220	890
Indiana	20	270	20	220	20	270	10	230	10	240	10	220
Iowa	160	200	210	140	230	180	240	140	280	140	250	120
Kansas‡	1,930	200	1,900	150	2,090	160	1,750	170	1,970	160	1,550	170
Kentucky	–	230	–	180	–	220	10	210	10	210	–	210
Louisiana	–	560	–	540	–	600	–	610	–	620	–	620
Maine†	210	70	190	50	190	60	180	70	220	50	180	50
Maryland§	3,210	650	2,930	520	3,000	560	2,930	530	3,000	590	2,840	430
Massachusetts§	1,740	360	1,680	320	1,710	340	1,490	340	1,640	370	1,430	300
Michigan‡	3,060	460	2,910	350	3,000	350	2,780	350	2,890	350	2,630	360
Minnesota†	980	360	900	370	960	350	990	360	1,020	340	980	360
Mississippi	–	390	–	380	–	420	–	390	–	400	–	380
Missouri	–	160	–	140	–	160	–	180	–	160	–	160
Montana*	140	90	130	70	130	80	130	70	150	80	120	80
Nebraska	200	70	200	60	190	80	210	70	220	80	240	70
Nevada§	1,170	520	1,080	450	1,170	500	980	440	1,080	430	1,000	470
New Hampshire‡	240	50	220	80	240	70	260	50	240	80	220	50
New Jersey‖	3,850	730	3,400	570	3,830	630	3,750	520	4,180	540	4,080	570
New Mexico‡	1,870	210	1,680	140	1,790	180	1,620	190	1,620	180	1,500	210
New York‖	9,890	890	9,250	680	9,460	740	9,530	780	10,120	880	9,050	770
North Carolina‡	3,800	510	3,830	360	3,980	420	4,300	420	4,110	400	4,220	370
North Dakota†	–	20	–	20	–	10	–	20	–	20	–	20
Ohio†	1,760	580	1,810	490	2,110	500	1,940	530	2,280	520	2,150	510
Oklahoma	–	220	–	190	–	220	–	260	–	240	–	250
Oregon†	880	180	950	150	890	140	890	160	850	160	810	150
Pennsylvania*	2,810	740	3,000	640	3,030	610	2,570	610	2,760	720	2,480	600
Rhode Island†	240	60	200	70	230	60	250	50	220	80	240	70
South Carolina*	300	280	280	240	310	280	250	260	300	270	230	280
South Dakota	–	30	–	20	–	20	–	20	–	30	–	30
Tennessee*	–	420	–	380	–	440	–	460	–	470	–	450
Texas	10	2,910	–	2,650	10	2,840	20	2,860	10	2,720	10	2,820
Utah*	360	90	340	80	350	70	330	110	370	90	320	80
Vermont§	120	30	130	30	120	40	120	40	130	30	120	20
Virginia§	2,580	1,040	2,630	740	2,870	790	2,470	810	2,940	870	2,670	830
Washington‡	1,860	390	1,750	300	1,700	340	1,760	300	1,830	290	1,580	250
West Virginia	–	60	–	50	–	50	–	60	–	50	–	50
Wisconsin§	410	140	350	130	460	130	450	150	450	160	330	130
Wyoming§	40	50	30	40	60	40	40	40	30	40	30	40

	Jan '24		Feb '24		Mar '24		Apr '24		May '24		Jun '24	
	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health	In-person	Tele-health
Restrictiveness level												
Banned	30	5,960	20	5,460	30	5,970	40	6,000	30	5,900	20	5,960
6-week ban	2,670	970	2,370	850	2,820	990	2,510	990	7,500	2,250	6,740	2,110
Permitted	79,320	13,640	75,210	11,240	78,590	12,030	77,410	11,970	71,740	11,420	66,130	10,550
Abortions provided under shield laws to states with telehealth restrictions	…	2,700	…	2,220	…	2,540	…	2,700	…	1,730	…	1,580
Abortions provided under shield laws to states with total bans and 6-week bans	…	6,930	…	6,310	…	6,960	…	6,990	…	8,150	…	8,070

National and state totals of telehealth abortions include those provided under shield laws.

All numbers have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

Table 3-2023 Q3 (July-September 2023). Estimated number of telehealth abortions by state and month

	Jul '23			Aug '23			Sep '23		
	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth
All US state totals	**13,210**	**1,290**	**14,500**	**13,070**	**1,500**	**14,570**	**12,590**	**1,650**	**14,240**
Alabama*	220	0	220	250	0	250	250	0	250
Alaska‡	30	0	30	30	0	30	30	0	30
Arizona*	250	0	250	230	0	230	290	0	290
Arkansas	130	0	130	140	0	140	140	0	140
California‡	1,310	190	1,500	1,300	260	1,560	1,110	210	1,320
Colorado†	530	10	540	530	40	570	520	30	550
Connecticut†	150	0	150	140	0	140	130	0	130
Delaware‡	90	0	90	90	10	100	70	10	80
District of Columbia‖	50	0	50	50	0	50	40	0	40
Florida¶	490	0	490	450	0	450	520	0	520
Georgia‡	370	0	370	370	0	370	420	0	420
Hawaii‡	40	30	70	40	20	60	50	20	70
Idaho§	30	0	30	30	0	30	40	0	40
Illinois‡	540	430	970	530	470	1,000	460	420	880
Indiana	160	0	160	160	0	160	150	0	150
Iowa	120	0	120	100	0	100	90	0	90
Kansas‡	170	0	170	140	0	140	110	0	110
Kentucky	140	0	140	120	0	120	150	0	150
Louisiana	310	0	310	380	0	380	320	0	320
Maine†	50	10	60	50	30	80	70	30	100
Maryland§	180	330	510	190	340	530	200	330	530
Massachusetts§	270	10	280	260	20	280	240	30	270
Michigan‡	300	0	300	320	0	320	330	0	330
Minnesota†	320	30	350	300	40	340	240	20	260
Mississippi	200	0	200	210	0	210	220	0	220
Missouri	110	0	110	120	0	120	100	0	100
Montana*	40	30	70	30	40	70	30	50	80
Nebraska	50	0	50	40	0	40	40	0	40
Nevada§	290	0	290	310	0	310	310	90	400
New Hampshire‡	50	10	60	50	10	60	30	10	40
New Jersey‖	510	0	510	510	0	510	440	0	440
New Mexico‡	140	30	170	110	20	130	140	20	160
New York‖	870	0	870	840	0	840	720	0	720
North Carolina‡	250	0	250	230	0	230	240	0	240
North Dakota†	10	0	10	10	0	10	30	0	30
Ohio†	250	0	250	300	0	300	290	0	290
Oklahoma	120	0	120	150	0	150	140	0	140
Oregon†	130	0	130	100	30	130	90	20	110
Pennsylvania*	370	90	460	340	20	360	360	210	570
Rhode Island†	70	0	70	60	0	60	50	0	50
South Carolina*	190	0	190	200	0	200	190	0	190
South Dakota	10	0	10	10	0	10	10	0	10
Tennessee*	230	0	230	270	0	270	260	0	260
Texas	1,770	0	1,770	1,680	0	1,680	1,770	0	1,770
Utah*	50	0	50	60	0	60	50	0	50
Vermont§	20	10	30	20	10	30	20	10	30
Virginia§	670	80	750	670	120	790	620	130	750
Washington‡	400	0	400	370	20	390	310	10	320
West Virginia	30	0	30	30	0	30	30	0	30
Wisconsin§	100	0	100	110	0	110	100	0	100
Wyoming§	30	0	30	40	0	40	30	0	30

	Jul '23			Aug '23			Sep '23		
	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth
Restrictiveness level									
Banned	3,410	0	3,410	3,670	0	3,670	3,610	0	3,610
6-week ban	490	0	490	370	0	370	610	0	610
Permitted	9,310	1,290	10,600	9,030	1,500	10,530	8,370	1,650	10,020
Abortions provided under shield laws to states with telehealth restrictions	1,720	…	1,720	1,640	…	1,640	1,650	…	1,650
Abortions provided under shield laws to states with total bans and 6-week bans	3,900	…	3,900	4,040	…	4,040	4,220	…	4,220

National and state totals of telehealth abortions include those provided under shield laws.

All numbers have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

Table 3-2023 Q4 (October-December 2023). Estimated number of telehealth abortions by state and month

	Oct '23			Nov '23			Dec '23		
	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth
All US state totals	**14,820**	**1,730**	**16,550**	**15,580**	**1,820**	**17,400**	**16,010**	**1,750**	**17,760**
Alabama*	300	0	300	340	0	340	360	0	360
Alaska‡	40	0	40	30	0	30	40	0	40
Arizona*	290	0	290	280	0	280	250	0	250
Arkansas	180	0	180	200	0	200	180	0	180
California‡	1,240	330	1,570	1,200	360	1,560	1,260	320	1,580
Colorado†	480	40	520	510	50	560	510	40	550
Connecticut†	140	0	140	170	0	170	170	0	170
Delaware‡	90	10	100	90	10	100	100	10	110
District of Columbia‖	70	0	70	80	0	80	70	0	70
Florida¶	620	0	620	650	0	650	710	0	710
Georgia‡	500	0	500	620	0	620	640	0	640
Hawaii‡	50	20	70	70	20	90	60	20	80
Idaho§	60	0	60	50	0	50	50	0	50
Illinois‡	560	370	930	520	440	960	490	480	970
Indiana	210	0	210	200	0	200	220	0	220
Iowa	120	0	120	160	0	160	170	0	170
Kansas‡	150	0	150	160	0	160	160	0	160
Kentucky	180	0	180	180	0	180	180	0	180
Louisiana	480	0	480	470	0	470	520	0	520
Maine†	60	20	80	50	30	80	60	20	80
Maryland§	200	340	540	200	350	550	170	370	540
Massachusetts§	250	40	290	290	50	340	280	40	320
Michigan‡	320	0	320	360	0	360	300	0	300
Minnesota†	260	30	290	270	30	300	320	20	340
Mississippi	280	0	280	300	0	300	360	0	360
Missouri	150	0	150	140	0	140	160	0	160
Montana*	40	40	80	50	40	90	30	50	80
Nebraska	50	0	50	60	0	60	70	0	70
Nevada§	340	60	400	360	20	380	390	30	420
New Hampshire‡	30	10	40	50	0	50	40	10	50
New Jersey‖	550	0	550	520	0	520	560	0	560
New Mexico‡	140	20	160	120	20	140	140	20	160
New York‖	770	0	770	780	0	780	820	0	820
North Carolina‡	340	0	340	350	0	350	360	0	360
North Dakota†	20	0	20	20	0	20	10	0	10
Ohio†	350	0	350	430	0	430	400	0	400
Oklahoma	190	0	190	180	0	180	200	0	200
Oregon†	120	30	150	120	20	140	120	10	130
Pennsylvania*	400	200	600	440	230	670	450	130	580
Rhode Island†	50	0	50	60	0	60	60	0	60
South Carolina*	240	0	240	270	0	270	280	0	280
South Dakota	20	0	20	20	0	20	20	0	20
Tennessee*	310	0	310	390	0	390	360	0	360
Texas	2,260	0	2,260	2,400	0	2,400	2,540	0	2,540
Utah*	70	0	70	90	0	90	80	0	80
Vermont§	10	10	20	20	10	30	20	10	30
Virginia§	700	130	830	710	120	830	740	150	890
Washington‡	350	30	380	340	20	360	320	20	340
West Virginia	40	0	40	40	0	40	40	0	40
Wisconsin§	120	0	120	130	0	130	140	0	140
Wyoming§	30	0	30	40	0	40	30	0	30

	Oct '23			Nov '23			Dec '23		
	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth
Restrictiveness level									
Banned	4,680	0	4,680	4,930	0	4,930	5,200	0	5,200
6-week ban	740	0	740	890	0	890	920	0	920
Permitted	9,400	1,730	11,130	9,760	1,820	11,580	9,890	1,750	11,640
Abortions provided under shield laws to states with telehealth restrictions	2,000	…	2,000	2,180	…	2,180	2,220	…	2,220
Abortions provided under shield laws to states with total bans and 6-week bans	5,420	…	5,420	5,820	…	5,820	6,120	…	6,120

National and state totals of telehealth abortions include those provided under shield laws.

All numbers have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

Table 3-2024 Q1 (January-March 2024). Estimated number of telehealth abortions by state and month

	Jan '24			Feb '24			Mar '24		
	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth
All US state totals	**18,680**	**1,890**	**20,570**	**15,850**	**1,700**	**17,550**	**17,290**	**1,700**	**18,990**
Alabama*	390	0	390	410	0	410	420	0	420
Alaska‡	20	0	20	20	0	20	30	0	30
Arizona*	320	0	320	290	0	290	350	0	350
Arkansas	230	0	230	230	0	230	260	0	260
California‡	1,500	340	1,840	1,120	390	1,510	1,180	340	1,520
Colorado†	530	40	570	500	20	520	510	30	540
Connecticut†	160	0	160	120	0	120	150	10	160
Delaware‡	110	20	130	100	0	100	110	10	120
District of Columbia‖	100	0	100	70	0	70	90	0	90
Florida¶	770	0	770	650	0	650	780	0	780
Georgia‡	690	0	690	610	0	610	710	0	710
Hawaii‡	70	20	90	60	30	90	50	30	80
Idaho§	70	0	70	50	0	50	40	0	40
Illinois‡	490	480	970	430	460	890	470	470	940
Indiana	270	0	270	220	0	220	270	0	270
Iowa	200	0	200	140	0	140	180	0	180
Kansas‡	200	0	200	150	0	150	160	0	160
Kentucky	230	0	230	180	0	180	220	0	220
Louisiana	560	0	560	540	0	540	600	0	600
Maine†	50	20	70	40	10	50	50	10	60
Maryland§	230	420	650	160	360	520	200	360	560
Massachusetts§	310	50	360	270	50	320	280	60	340
Michigan‡	460	0	460	350	0	350	350	0	350
Minnesota†	330	30	360	350	20	370	320	30	350
Mississippi	390	0	390	380	0	380	420	0	420
Missouri	160	0	160	140	0	140	160	0	160
Montana*	40	50	90	30	40	70	30	50	80
Nebraska	70	0	70	60	0	60	80	0	80
Nevada§	500	20	520	440	10	450	490	10	500
New Hampshire‡	40	10	50	70	10	80	60	10	70
New Jersey‖	730	0	730	570	0	570	630	0	630
New Mexico‡	190	20	210	120	20	140	150	30	180
New York‖	890	0	890	680	0	680	740	0	740
North Carolina‡	510	0	510	360	0	360	420	0	420
North Dakota†	20	0	20	20	0	20	10	0	10
Ohio†	580	0	580	490	0	490	500	0	500
Oklahoma	220	0	220	190	0	190	220	0	220
Oregon†	160	20	180	130	20	150	120	20	140
Pennsylvania*	570	170	740	460	180	640	480	130	610
Rhode Island†	60	0	60	70	0	70	50	10	60
South Carolina*	280	0	280	240	0	240	280	0	280
South Dakota	30	0	30	20	0	20	20	0	20
Tennessee*	420	0	420	380	0	380	440	0	440
Texas	2,910	0	2,910	2,650	0	2,650	2,840	0	2,840
Utah*	90	0	90	80	0	80	70	0	70
Vermont§	20	10	30	20	10	30	30	10	40
Virginia§	890	150	1,040	680	60	740	710	80	790
Washington‡	370	20	390	300	0	300	340	0	340
West Virginia	60	0	60	50	0	50	50	0	50
Wisconsin§	140	0	140	130	0	130	130	0	130
Wyoming§	50	0	50	30	10	40	40	0	40

	Jan '24			Feb '24			Mar '24		
	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth
Restrictiveness level									
Banned	5,960	0	5,960	5,460	0	5,460	5,970	0	5,970
6-week ban	970	0	970	850	0	850	990	0	990
Permitted	11,750	1,890	13,640	9,540	1,700	11,240	10,330	1,700	12,030
Abortions provided under shield laws to states with telehealth restrictions	2,700	…	2,700	2,220	…	2,220	2,540	…	2,540
Abortions provided under shield laws to states with total bans and 6-week bans	6,930	…	6,930	6,310	…	6,310	6,960	…	6,960

National and state totals of telehealth abortions include those provided under shield laws.

All numbers have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

Table 3-2024 Q2 (April-June 2024). Estimated number of telehealth abortions by state and month

	Apr '24			May '24			Jun '24		
	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth
All US state totals	**17,380**	**1,580**	**18,960**	**17,690**	**1,880**	**19,570**	**17,080**	**1,540**	**18,620**
Alabama*	420	0	420	440	0	440	440	0	440
Alaska‡	30	0	30	30	0	30	40	0	40
Arizona*	360	0	360	310	0	310	260	0	260
Arkansas	220	0	220	240	0	240	260	0	260
California‡	1,250	260	1,510	1,230	270	1,500	1,170	230	1,400
Colorado†	540	30	570	540	30	570	520	20	540
Connecticut†	140	10	150	150	10	160	110	10	120
Delaware‡	90	10	100	100	10	110	80	10	90
District of Columbia‖	80	0	80	80	0	80	70	0	70
Florida¶	890	0	890	1,190	0	1,190	1,090	0	1,090
Georgia‡	730	0	730	790	0	790	740	0	740
Hawaii‡	60	30	90	50	20	70	60	20	80
Idaho§	60	0	60	60	0	60	50	0	50
Illinois‡	460	430	890	480	480	960	420	470	890
Indiana	230	0	230	240	0	240	220	0	220
Iowa	140	0	140	140	0	140	120	0	120
Kansas‡	170	0	170	160	0	160	170	0	170
Kentucky	210	0	210	210	0	210	210	0	210
Louisiana	610	0	610	620	0	620	620	0	620
Maine†	60	10	70	40	10	50	40	10	50
Maryland§	180	350	530	190	400	590	170	260	430
Massachusetts§	290	50	340	310	60	370	290	10	300
Michigan‡	350	0	350	350	0	350	360	0	360
Minnesota†	330	30	360	310	30	340	330	30	360
Mississippi	390	0	390	400	0	400	380	0	380
Missouri	180	0	180	160	0	160	160	0	160
Montana*	30	40	70	20	60	80	30	50	80
Nebraska	70	0	70	80	0	80	70	0	70
Nevada§	430	10	440	410	20	430	440	30	470
New Hampshire‡	40	10	50	60	20	80	50	0	50
New Jersey‖	520	0	520	540	0	540	570	0	570
New Mexico‡	150	40	190	140	40	180	130	80	210
New York‖	780	0	780	880	0	880	770	0	770
North Carolina‡	420	0	420	400	0	400	370	0	370
North Dakota†	20	0	20	20	0	20	20	0	20
Ohio†	530	0	530	520	0	520	510	0	510
Oklahoma	260	0	260	240	0	240	250	0	250
Oregon†	140	20	160	140	20	160	150	0	150
Pennsylvania*	460	150	610	500	220	720	440	160	600
Rhode Island†	50	0	50	70	10	80	60	10	70
South Carolina*	260	0	260	270	0	270	280	0	280
South Dakota	20	0	20	30	0	30	30	0	30
Tennessee*	460	0	460	470	0	470	450	0	450
Texas	2,860	0	2,860	2,720	0	2,720	2,820	0	2,820
Utah*	110	0	110	90	0	90	80	0	80
Vermont§	30	10	40	20	10	30	20	0	20
Virginia§	730	80	810	720	150	870	700	130	830
Washington‡	290	10	300	290	0	290	250	0	250
West Virginia	60	0	60	50	0	50	50	0	50
Wisconsin§	150	0	150	160	0	160	130	0	130
Wyoming§	40	0	40	30	10	40	30	10	40

	Apr '24			May '24			Jun '24		
	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth	Virtual-only	Brick and mortar	Total telehealth
Restrictiveness level									
Banned	6,000	0	6,000	5,900	0	5,900	5,960	0	5,960
6-week ban	990	0	990	2,250	0	2,250	2,110	0	2,110
Permitted	10,390	1,580	11,970	9,540	1,880	11,420	9,010	1,540	10,550
Abortions provided under shield laws to states with telehealth restrictions	2,700	…	2,700	1,730	…	1,730	1,580	…	1,580
Abortions provided under shield laws to states with total bans and 6-week bans	6,990	…	6,990	8,150	…	8,150	8,070	…	8,070

National and state totals of telehealth abortions include those provided under shield laws.

All numbers have been rounded to the nearest 10. Data that are suppressed are represented by '–". Numbers 0-9 have been rounded up to 10 or are represented by "–". Data that were not collected are represented by "...". Numbers have been corrected as needed for missingness with imputation.

Contributors

This report was prepared by #WeCount Co-Chairs and Society of Family Planning staff, with guidance from the Research Steering Committee, as well as the support of many members of the Society of Family Planning community.

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EXHIBIT 2

Society of Family Planning, #WeCount
Report April 2022 to December 2024
(Jun. 23, 2025)

National findings

Summary of findings

- Abortion volume is **higher in 2024** than it was in 2023 or 2022.
- The majority of abortions occur **in-person**.
- The number of abortions delivered via **telehealth continued to increase**.
  - By the end of 2024, 1 in 4 abortions was delivered via telehealth.
- **Shield laws** continue to facilitate abortion access, with an average of 12,330 abortions per month in the final quarter of 2024.
- Implications of these trends are unclear in the context of multiple changes in the service delivery environment:
  - Shifting price of abortion
  - Decreases in abortion funds to cover patient costs
  - Election-related spikes in demand
  - Ongoing financial pressure on brick-and-mortar clinics

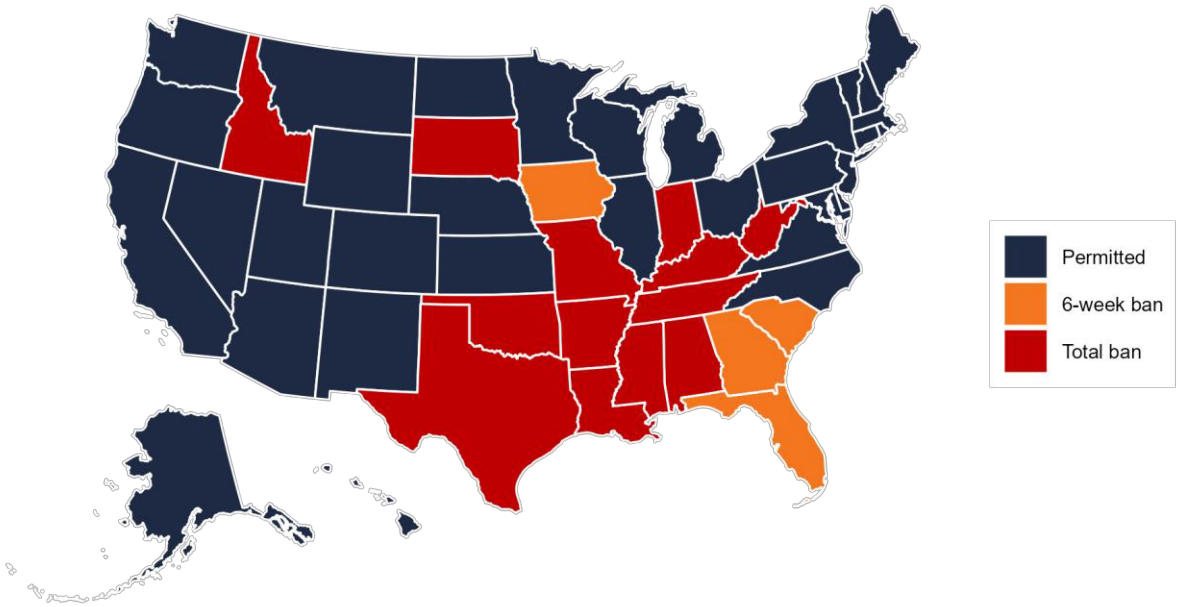
Changes in legal status since January 2024

- In **Florida**, a 6-week ban went into effect in May 2024
- In **Iowa**, a 6-week ban went into effect in August 2024
- In **North Dakota**, a total ban was ruled unconstitutional in October 2024

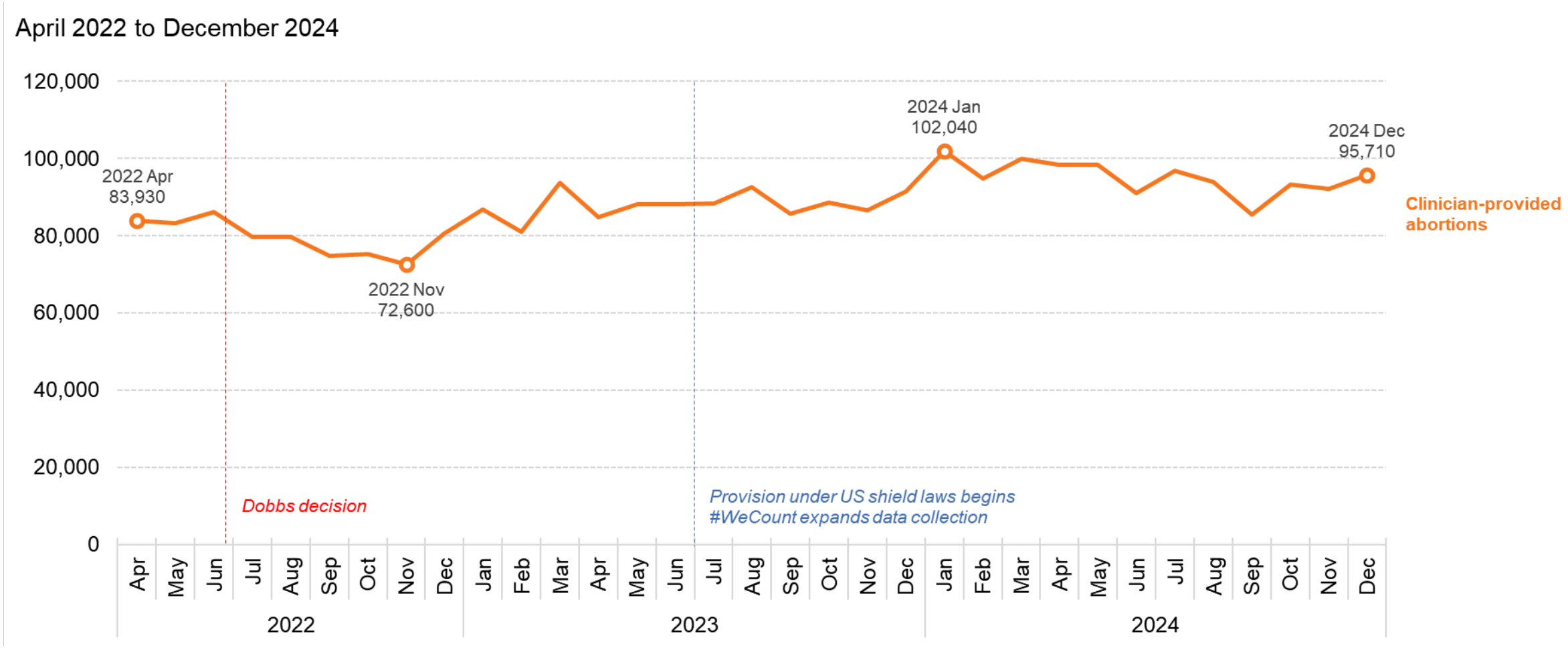
  No brick-and-mortar facilities providing
- States with total bans as of December 2024:

  Alabama, Arkansas, Idaho, Indiana, Kentucky, Louisiana, Mississippi, Missouri, Oklahoma, South Dakota, Tennessee, Texas, West Virginia
- States with 6-week bans as of December 2024:

  Florida, Georgia, Iowa, South Carolina

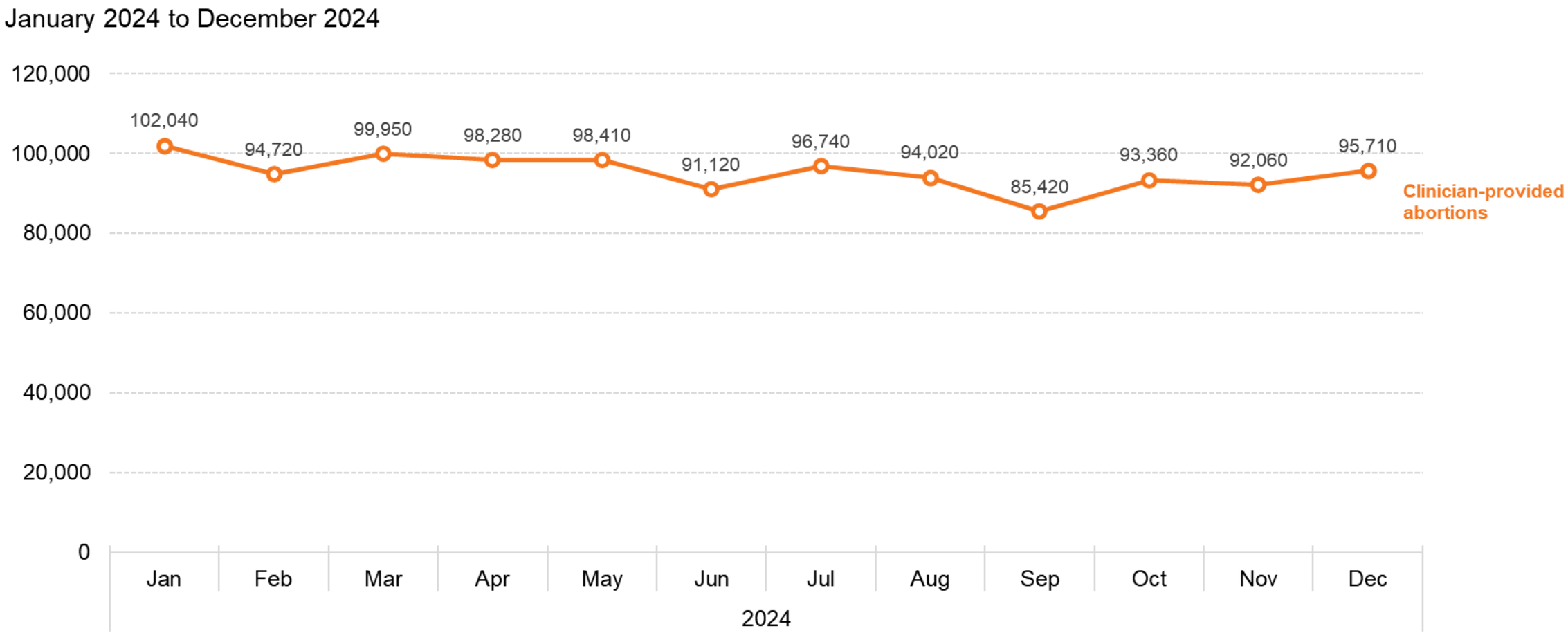


Total abortions in the US have increased since *Dobbs*



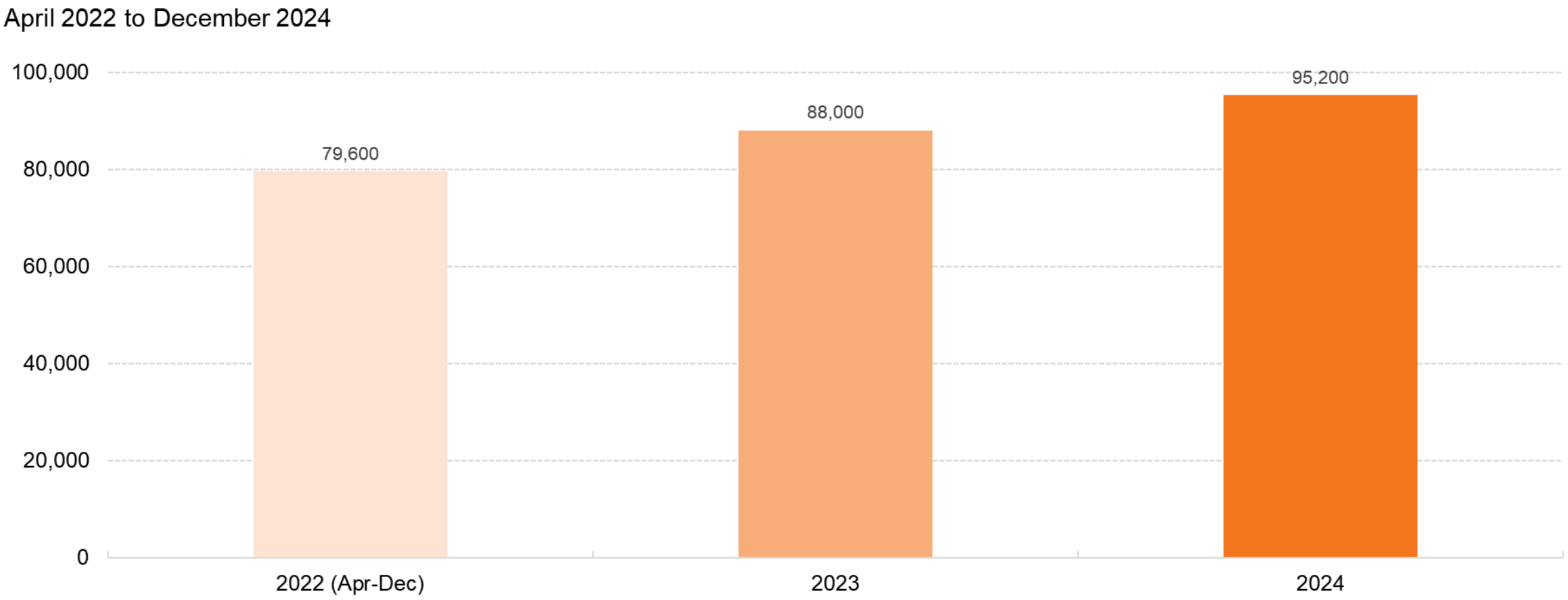
Source: Society of Family Planning, June 2025

US abortions totaled 1.14 million in 2024



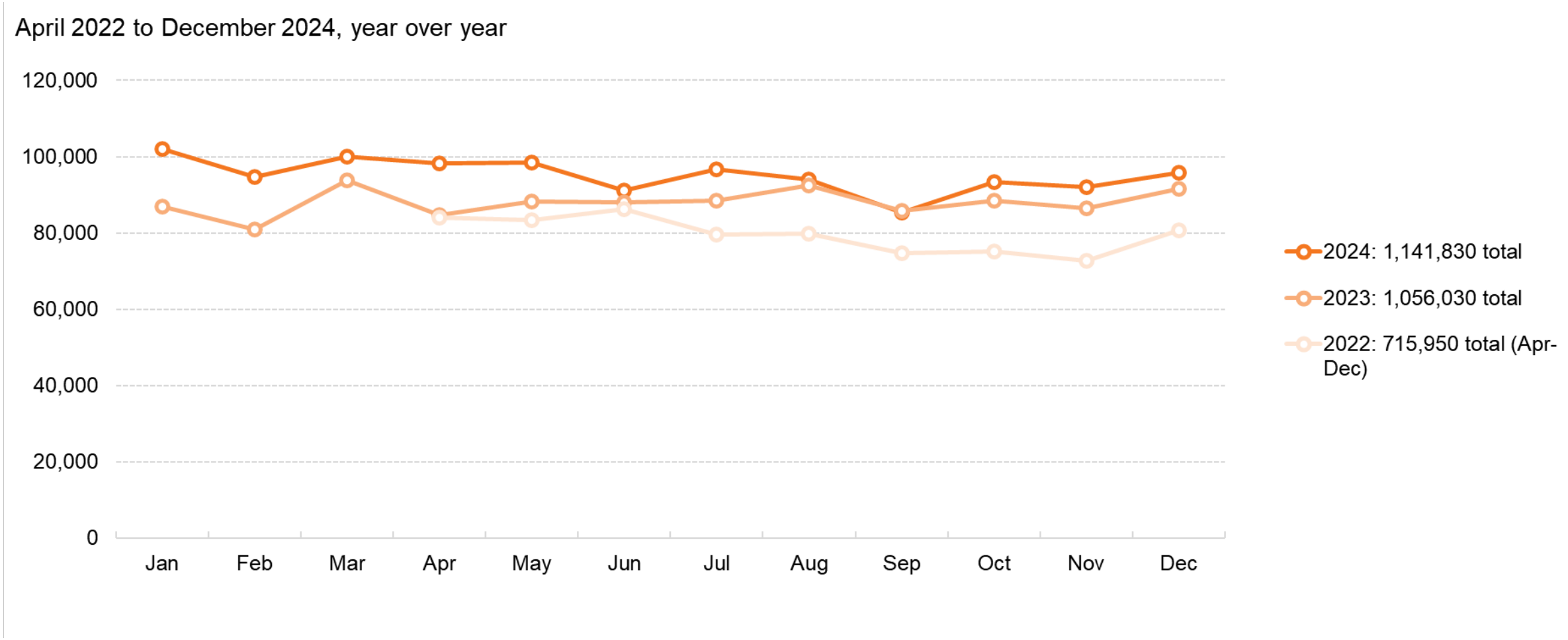
Source: Society of Family Planning, June 2025

Monthly average number of abortions increased each year



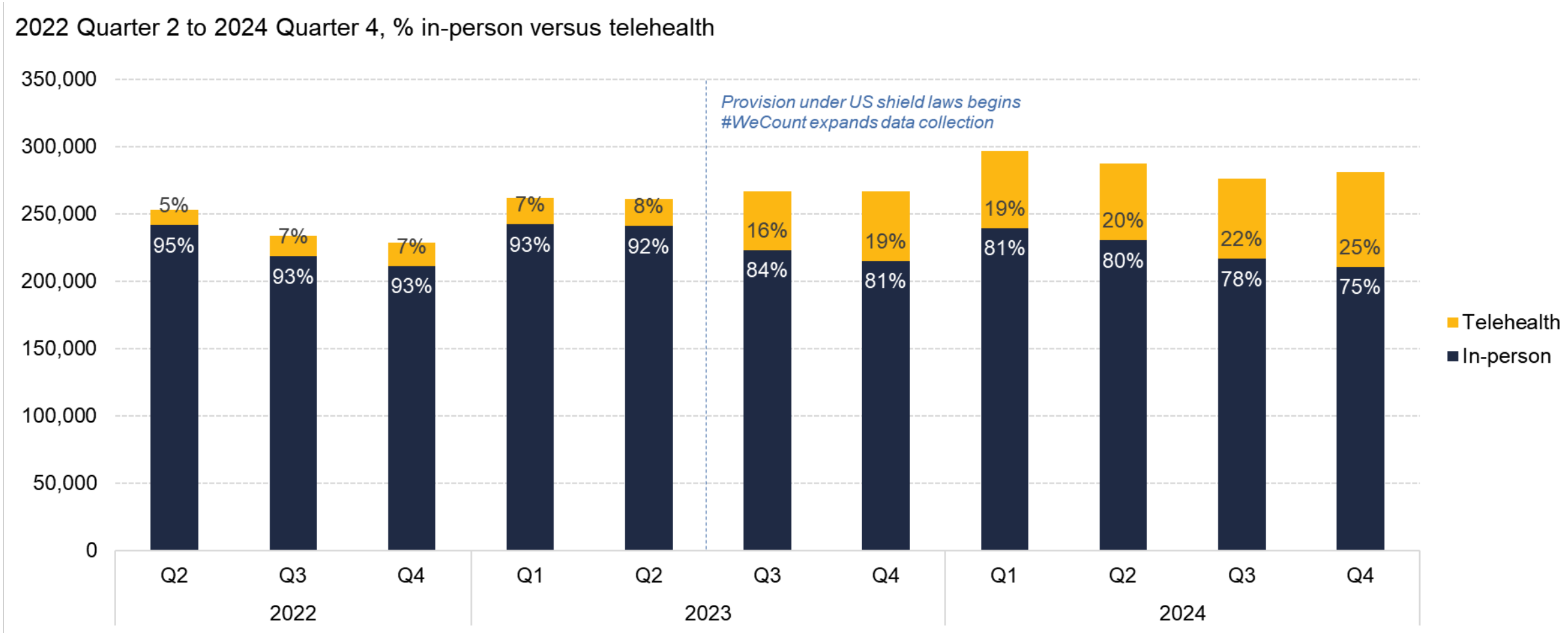
Source: Society of Family Planning, June 2025

The monthly number of abortions increased each year



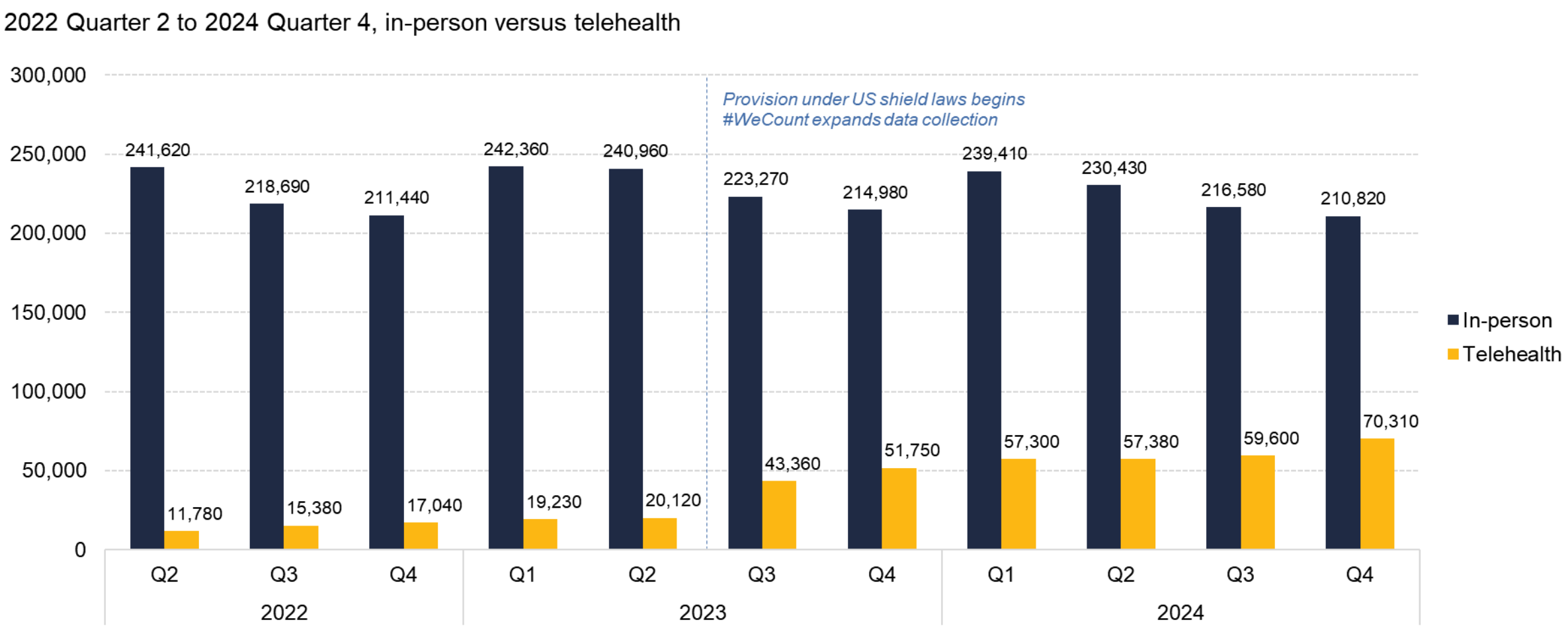
Source: Society of Family Planning, June 2025

By Q4 of 2024, 1 in 4 abortions were provided via telehealth



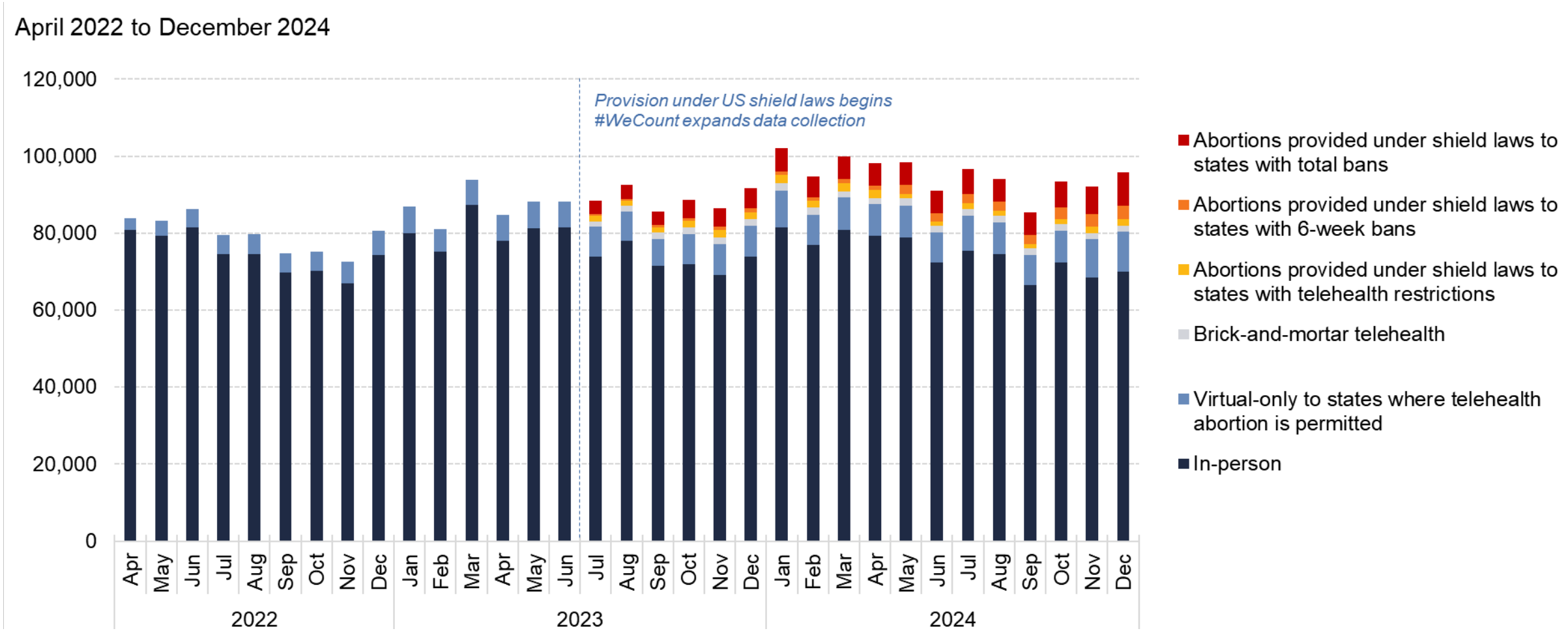
Source: Society of Family Planning, June 2025

In-person abortion care declined slightly, while telehealth grew



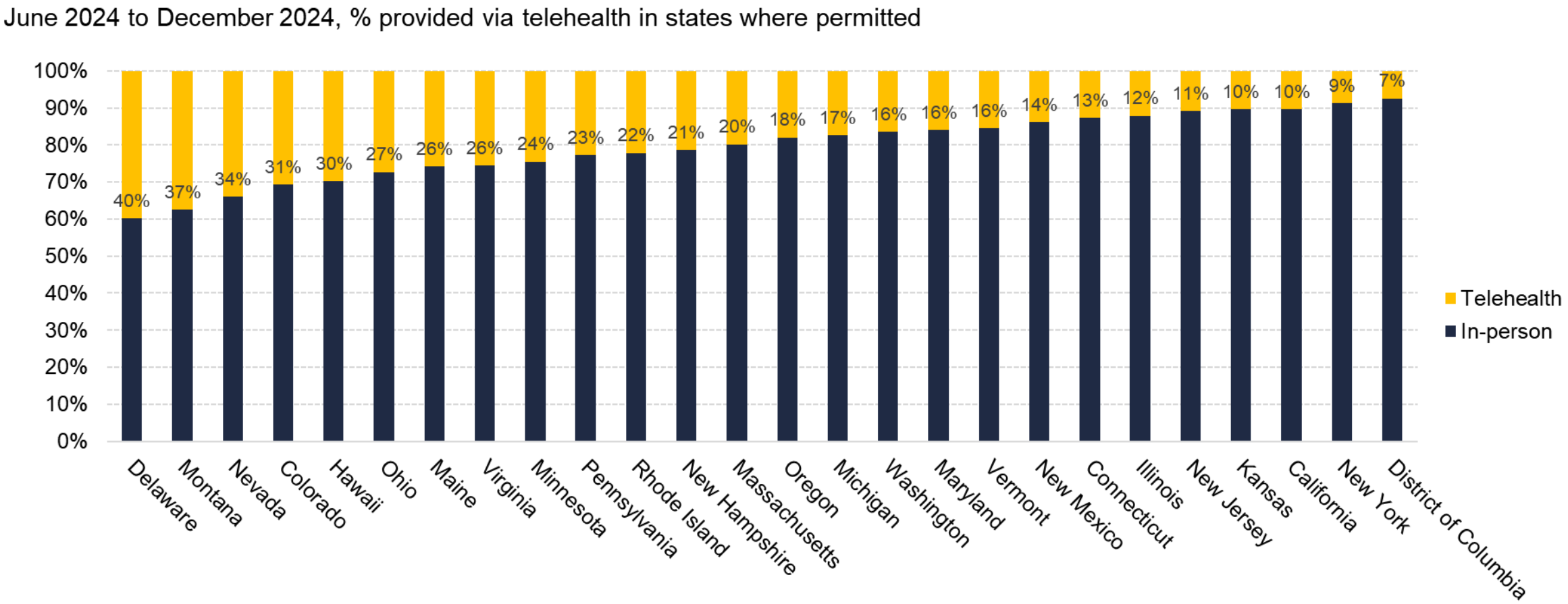
Source: Society of Family Planning, June 2025

The majority of abortions still take place in-person



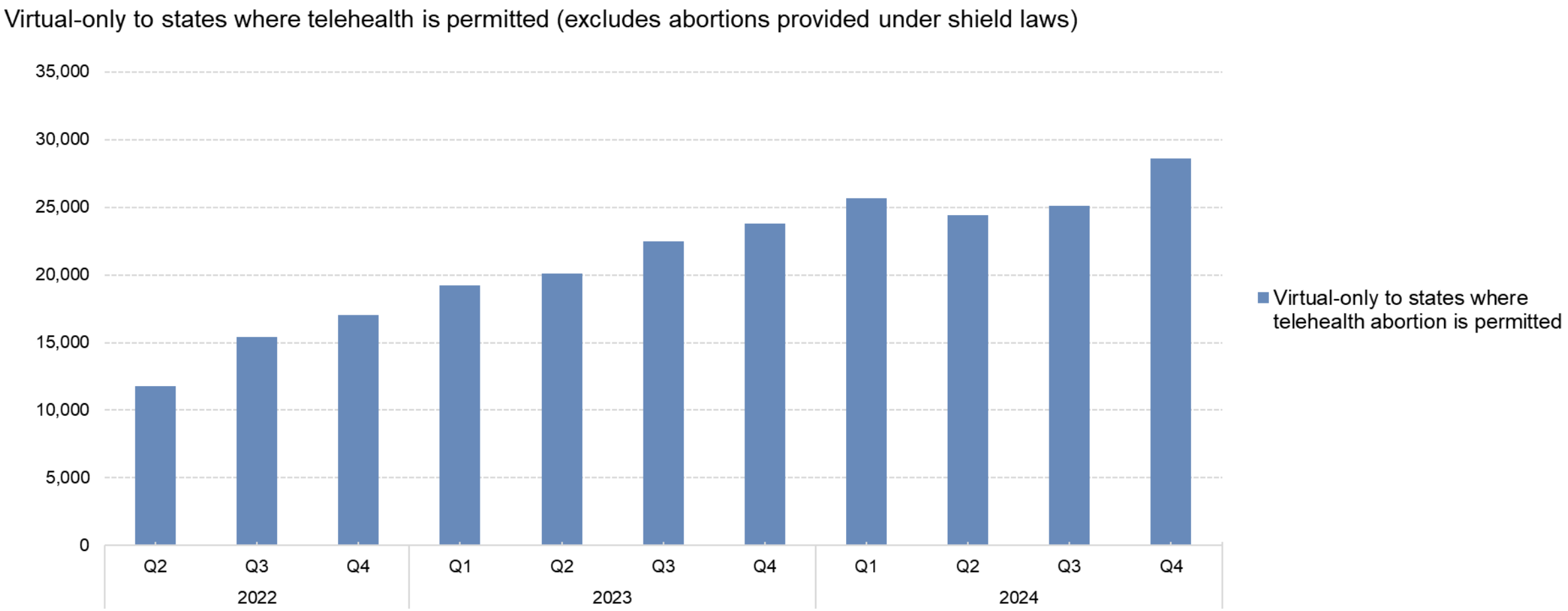
Source: Society of Family Planning, June 2025

The proportion of abortions provided via telehealth varied by state, 2024



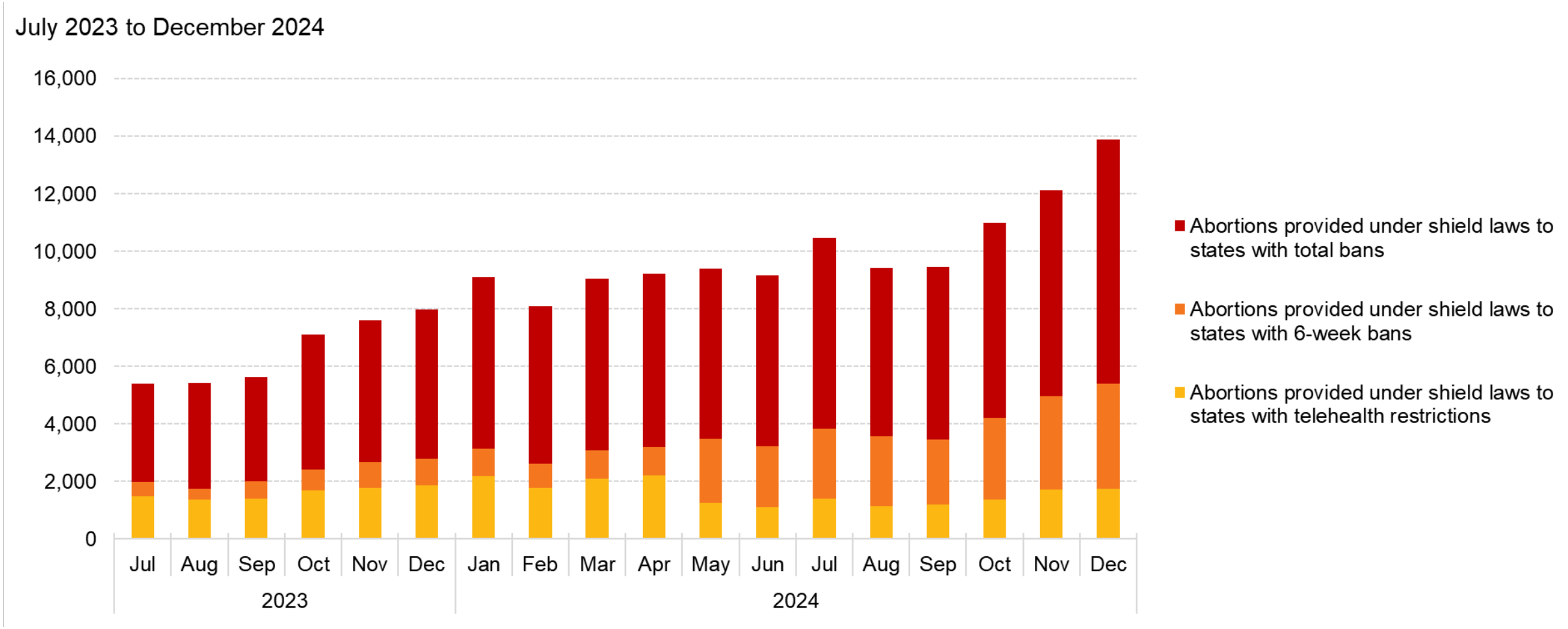
Source: Society of Family Planning, June 2025

Abortions provided by virtual-only clinics have increased since *Dobbs*



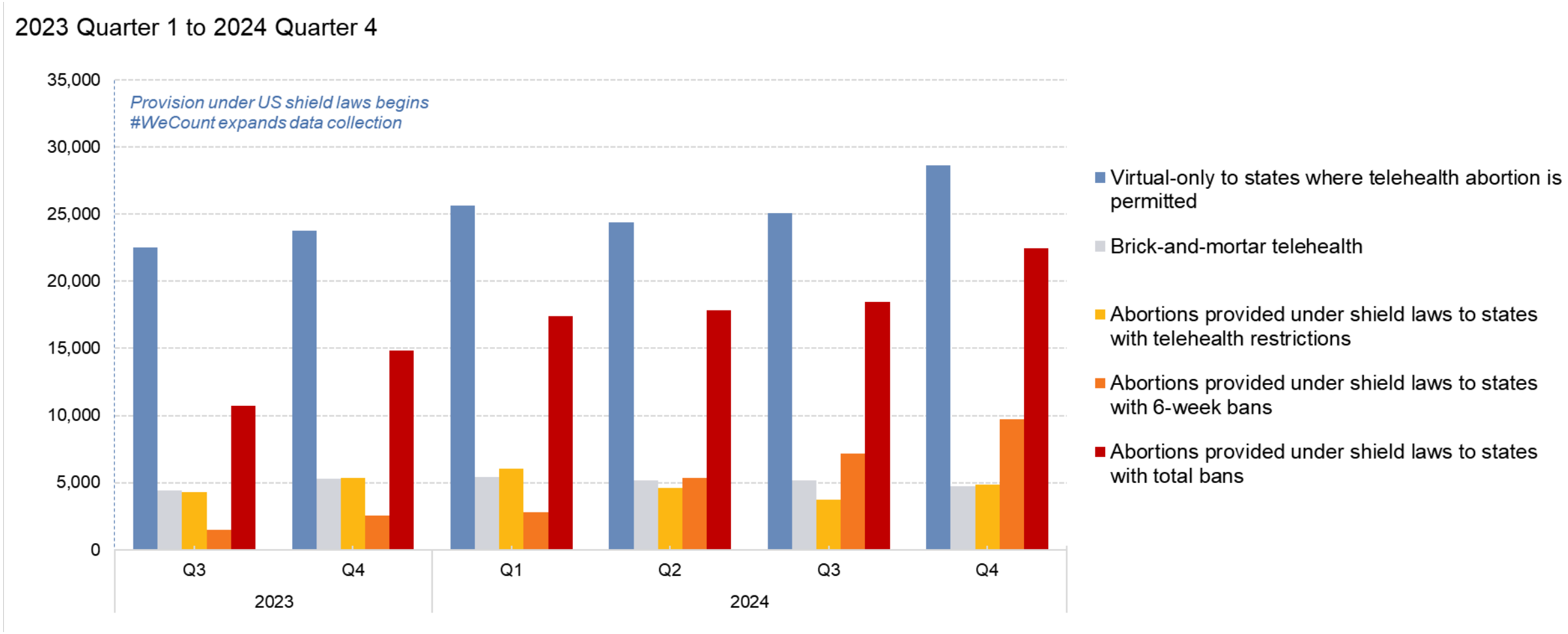
Source: Society of Family Planning, June 2025

Abortions provided under shield laws have increased since this route to care became available



Source: Society of Family Planning, June 2025

Legal climates appear to play an important role in telehealth use



Source: Society of Family Planning, June 2025

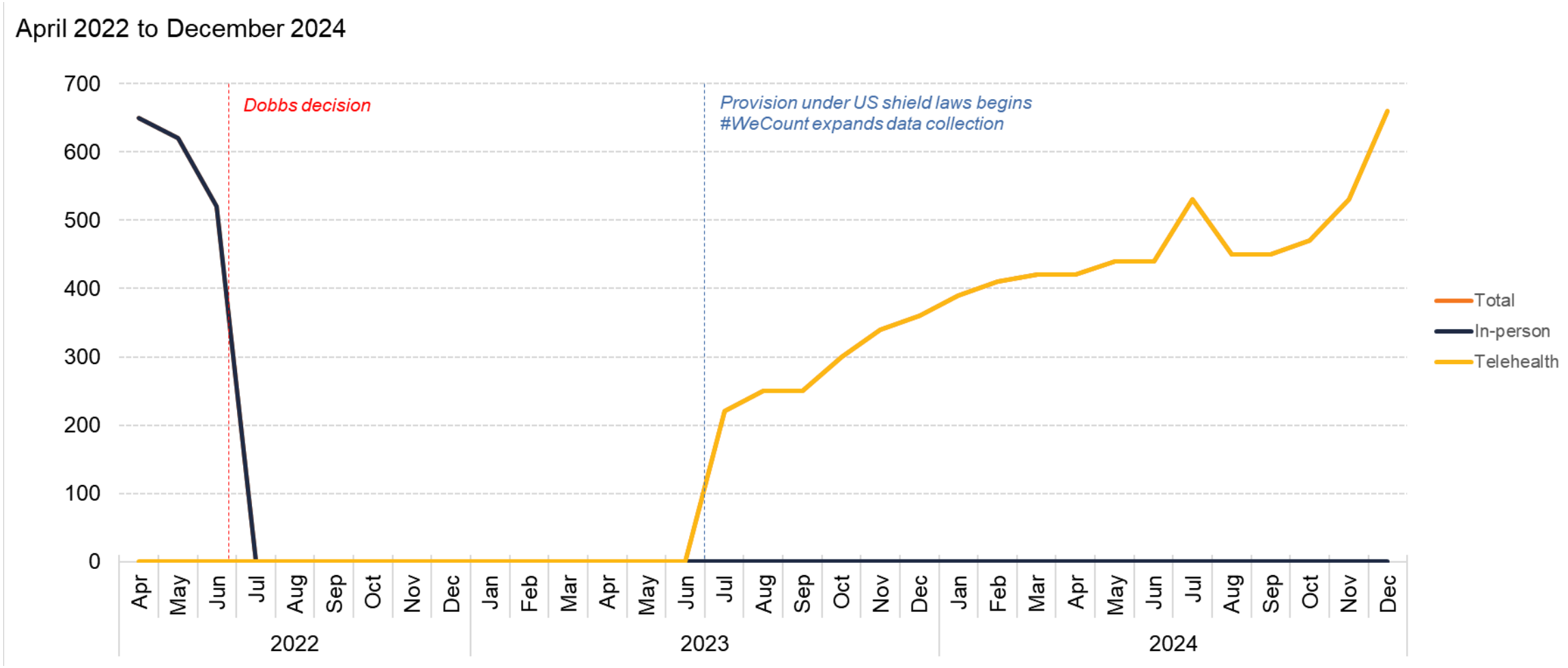
Half of abortions provided via telehealth in 2024 were facilitated by shield laws

2024 monthly average number of abortions		
	In-person	Telehealth
Abortion and telehealth permitted	60,780	10,360
Abortion permitted, telehealth restricted	8,610	1,610
6-week abortion ban, telehealth restricted	5,350	2,080
Abortion is totally banned	30	6,350

Source: Society of Family Planning, June 2025

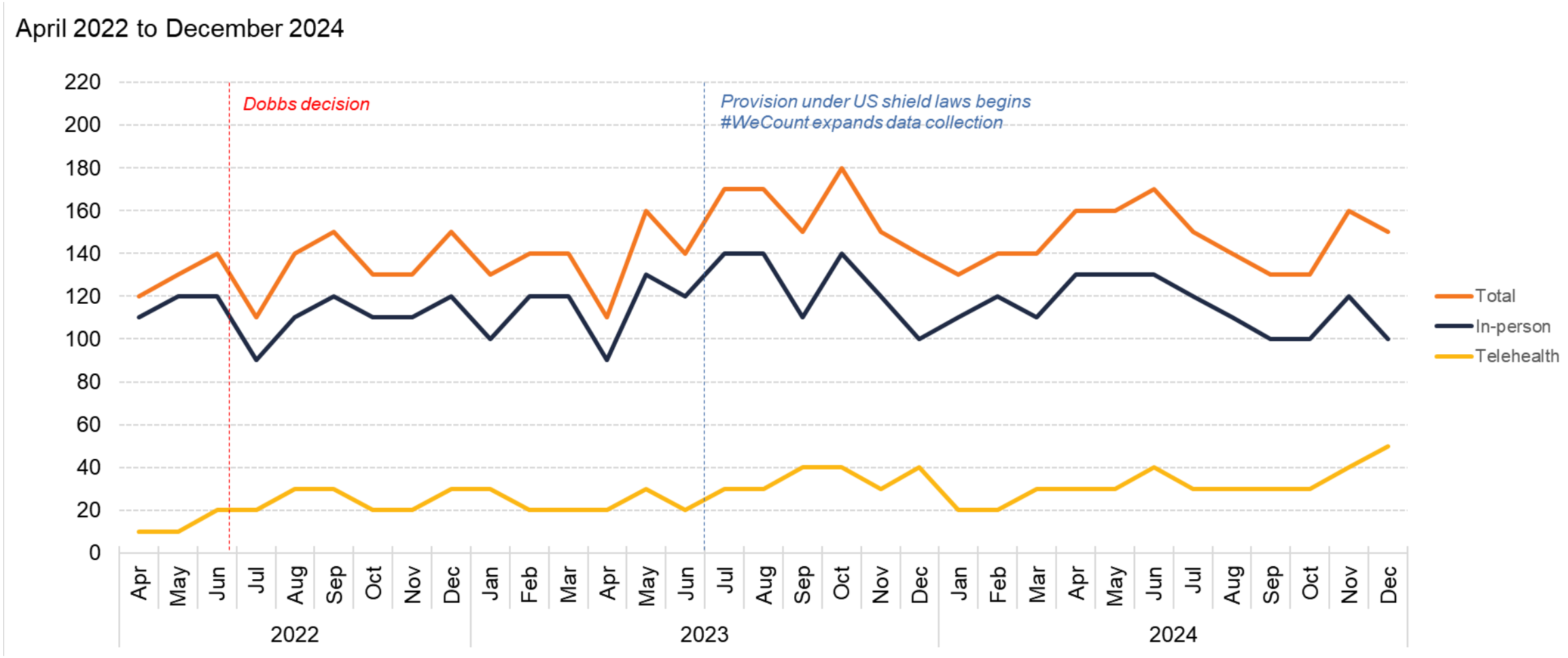
State-level findings

Alabama



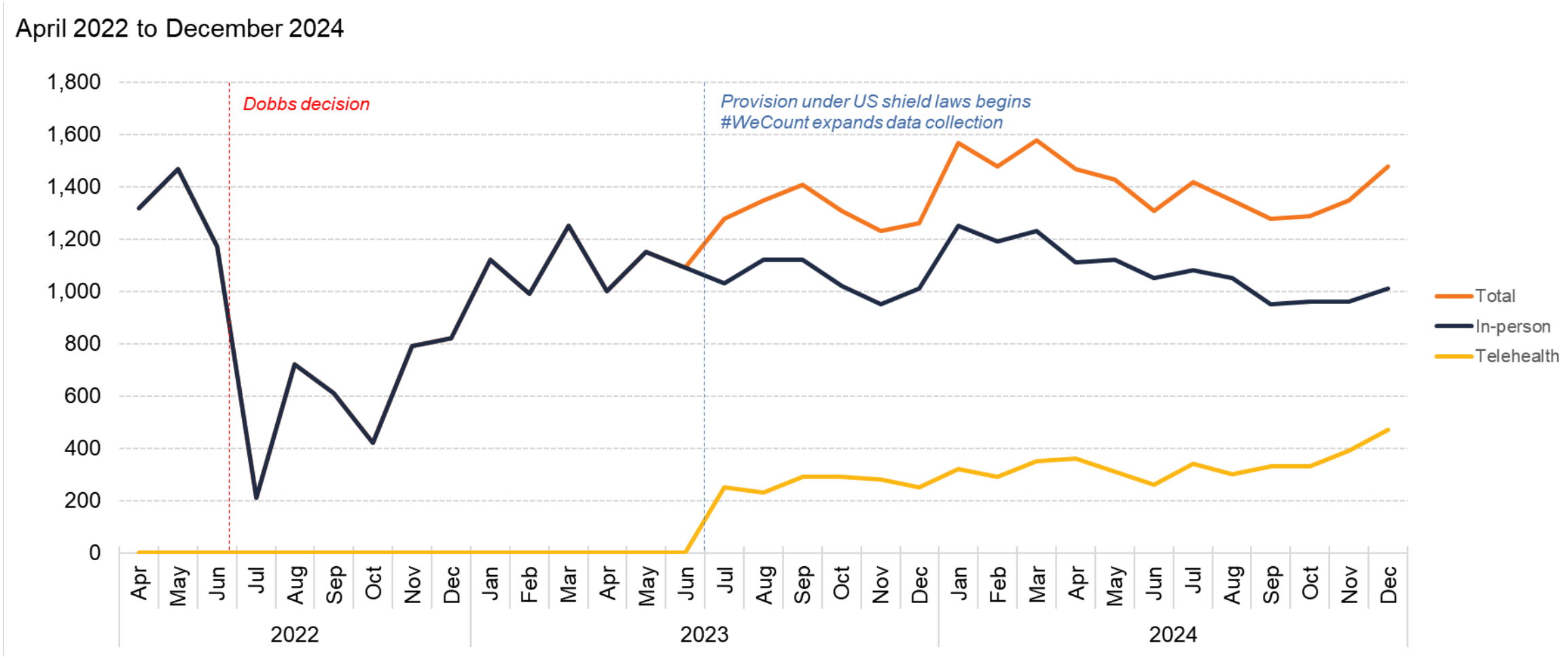
Source: Society of Family Planning, June 2025

Alaska



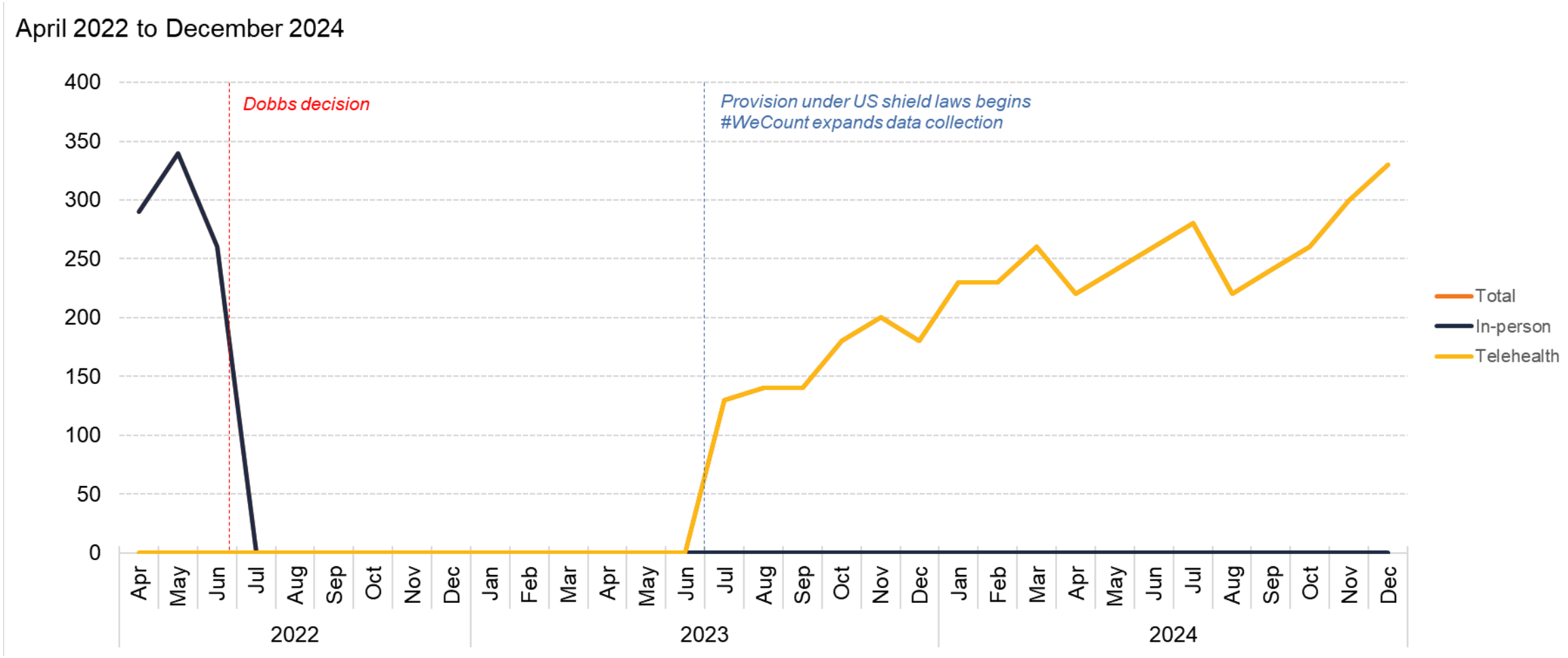
Source: Society of Family Planning, June 2025

Arizona



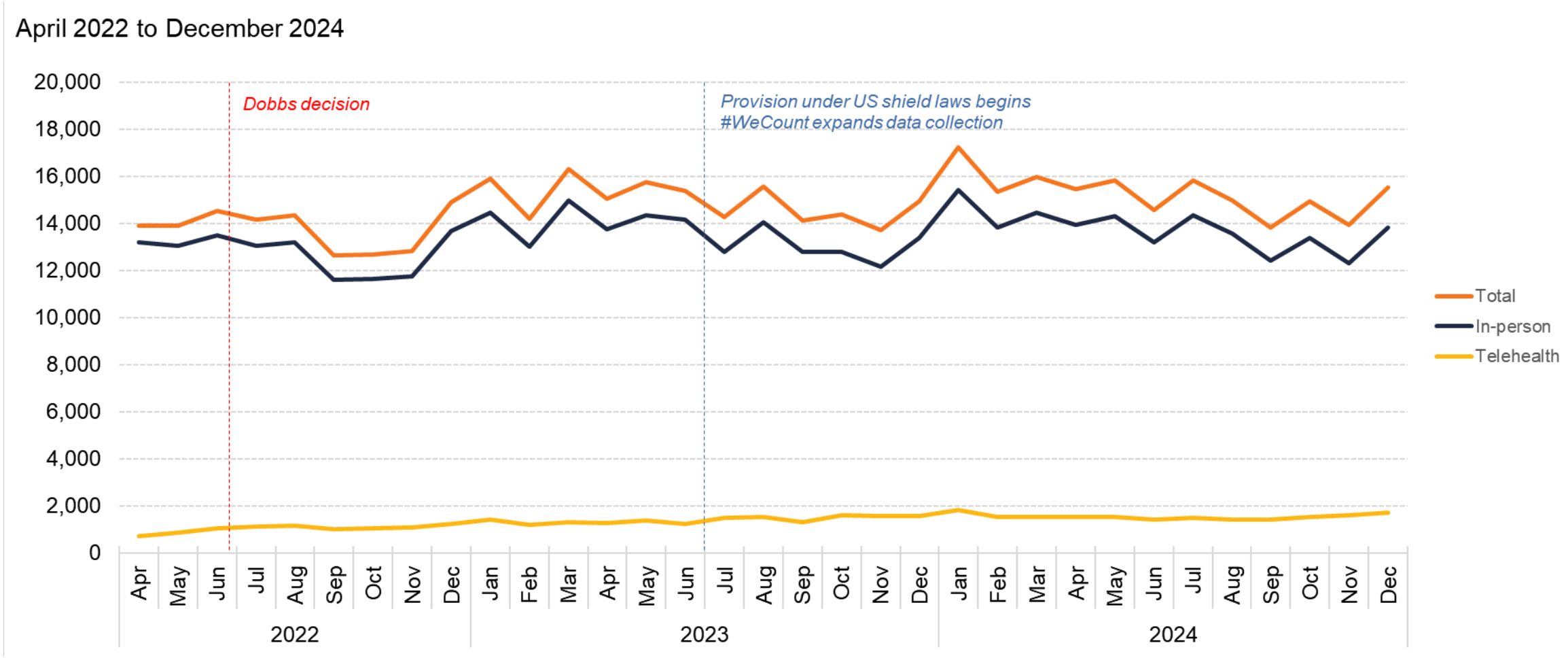
Source: Society of Family Planning, June 2025

Arkansas



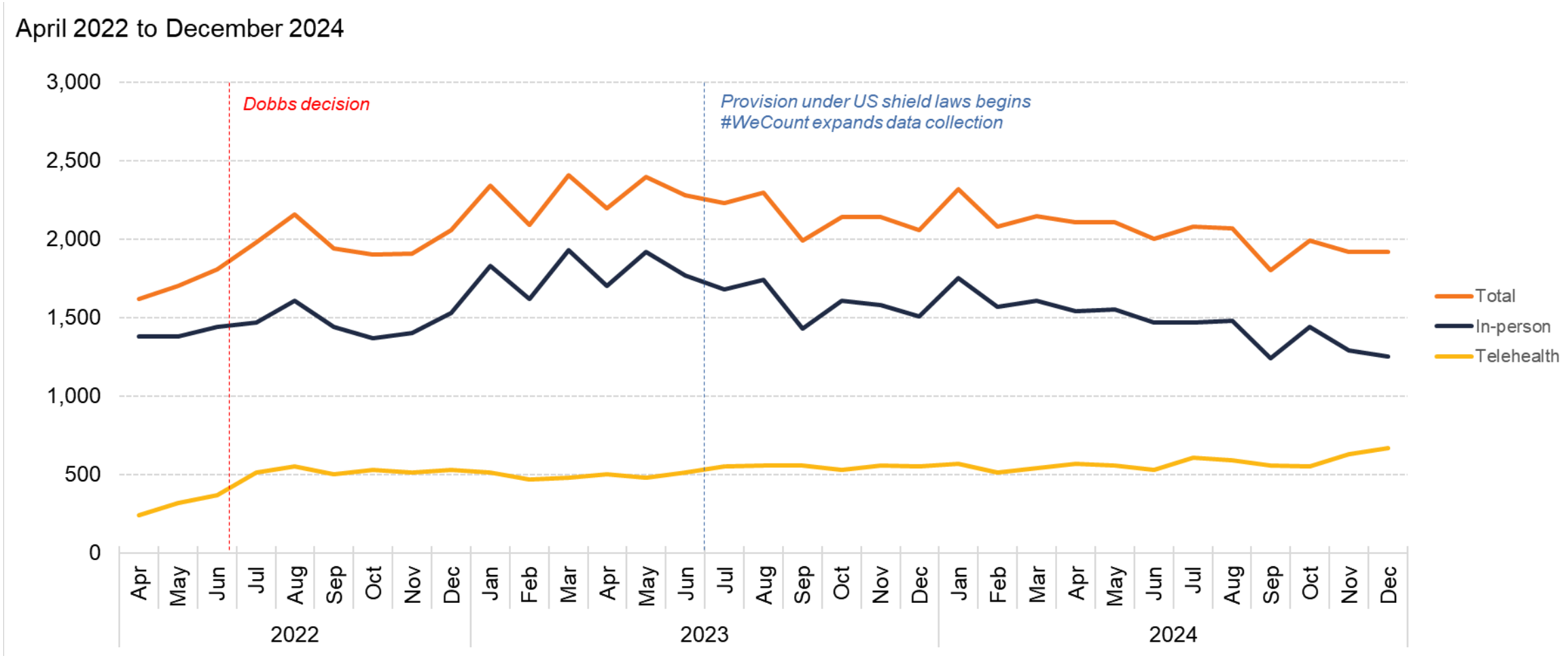
Source: Society of Family Planning, June 2025

California



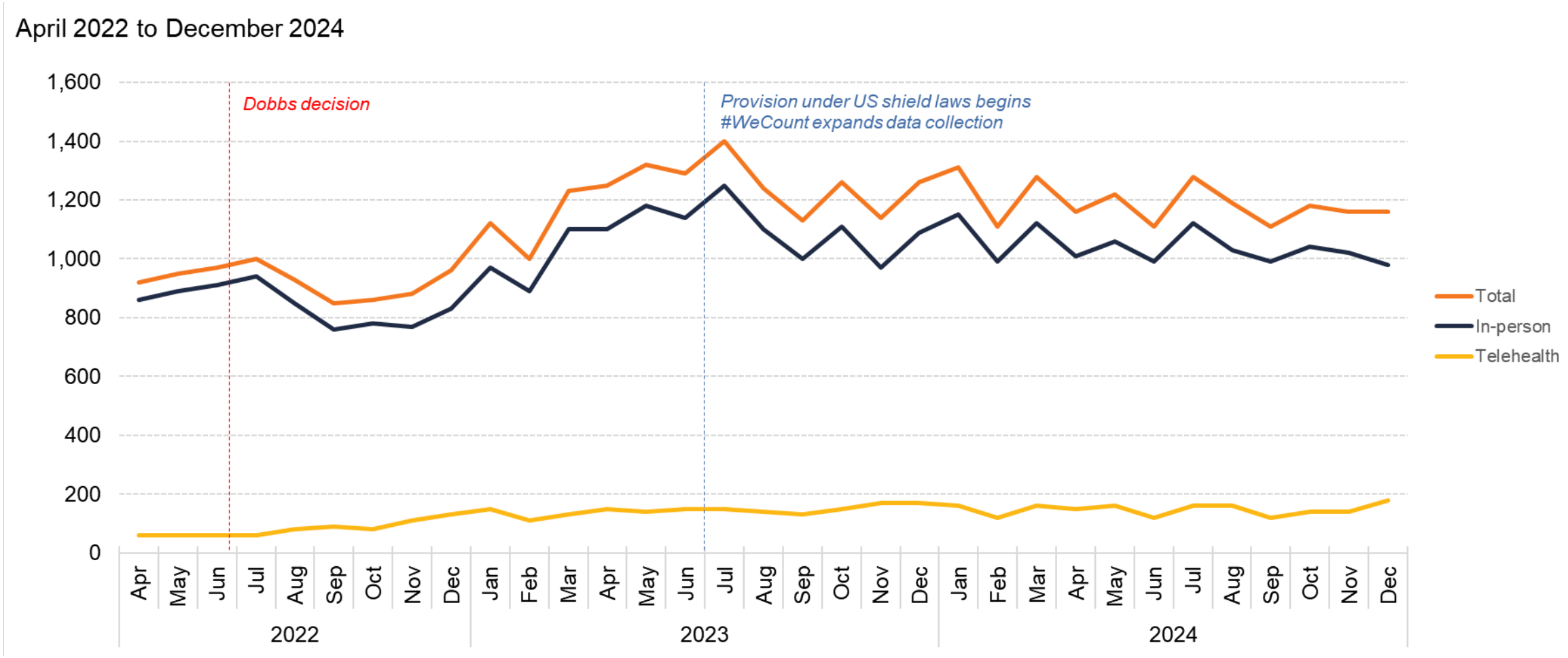
Source: Society of Family Planning, June 2025

Colorado



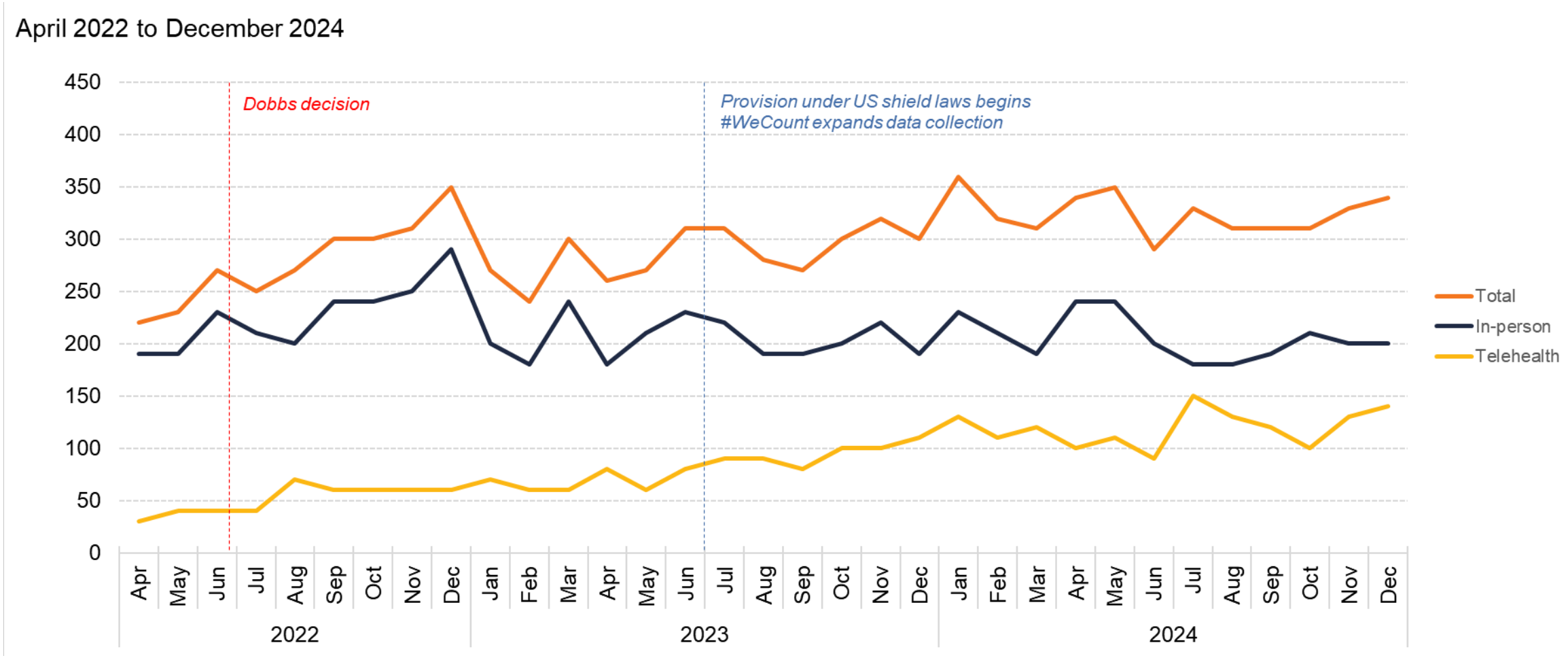
Source: Society of Family Planning, June 2025

Connecticut



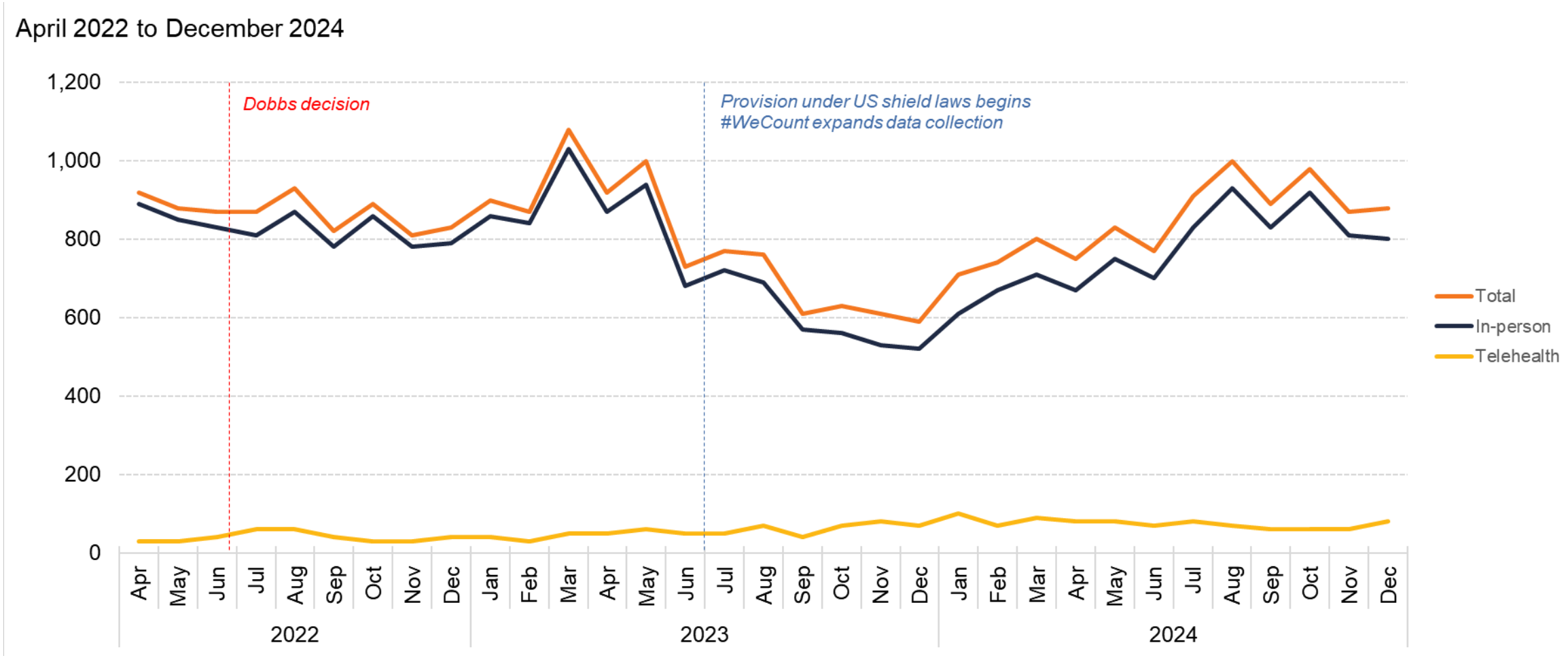
Source: Society of Family Planning, June 2025

Delaware



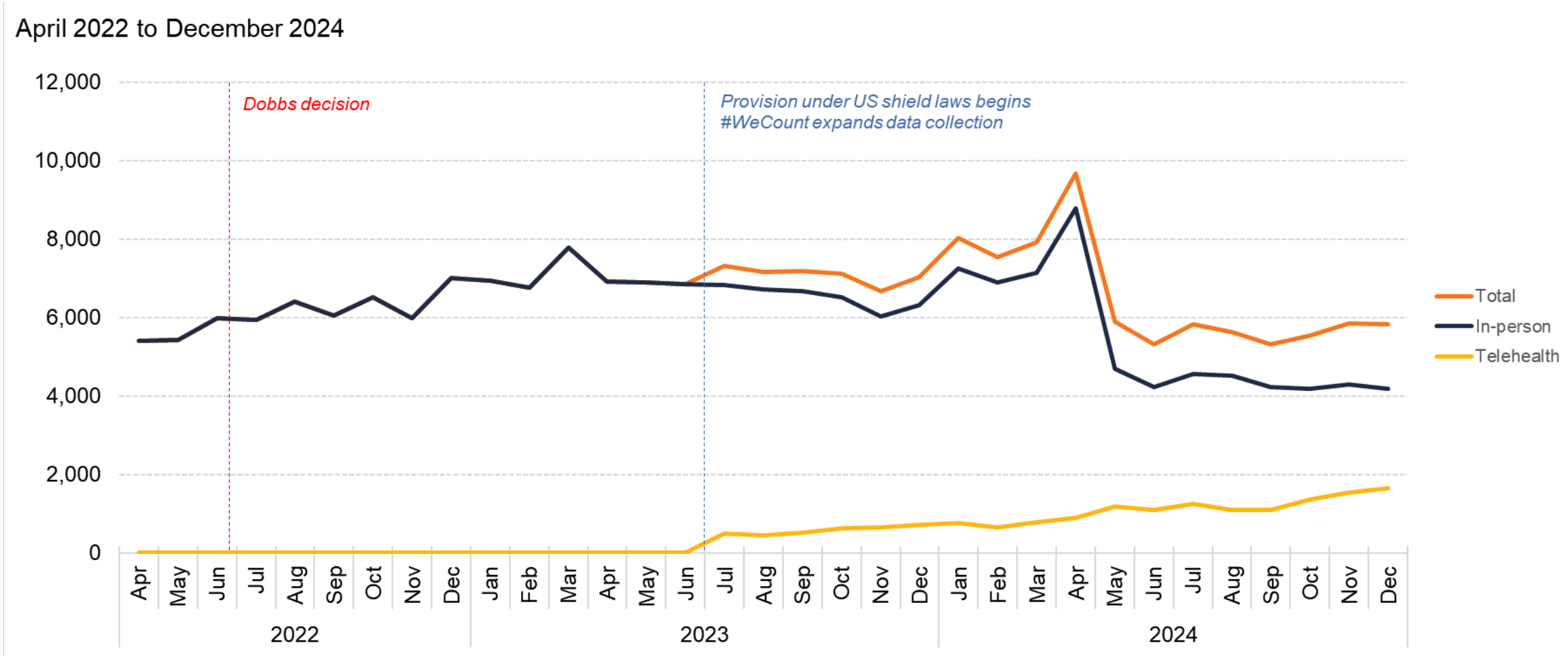
Source: Society of Family Planning, June 2025

District of Columbia



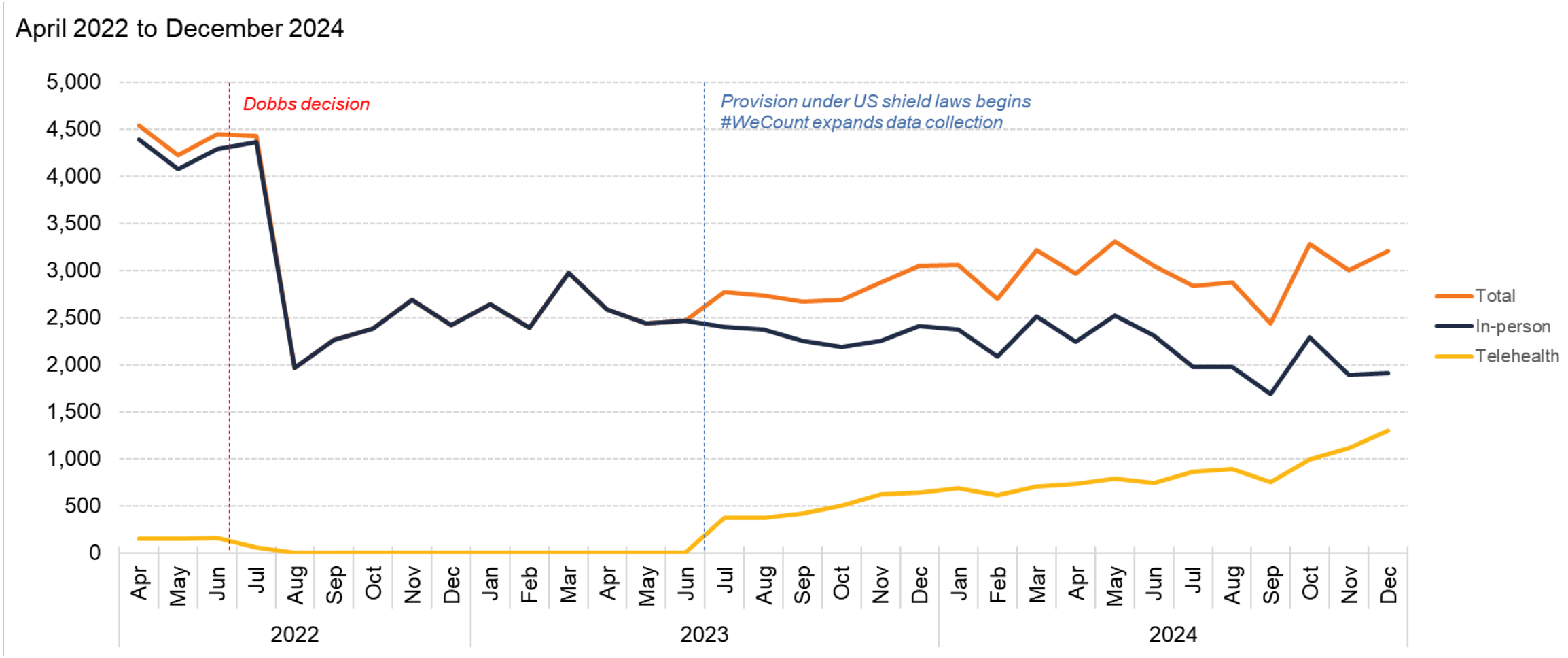
Source: Society of Family Planning, June 2025

Florida



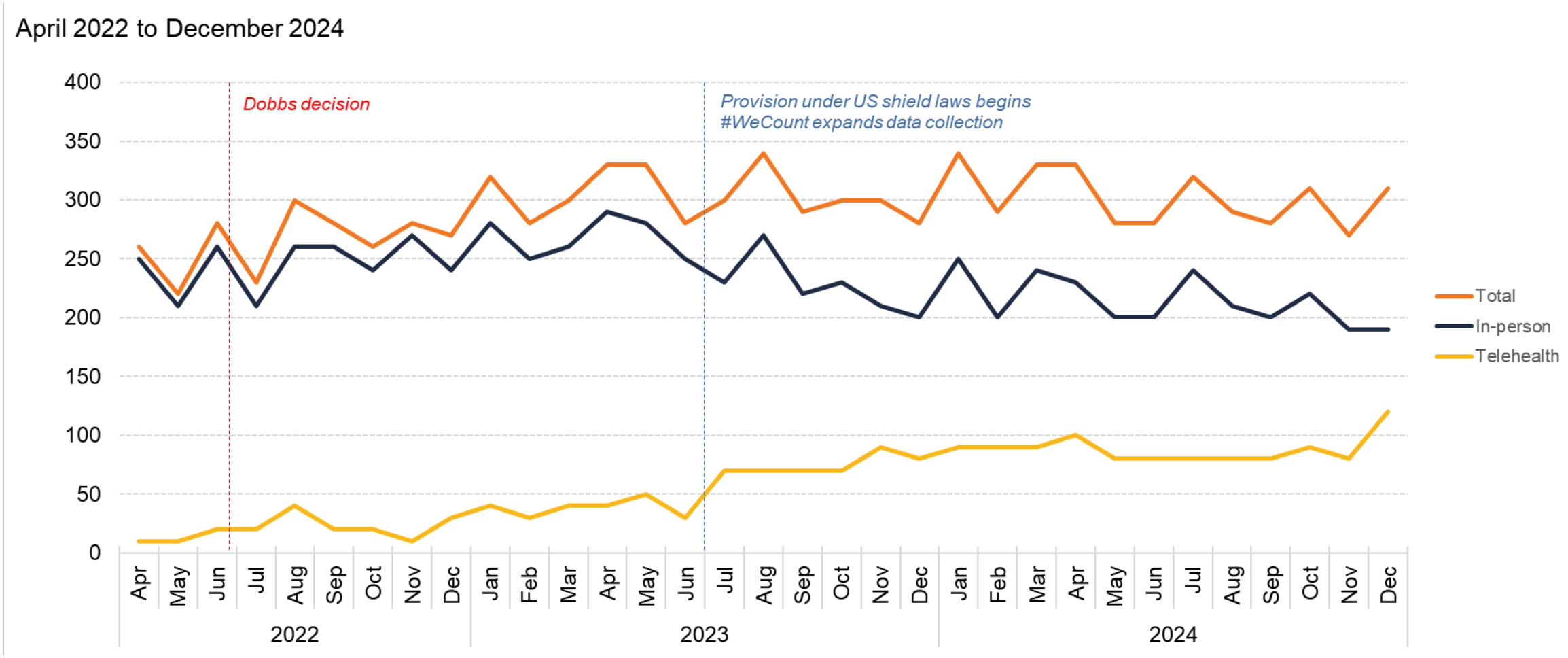
Source: Society of Family Planning, June 2025

Georgia



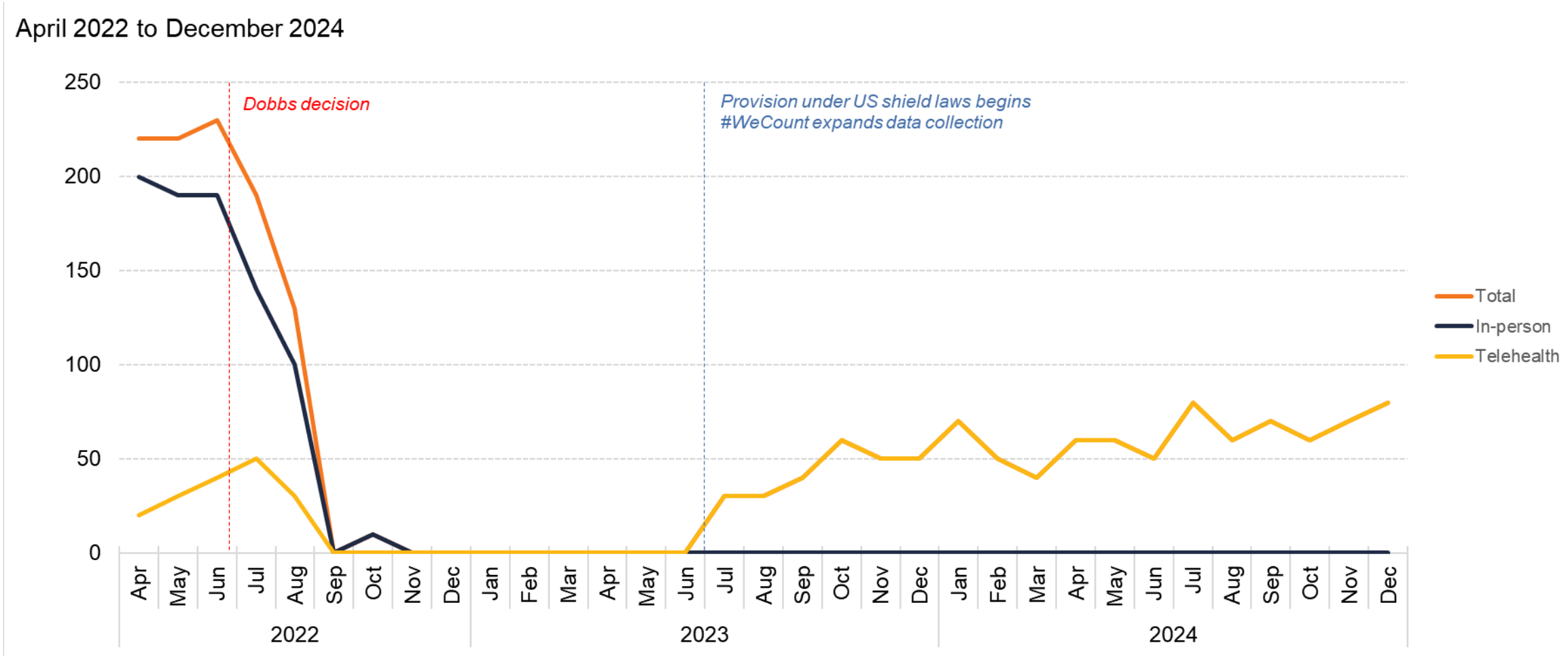
Source: Society of Family Planning, June 2025

Hawaii



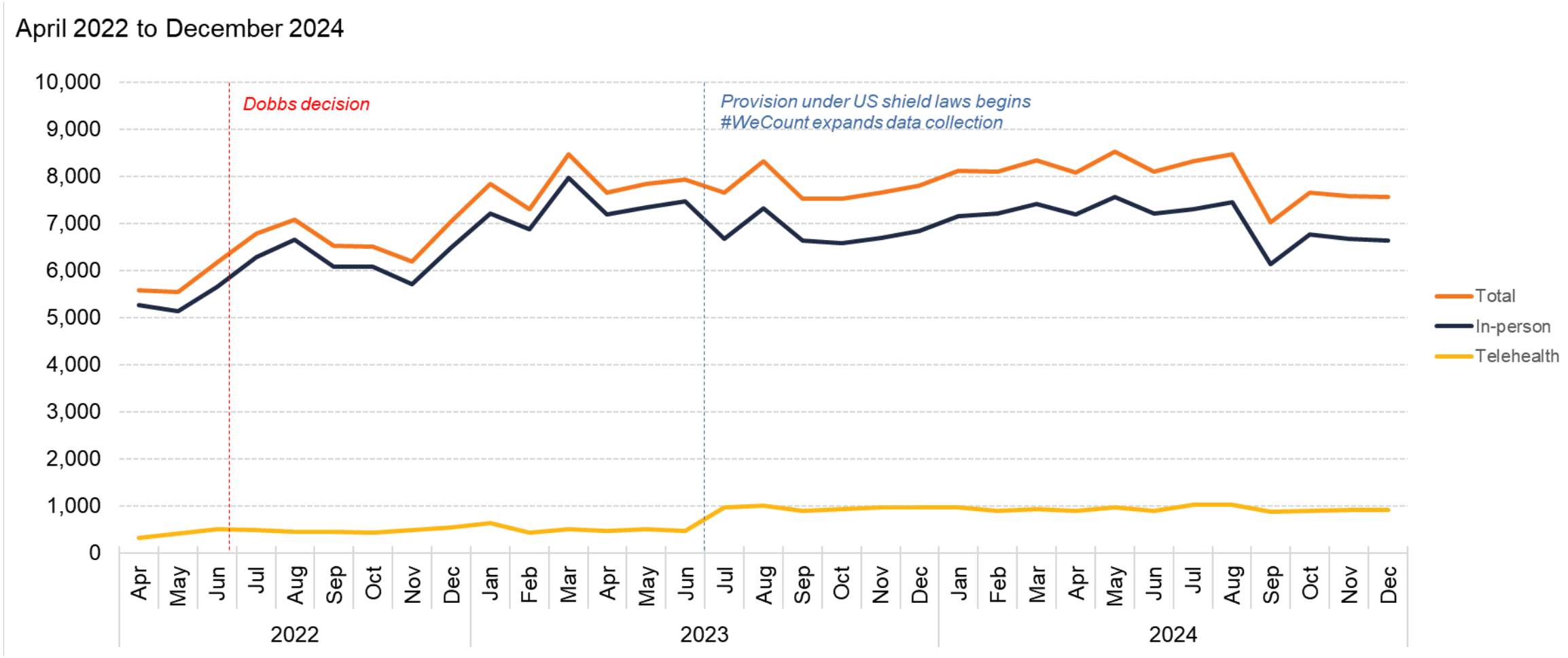
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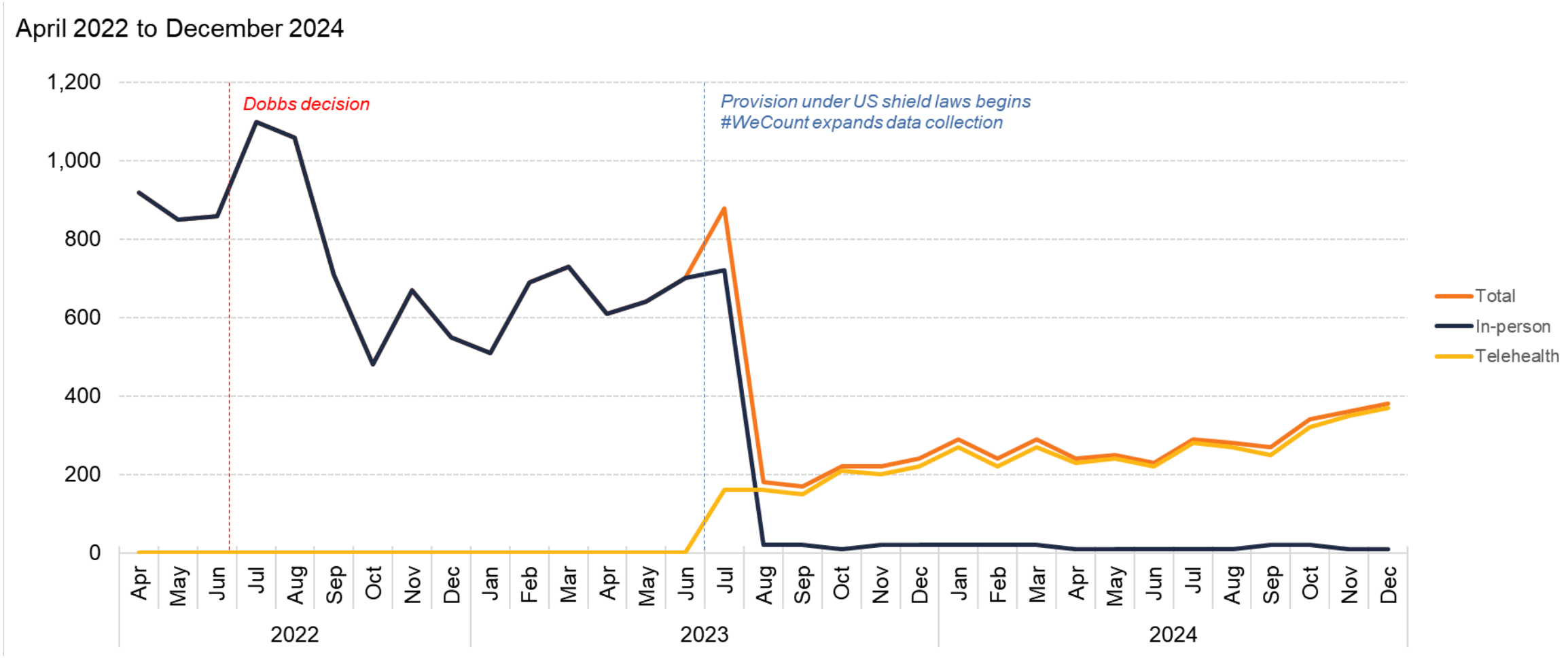
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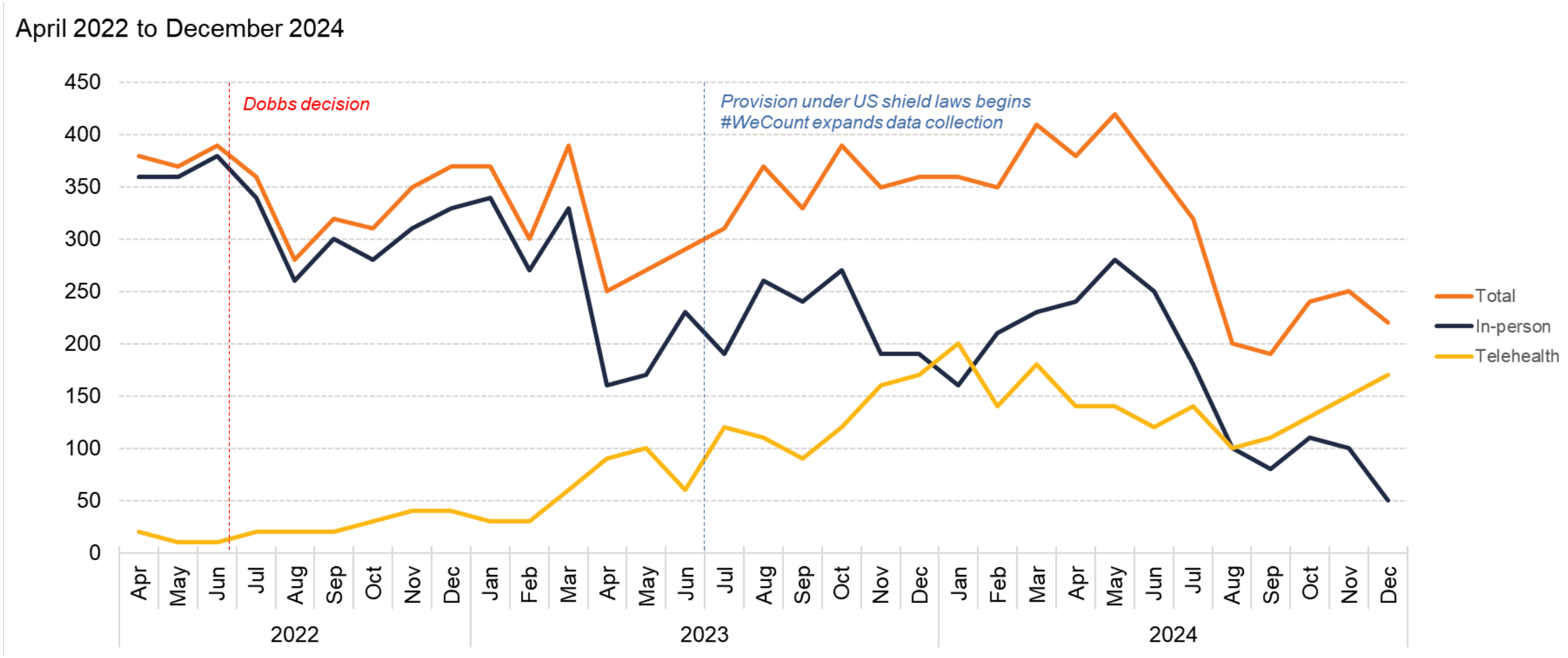
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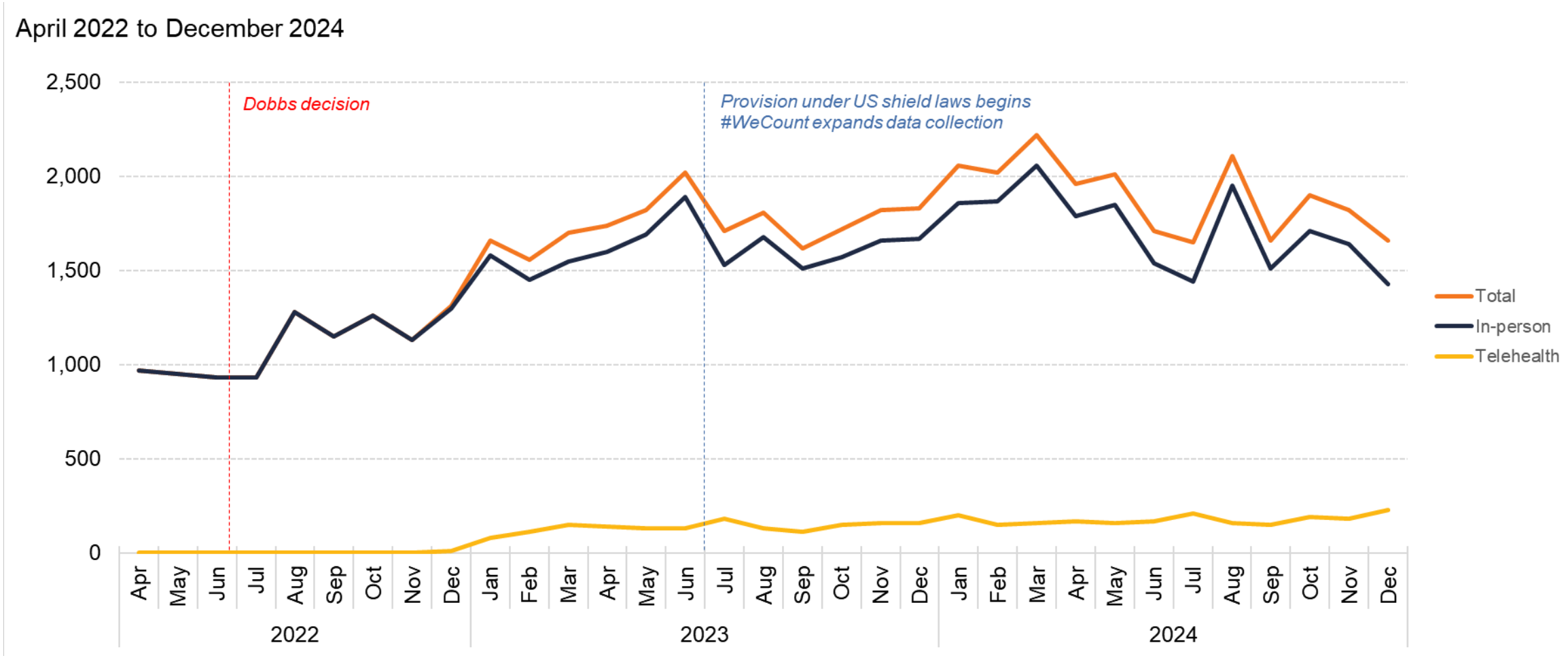
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Iowa



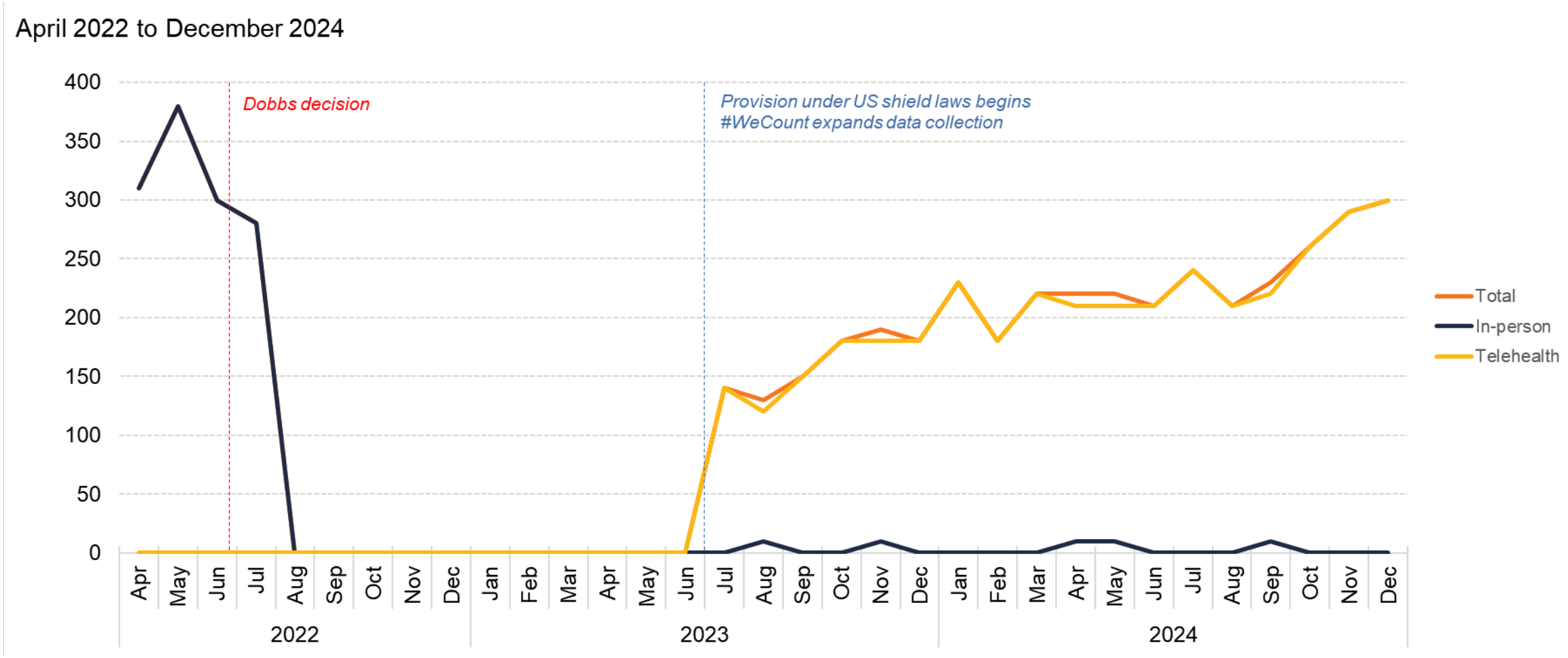
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Kansas



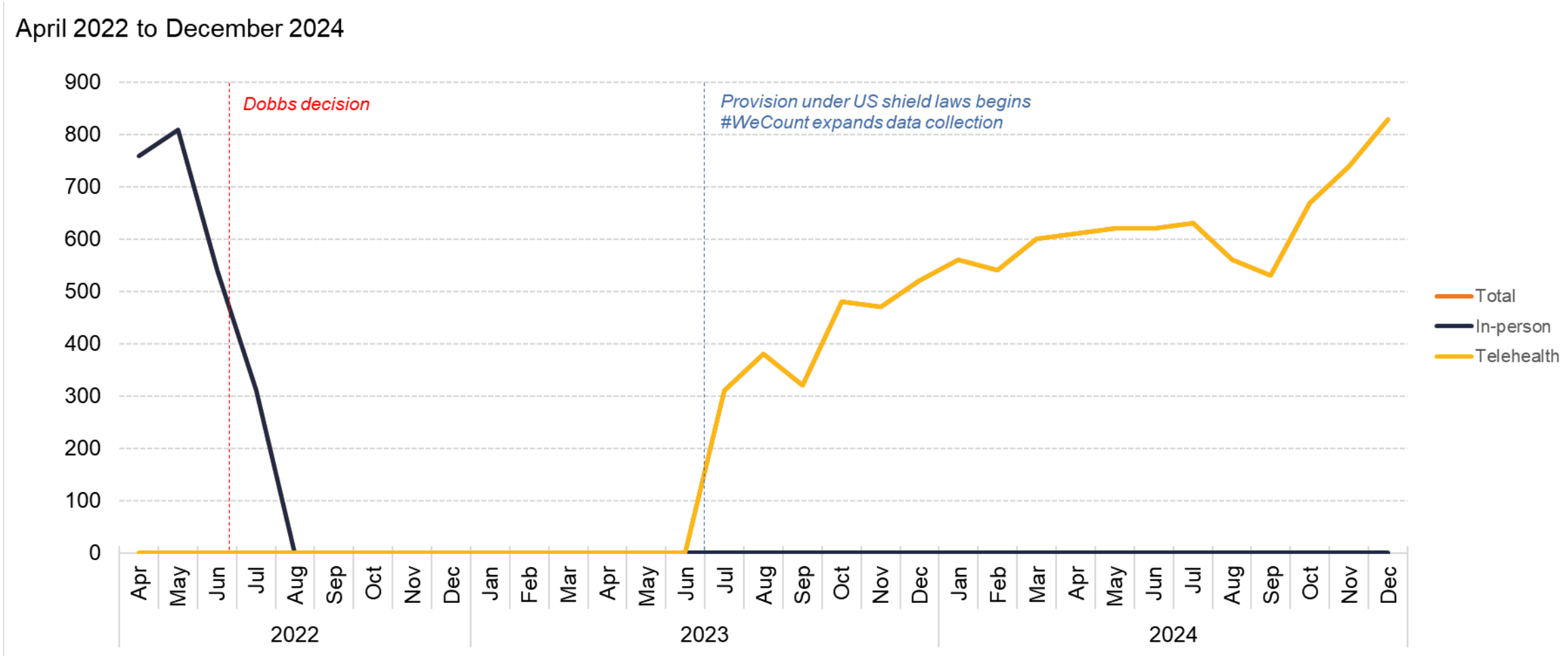
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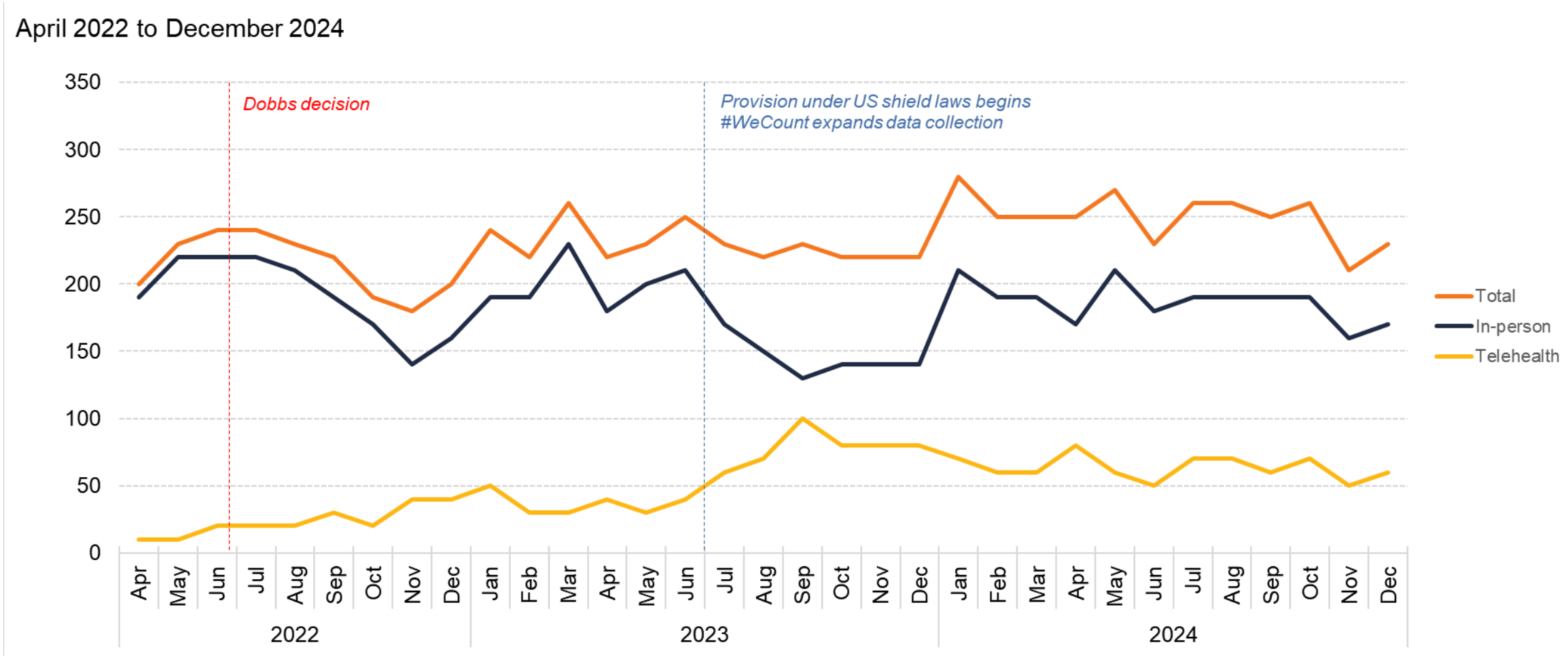
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Louisiana



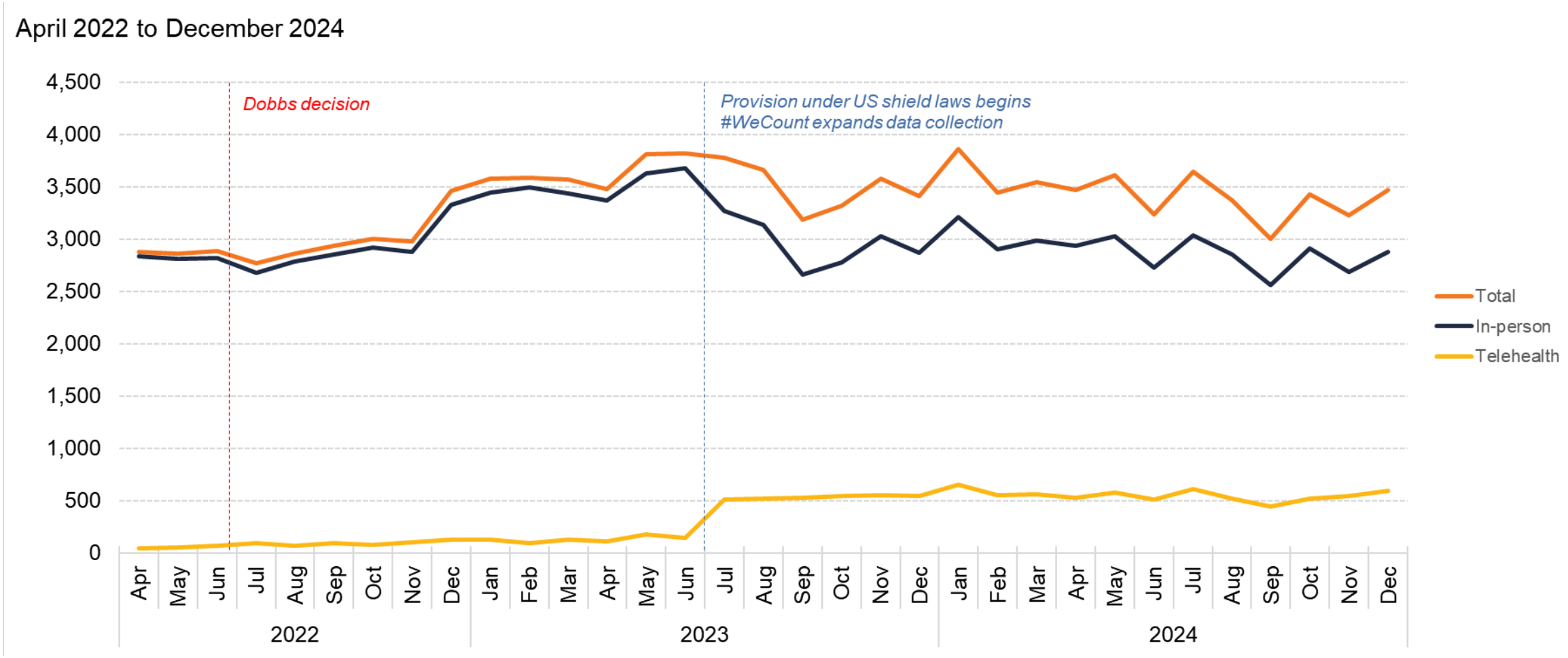
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Maine



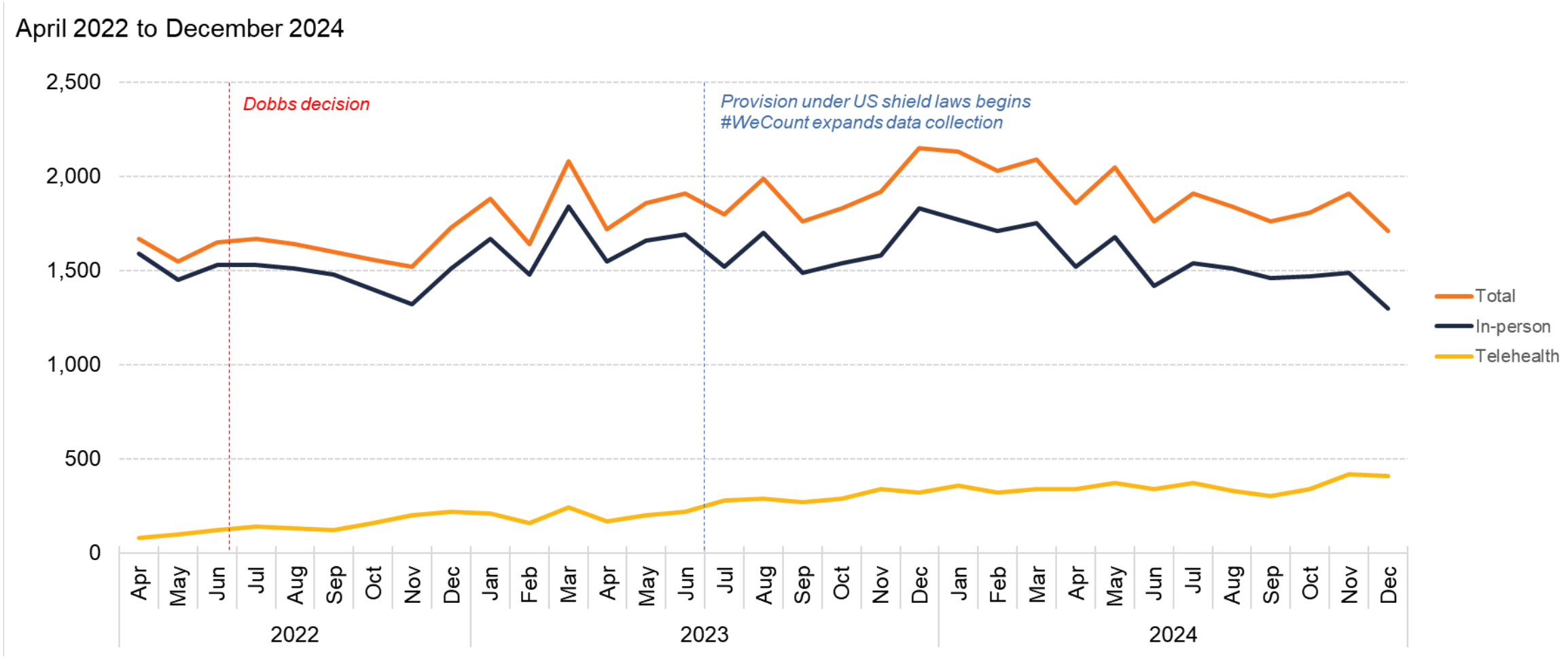
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Maryland



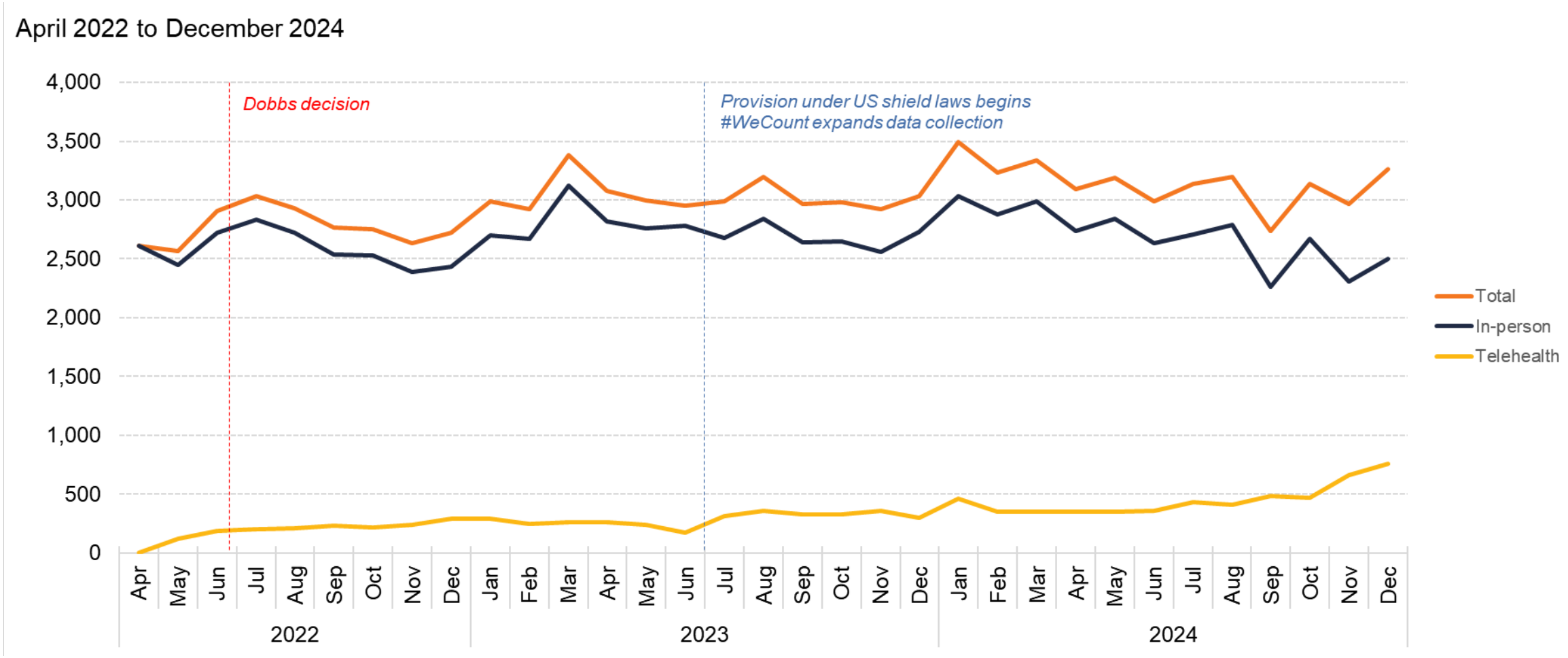
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Massachusetts



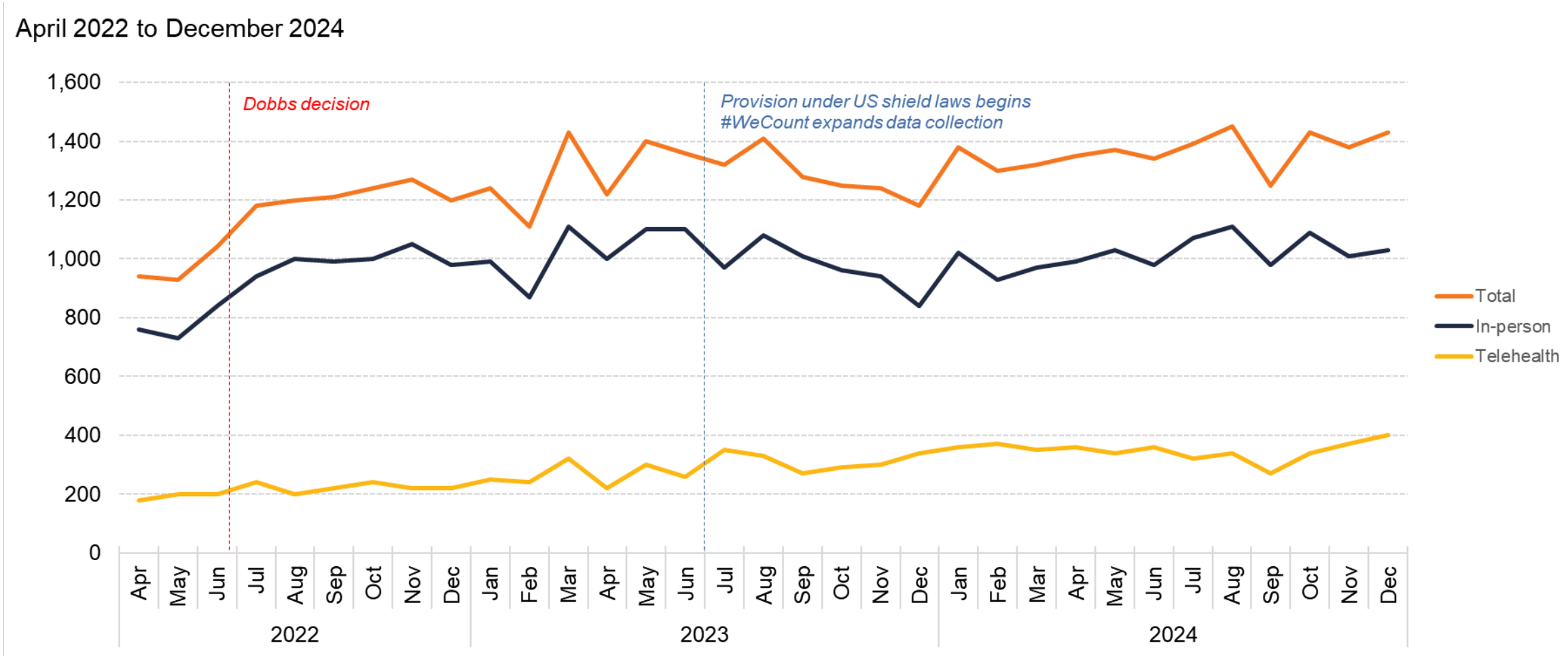
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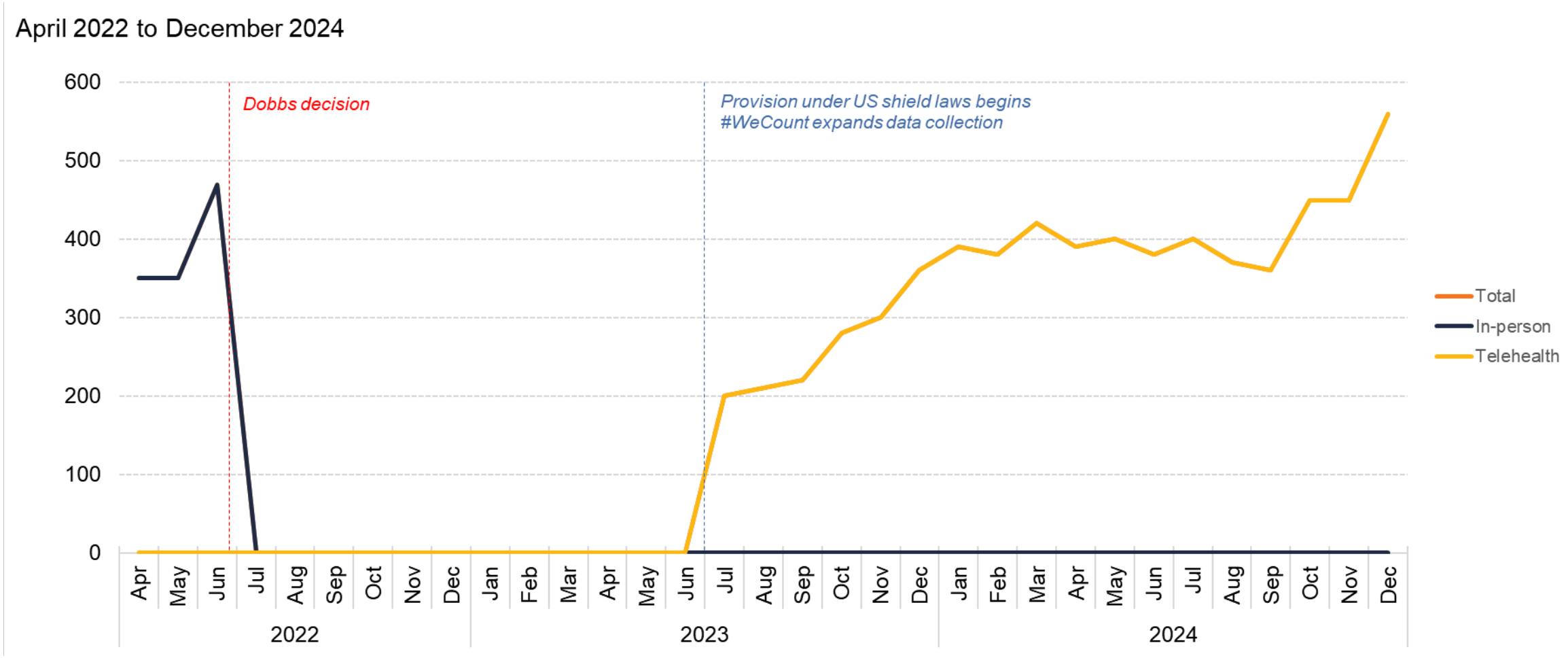
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Minnesota



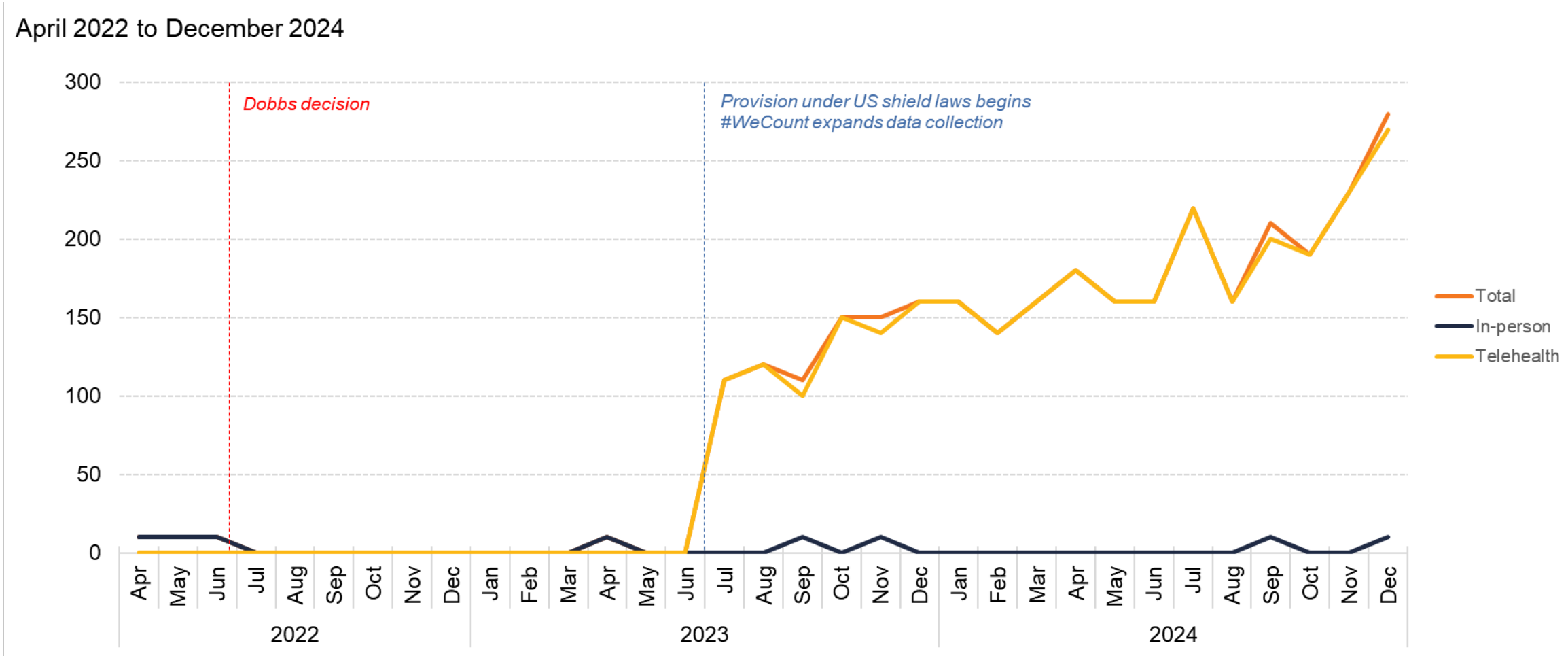
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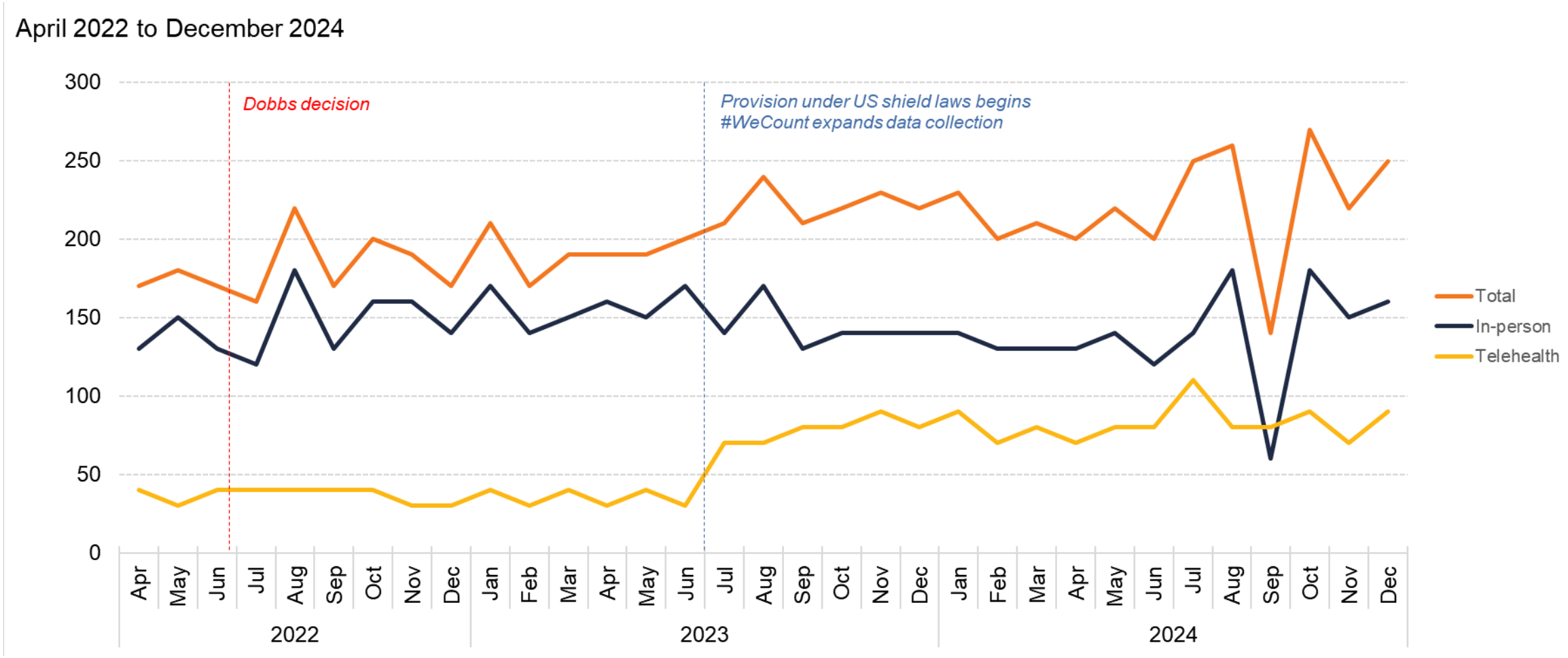
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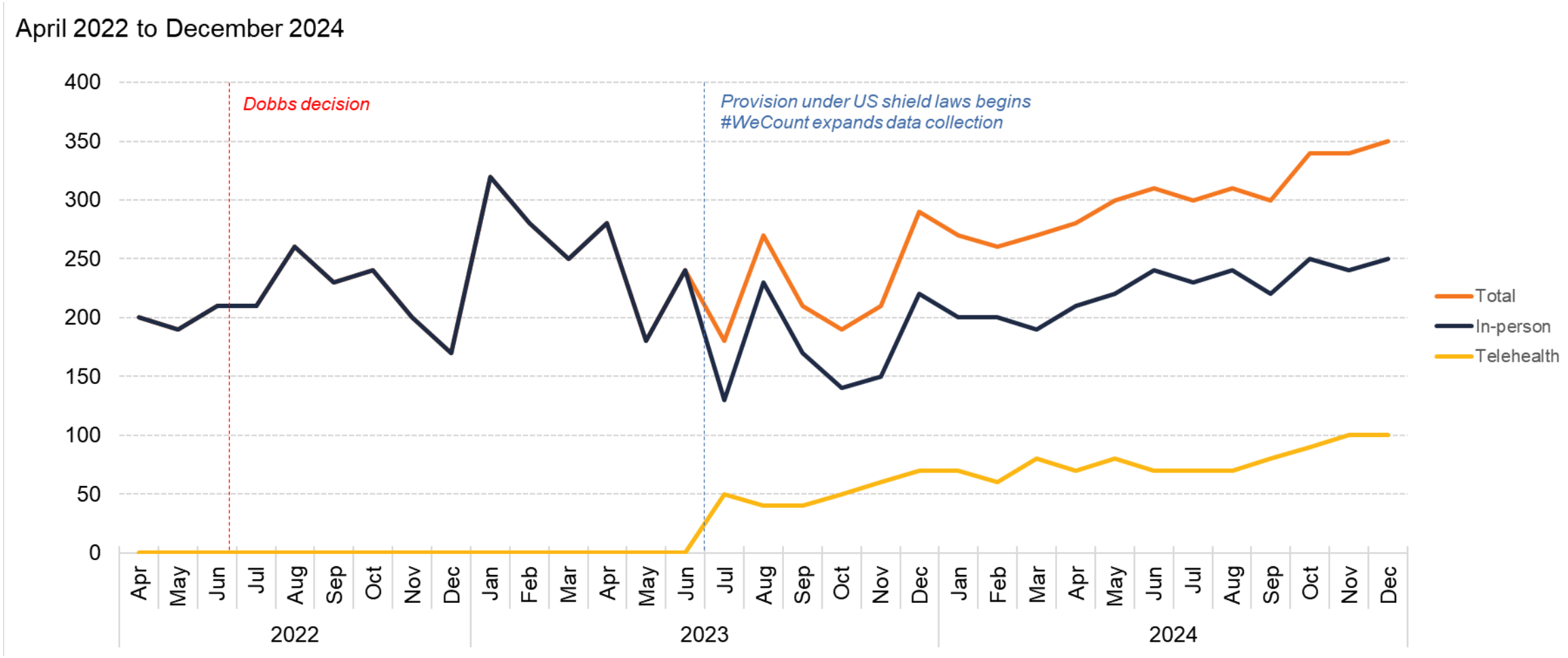
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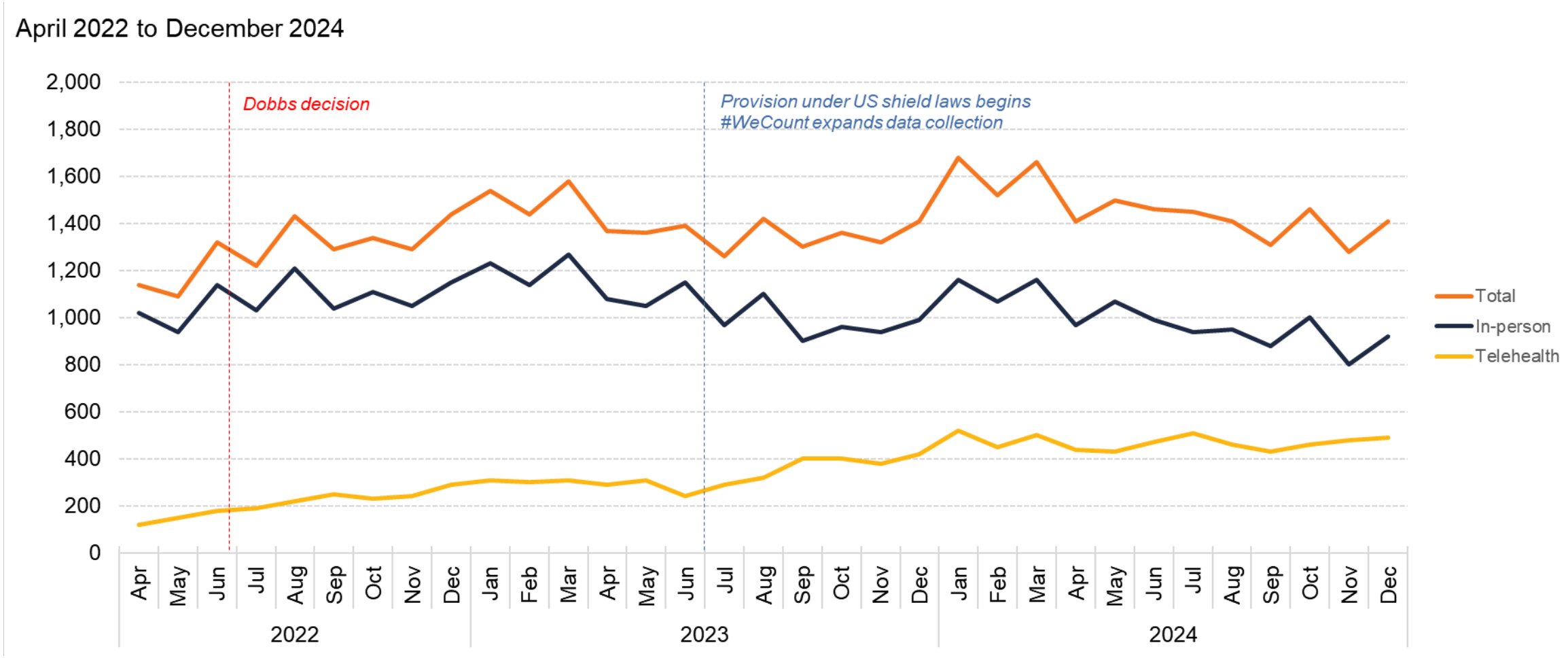
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Nebraska



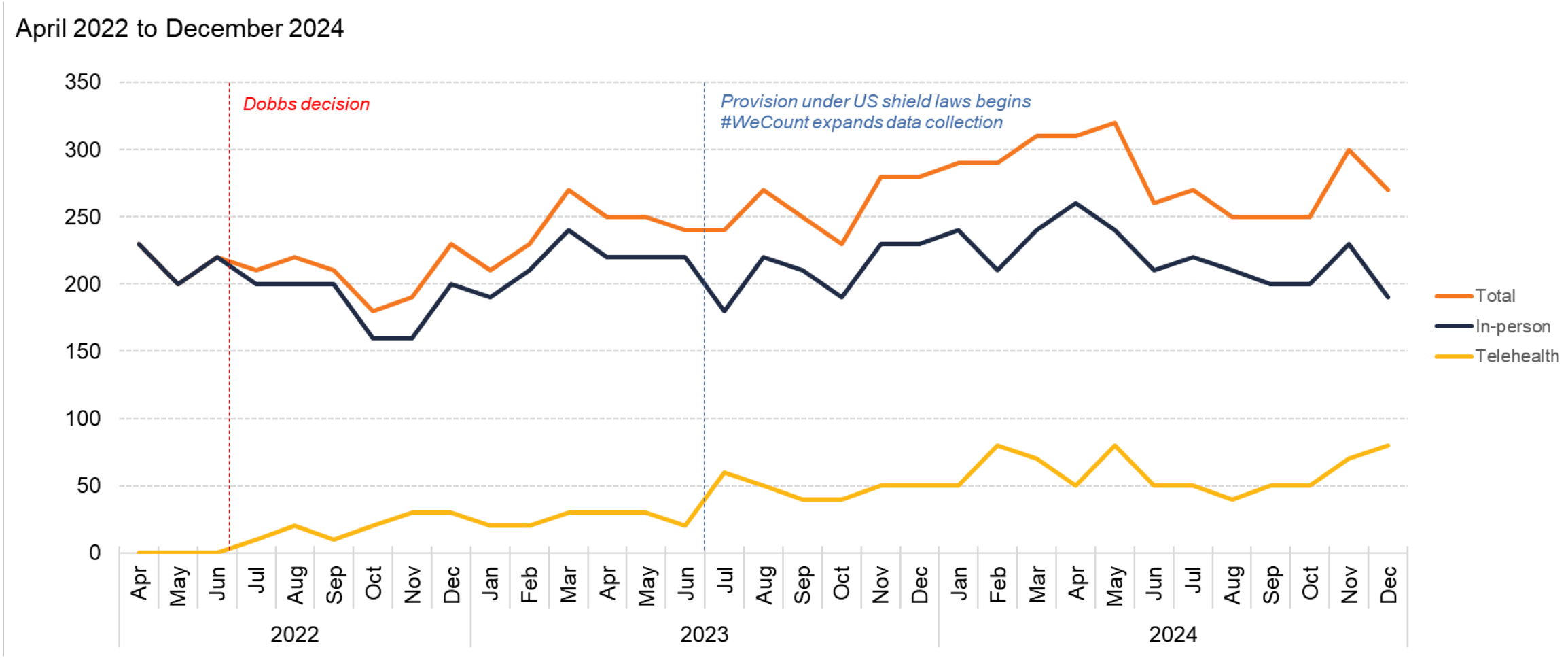
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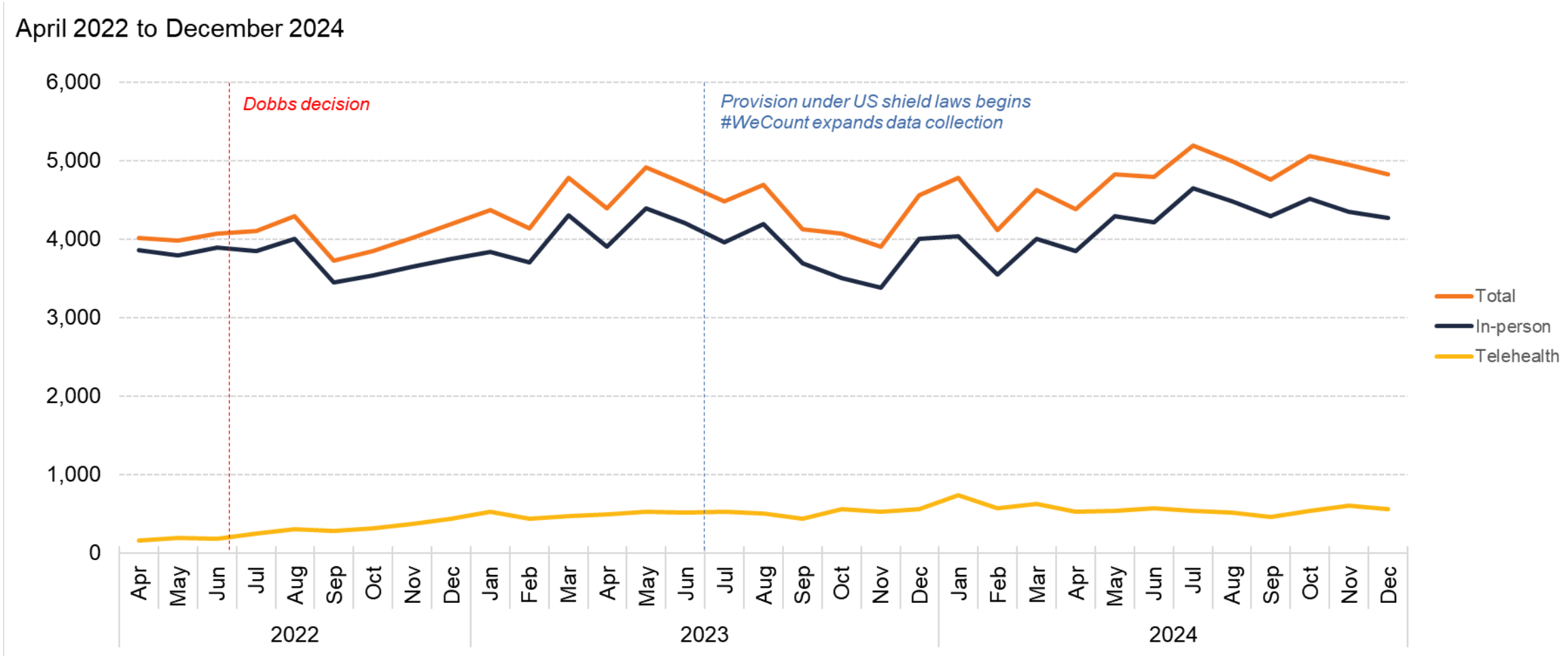
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New Hampshire



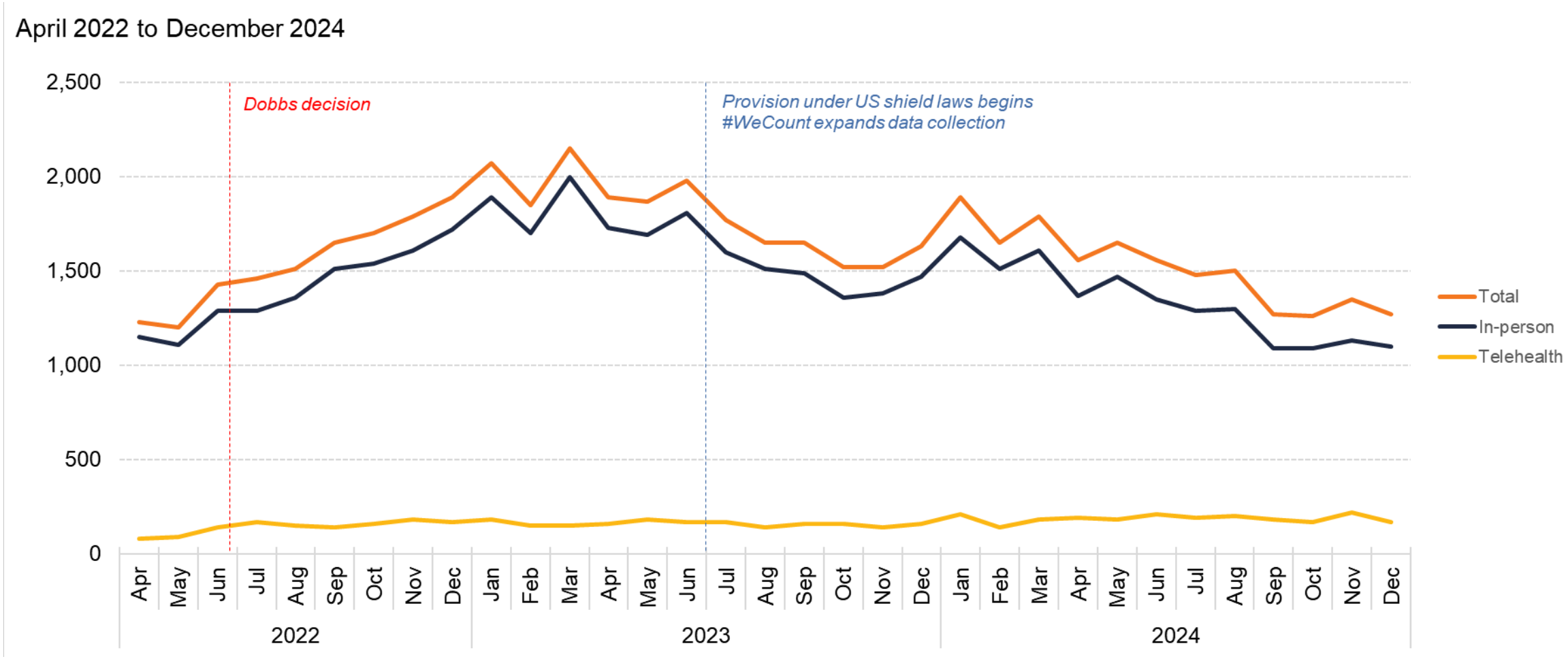
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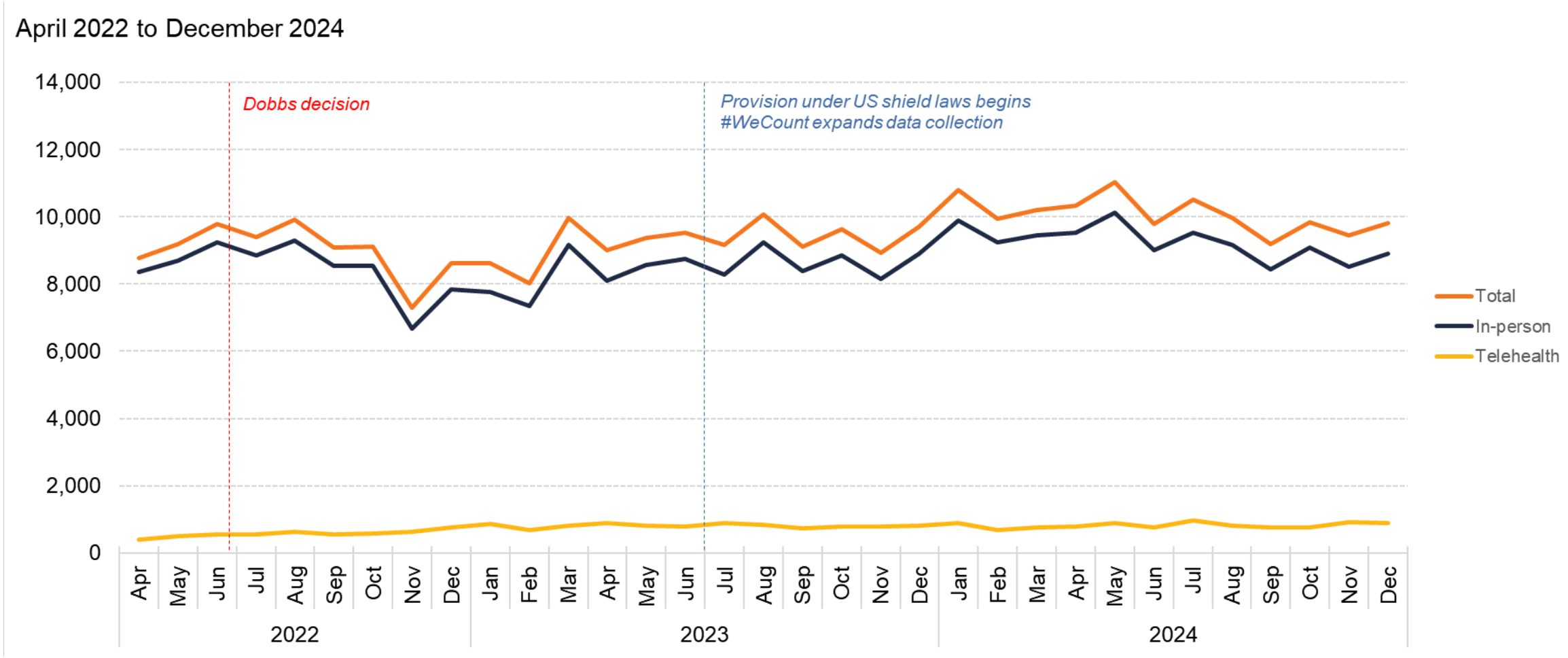
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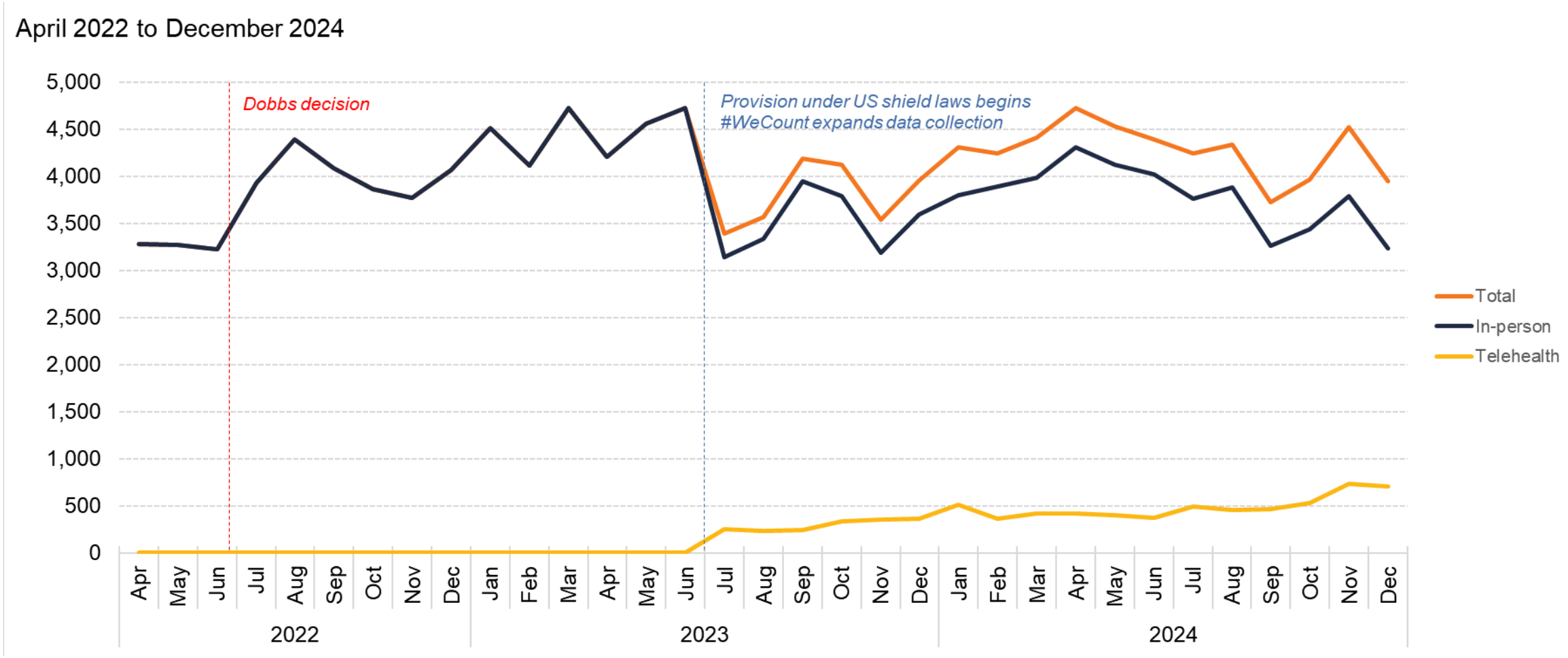
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New York



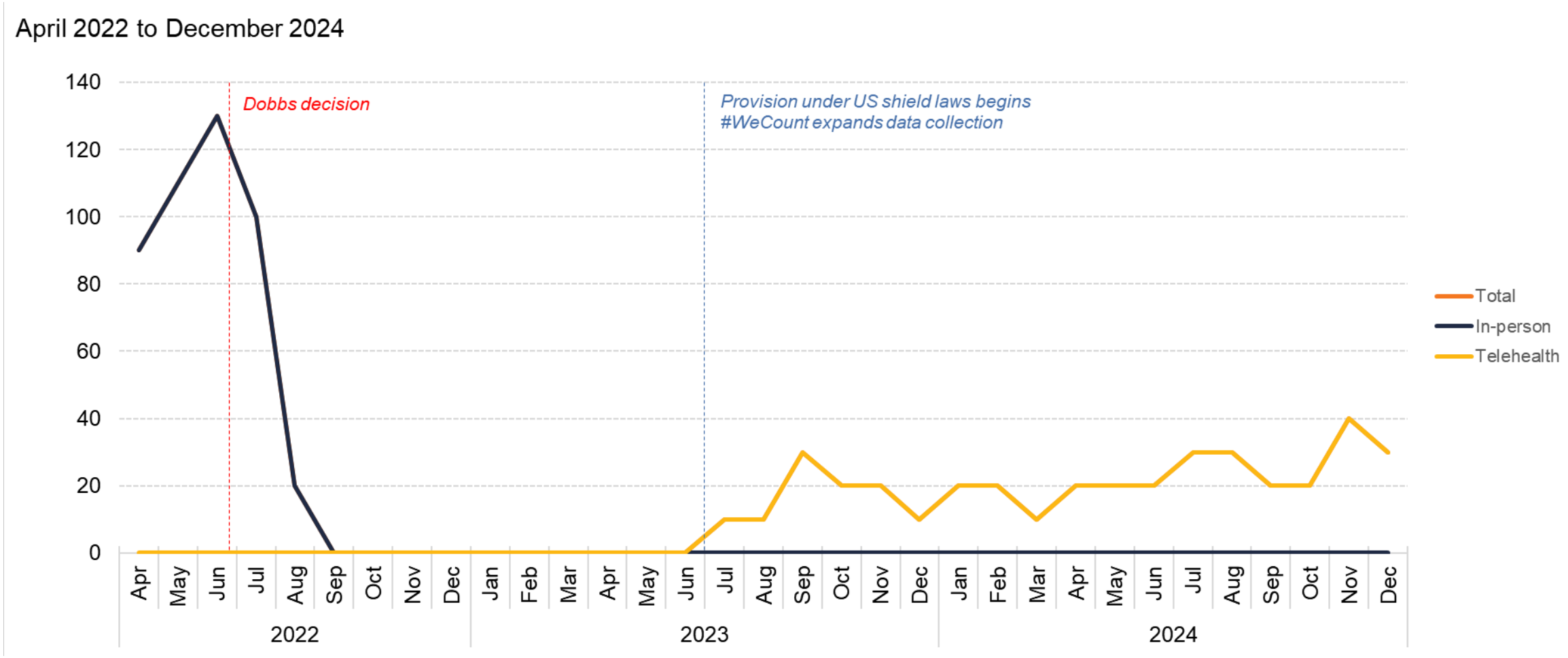
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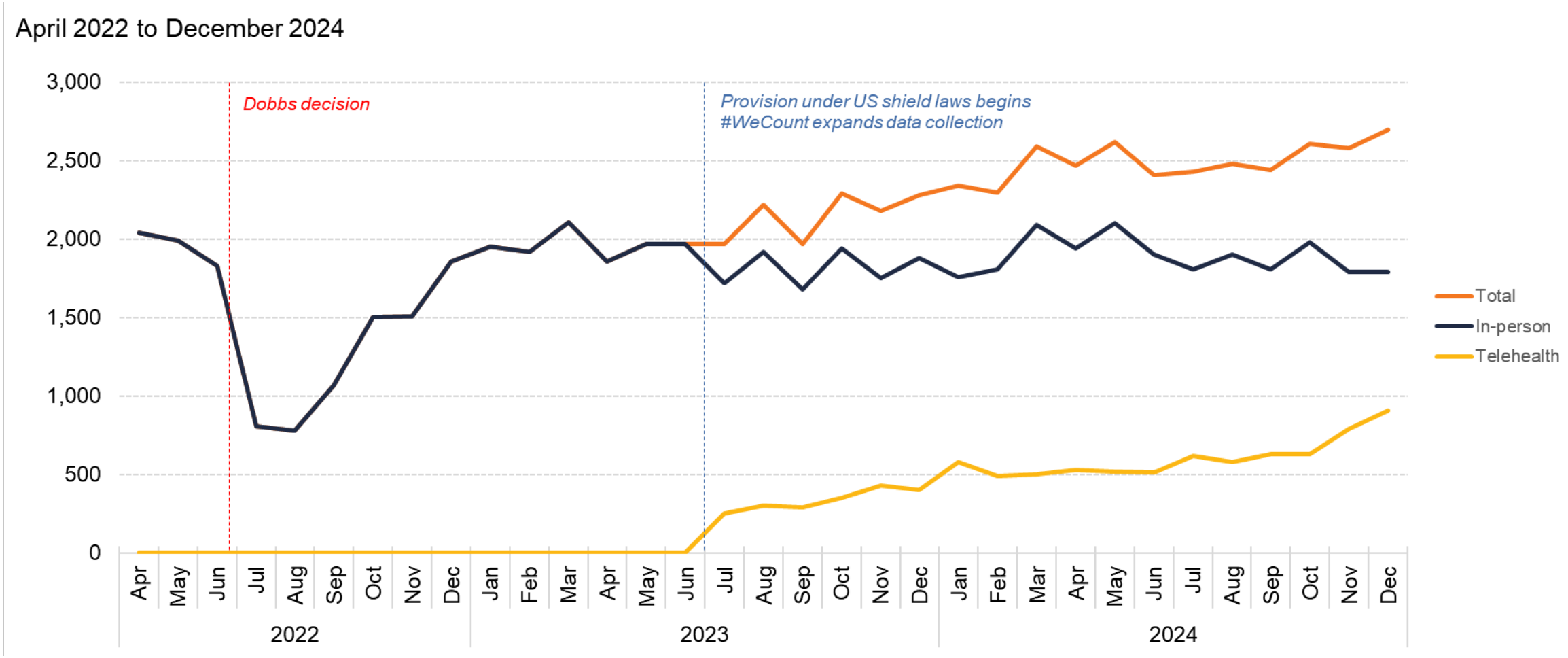
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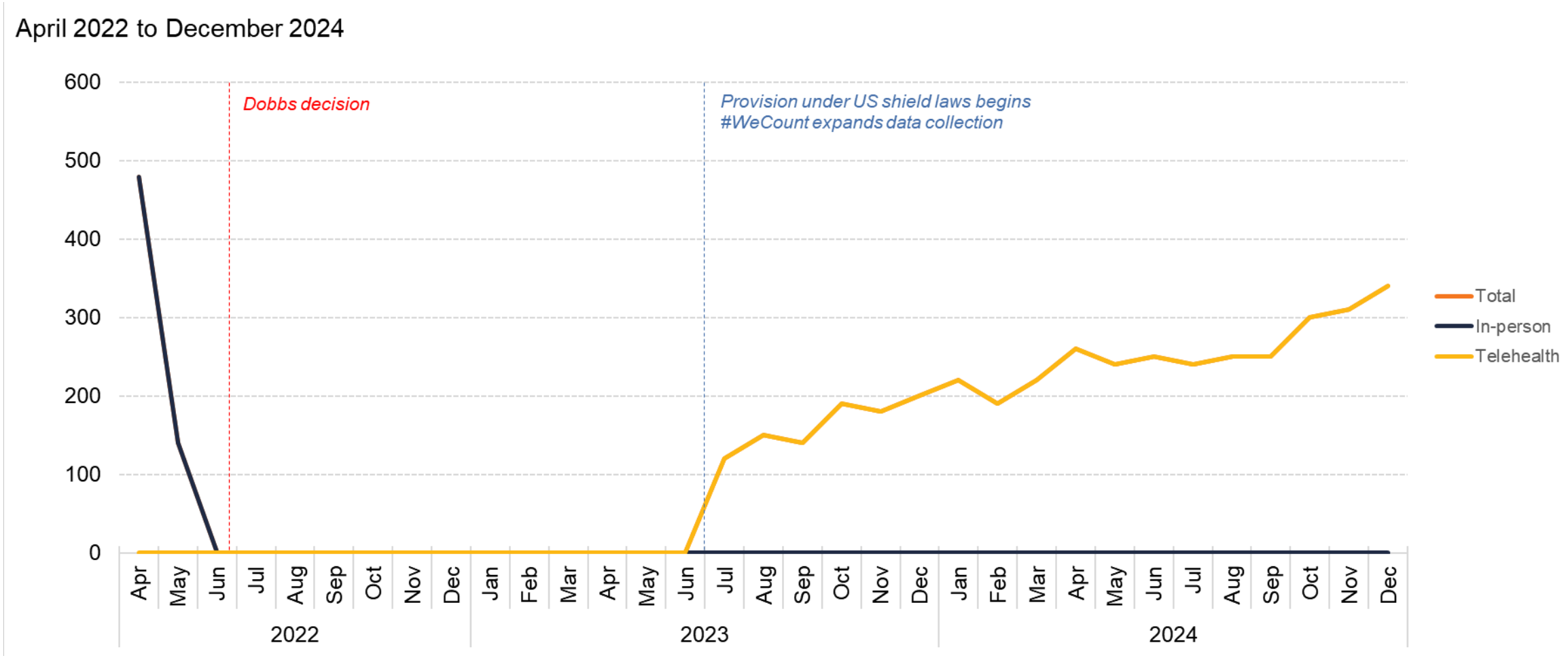
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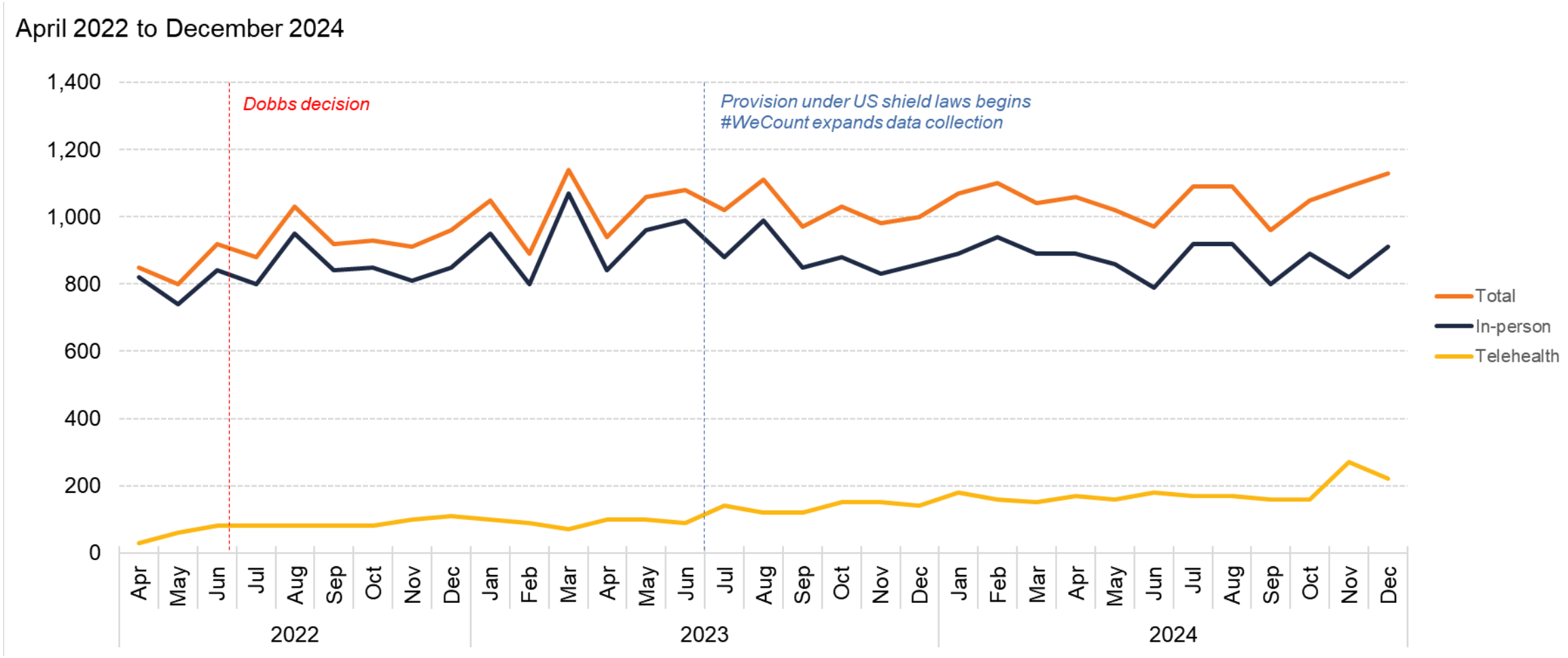
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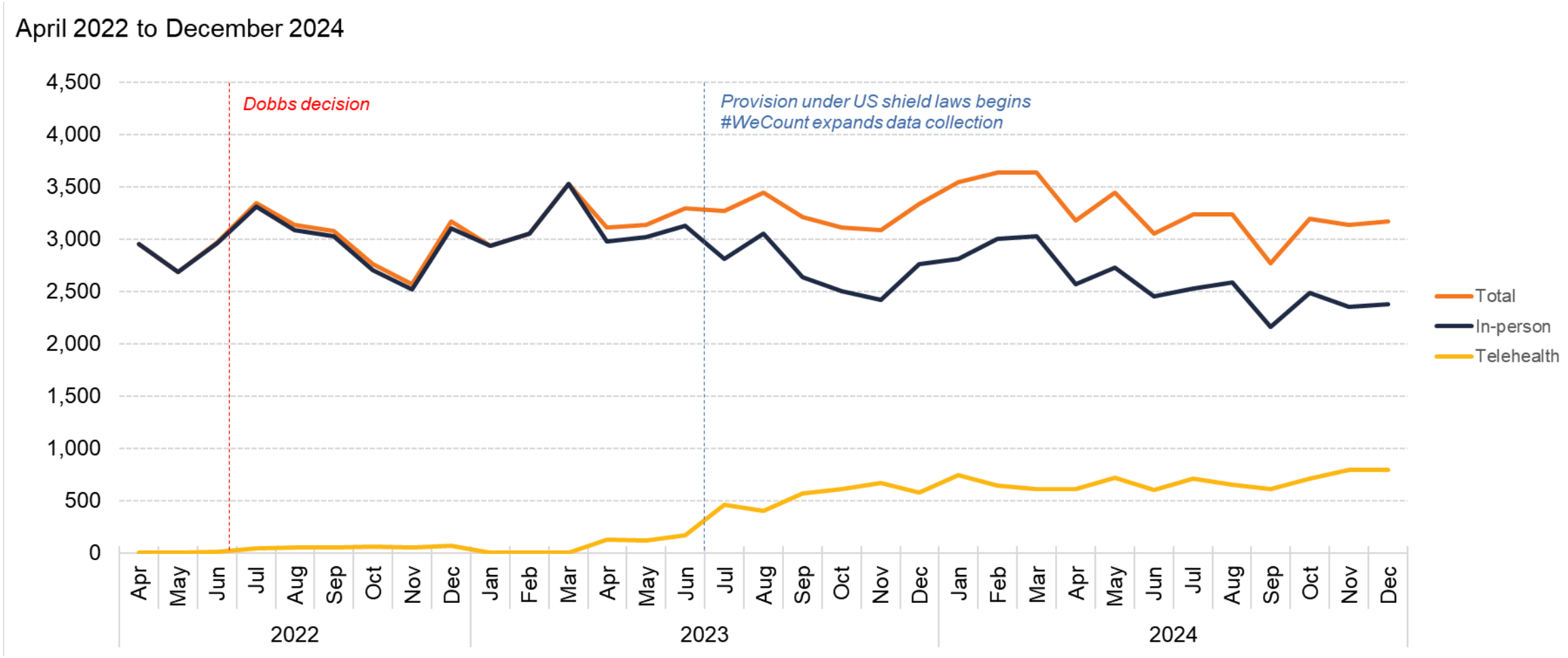
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Oregon



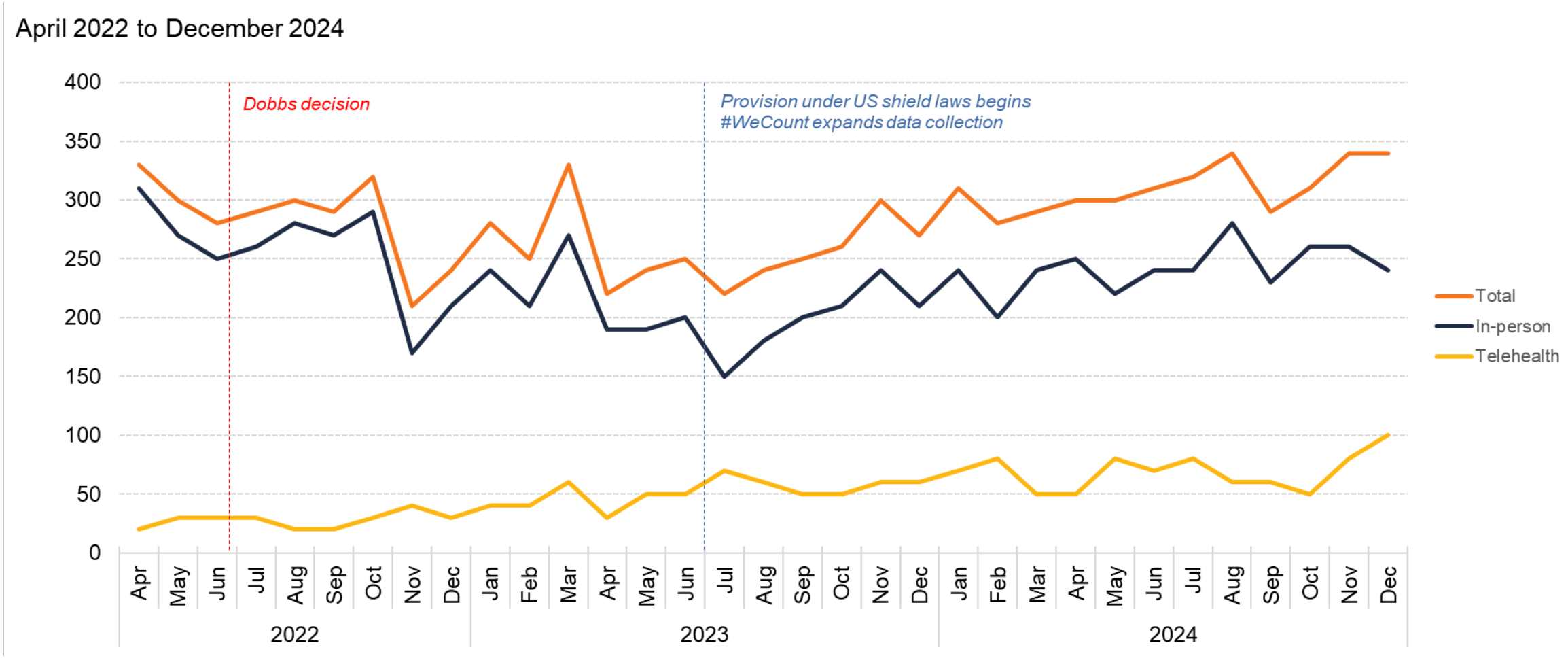
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Pennsylvania



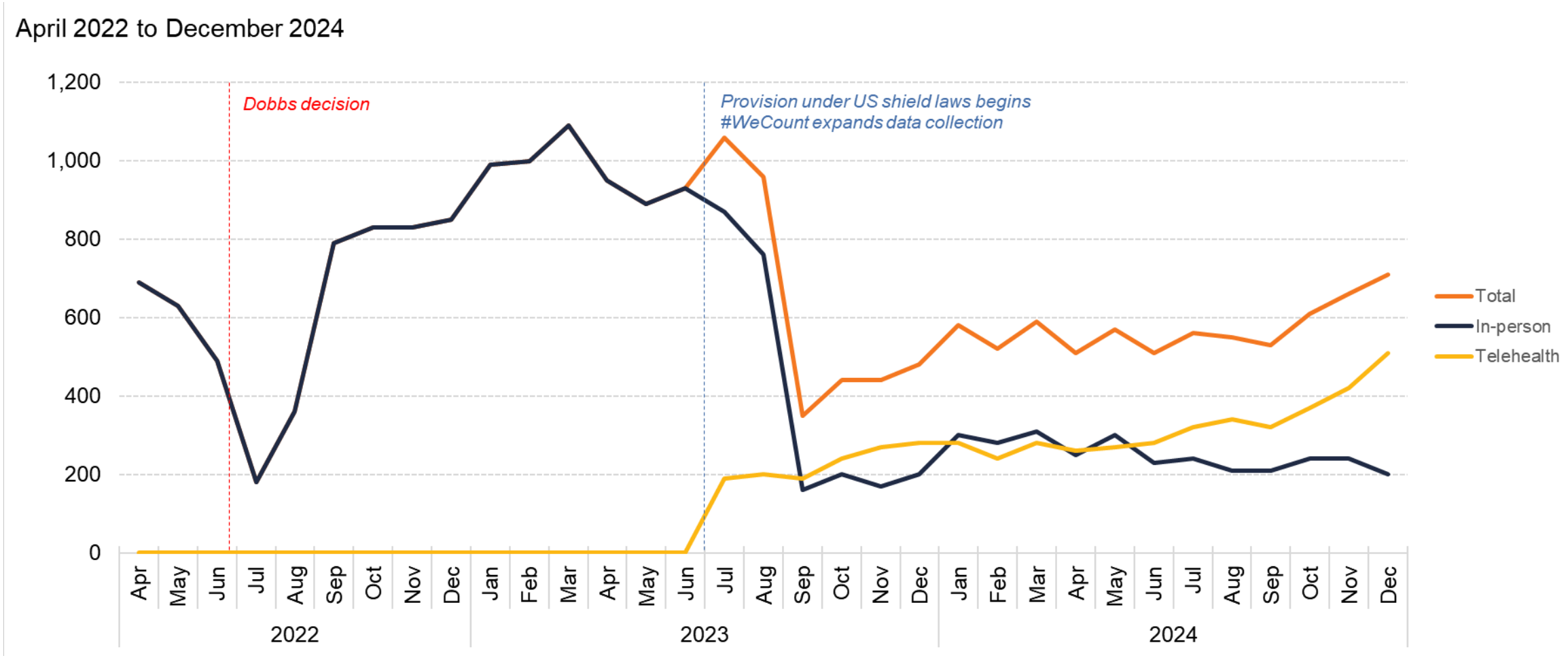
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Rhode Island



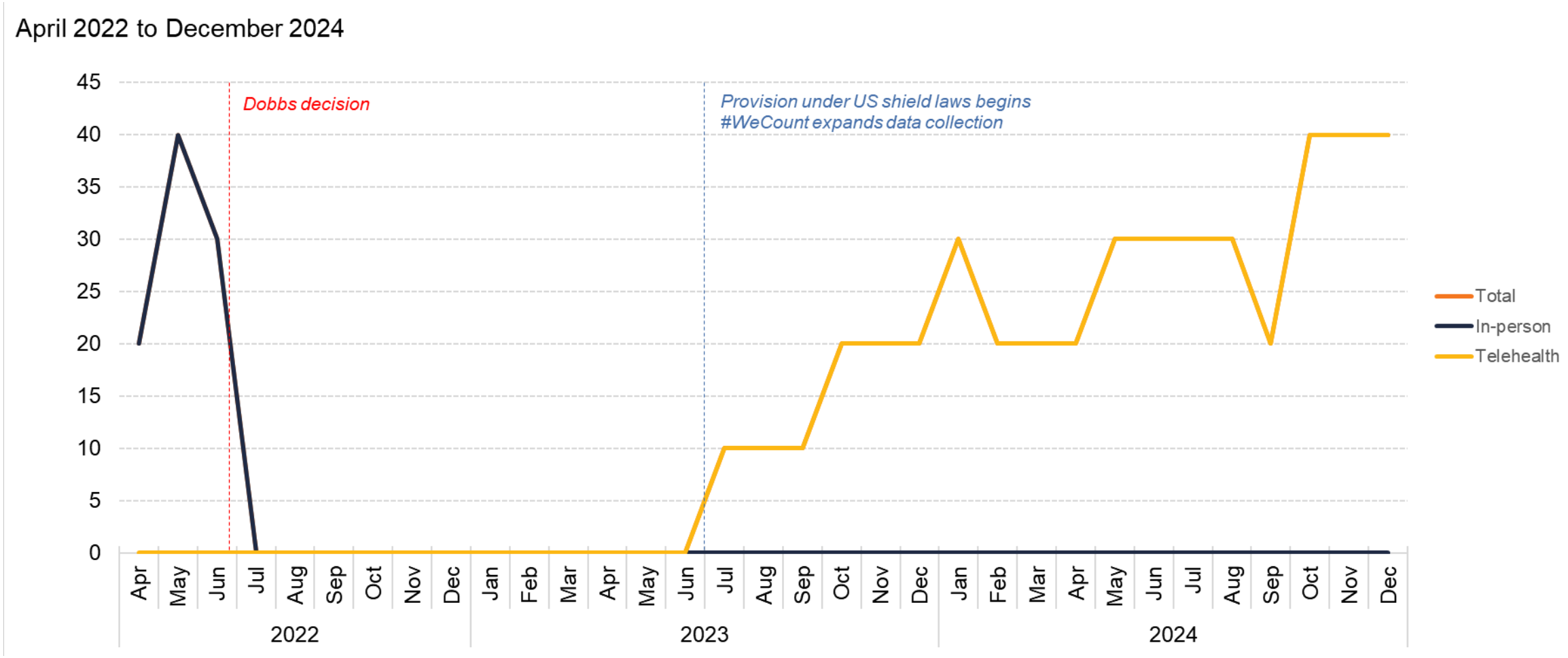
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South Carolina



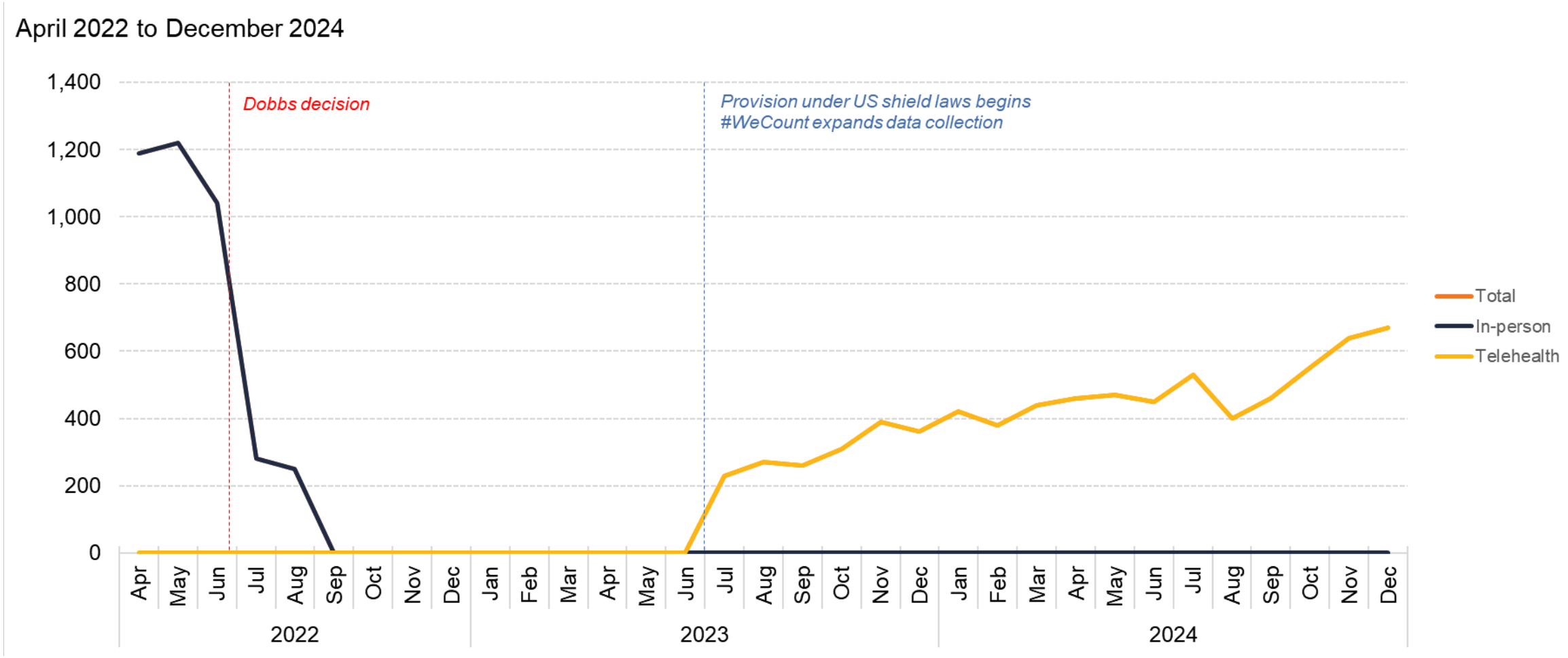
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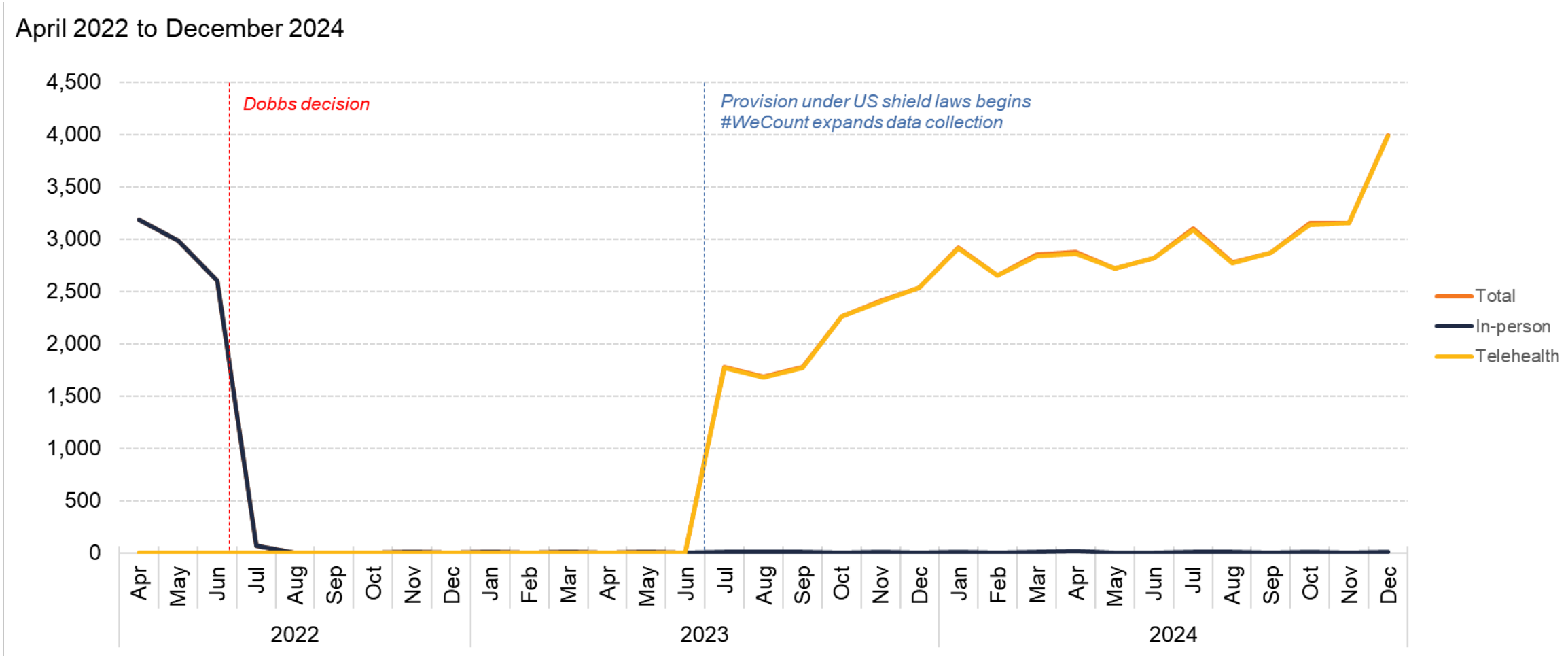
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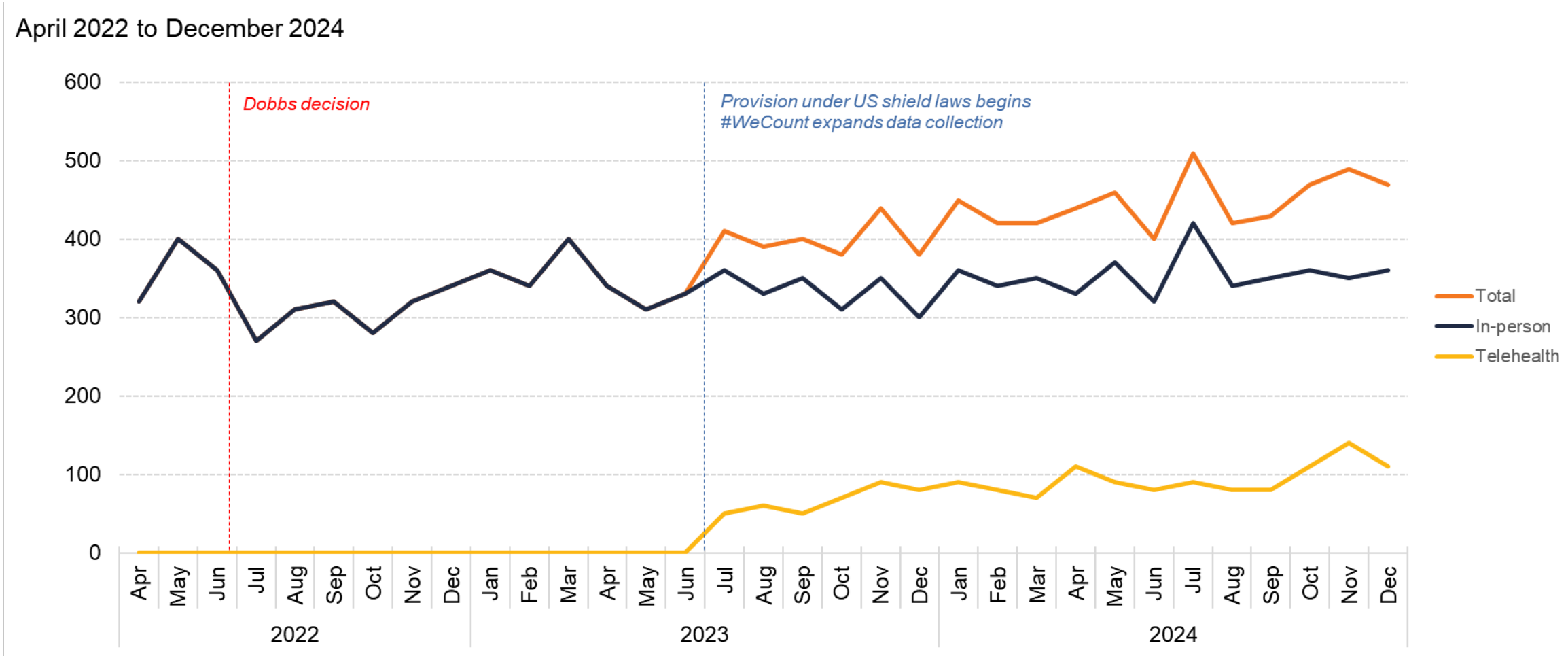
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Texas



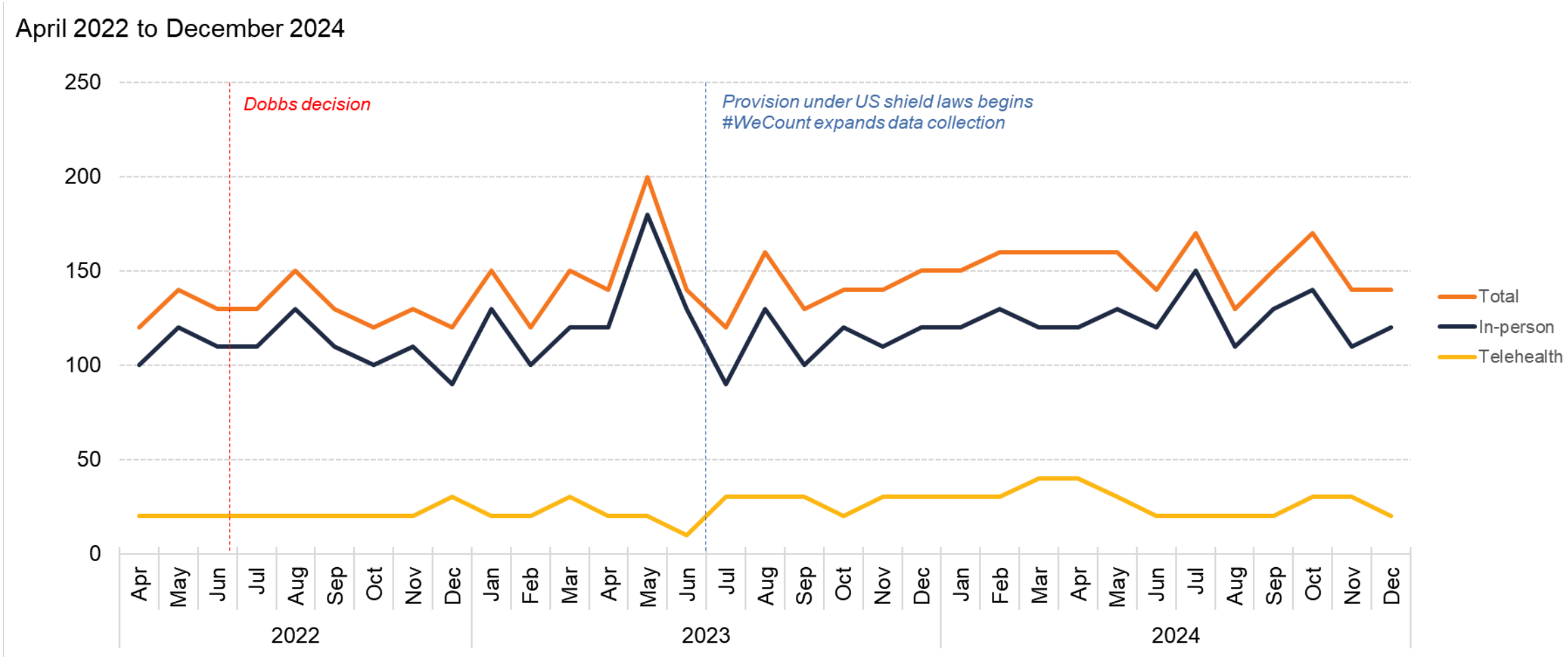
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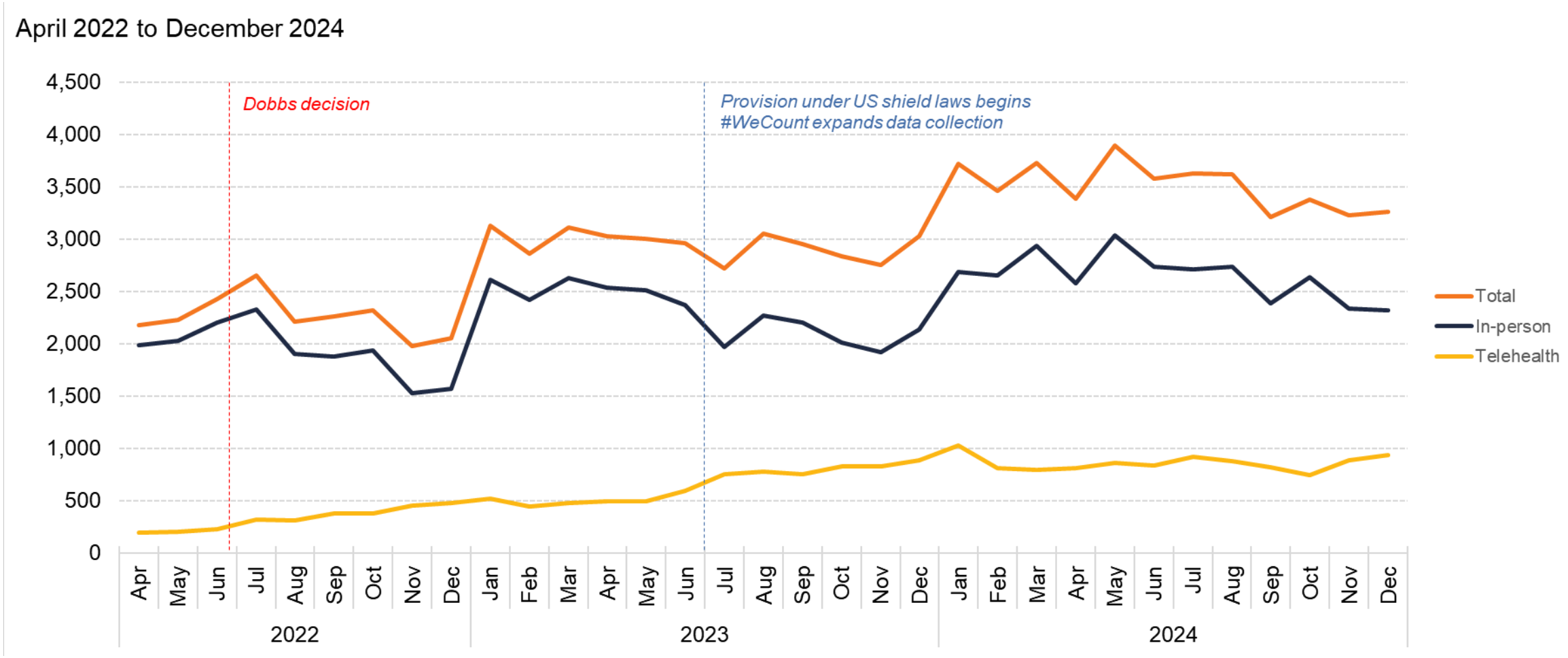
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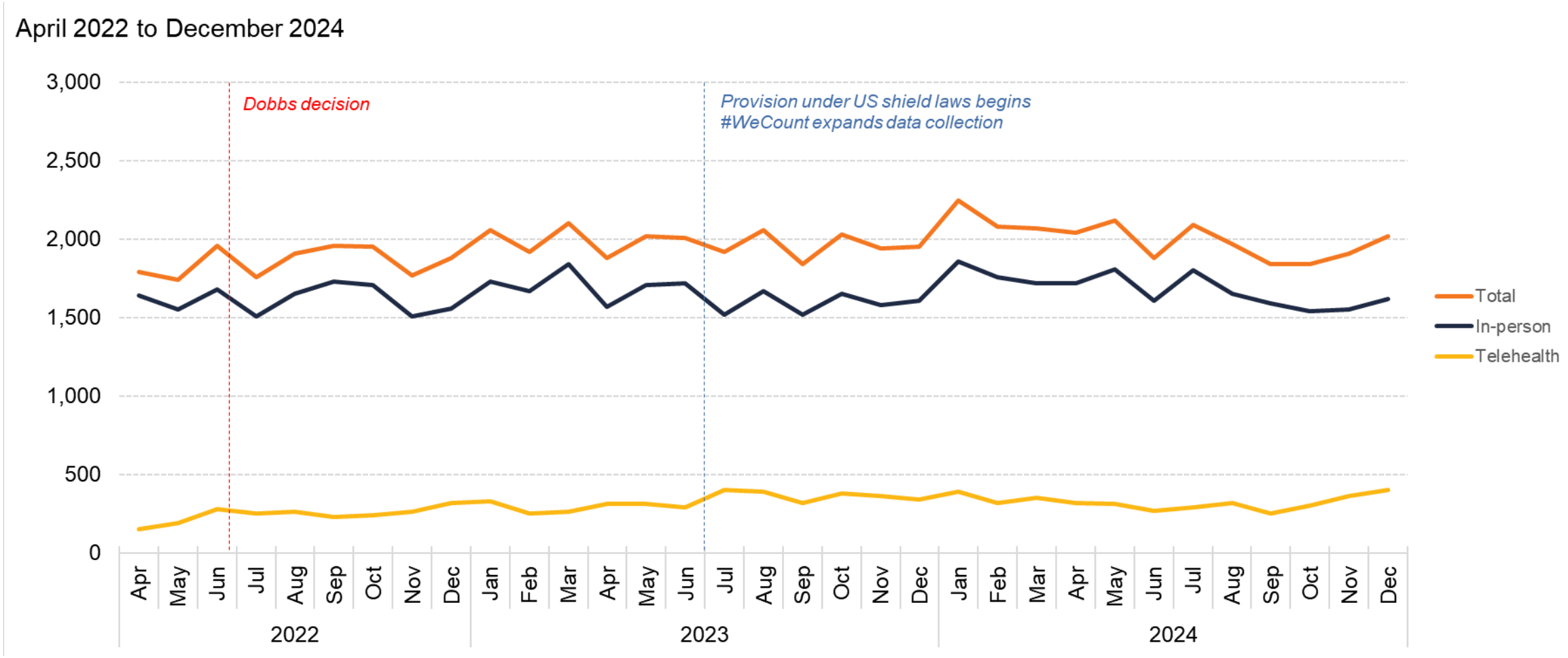
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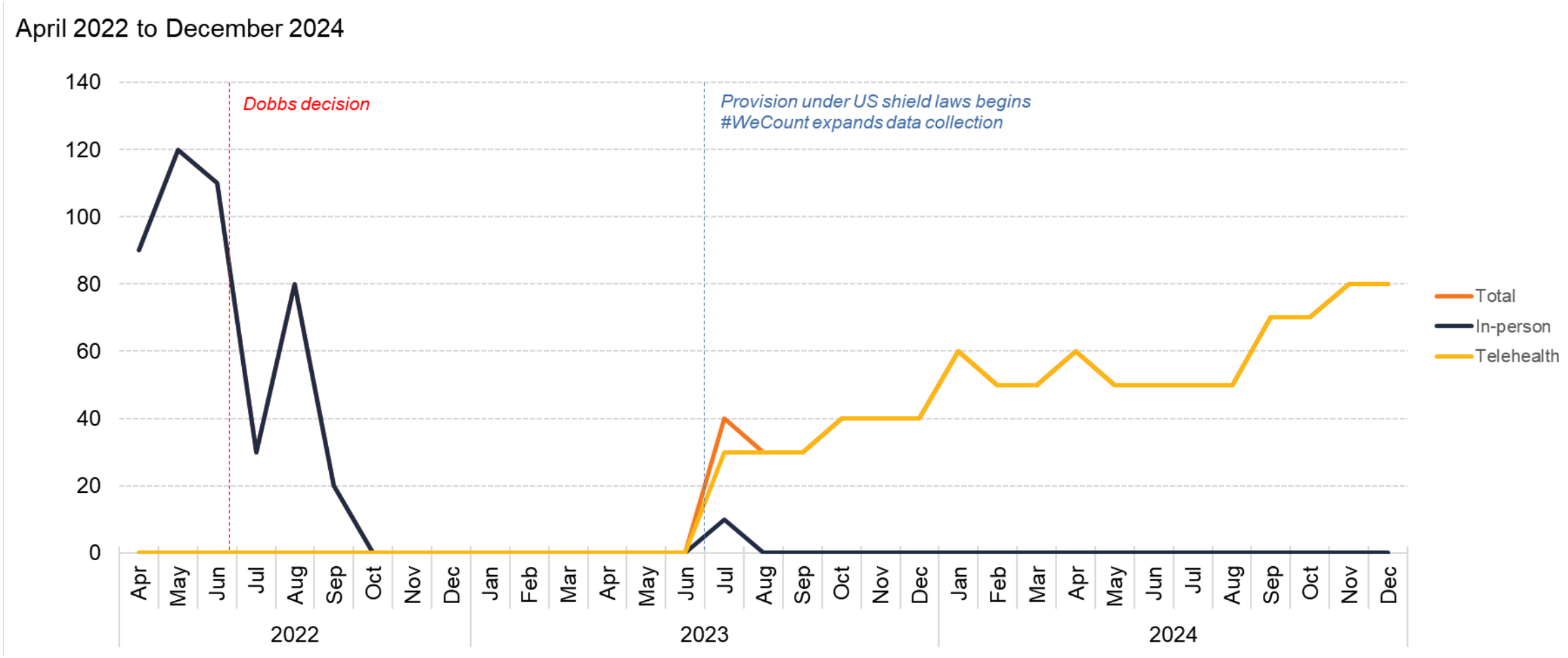
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Washington



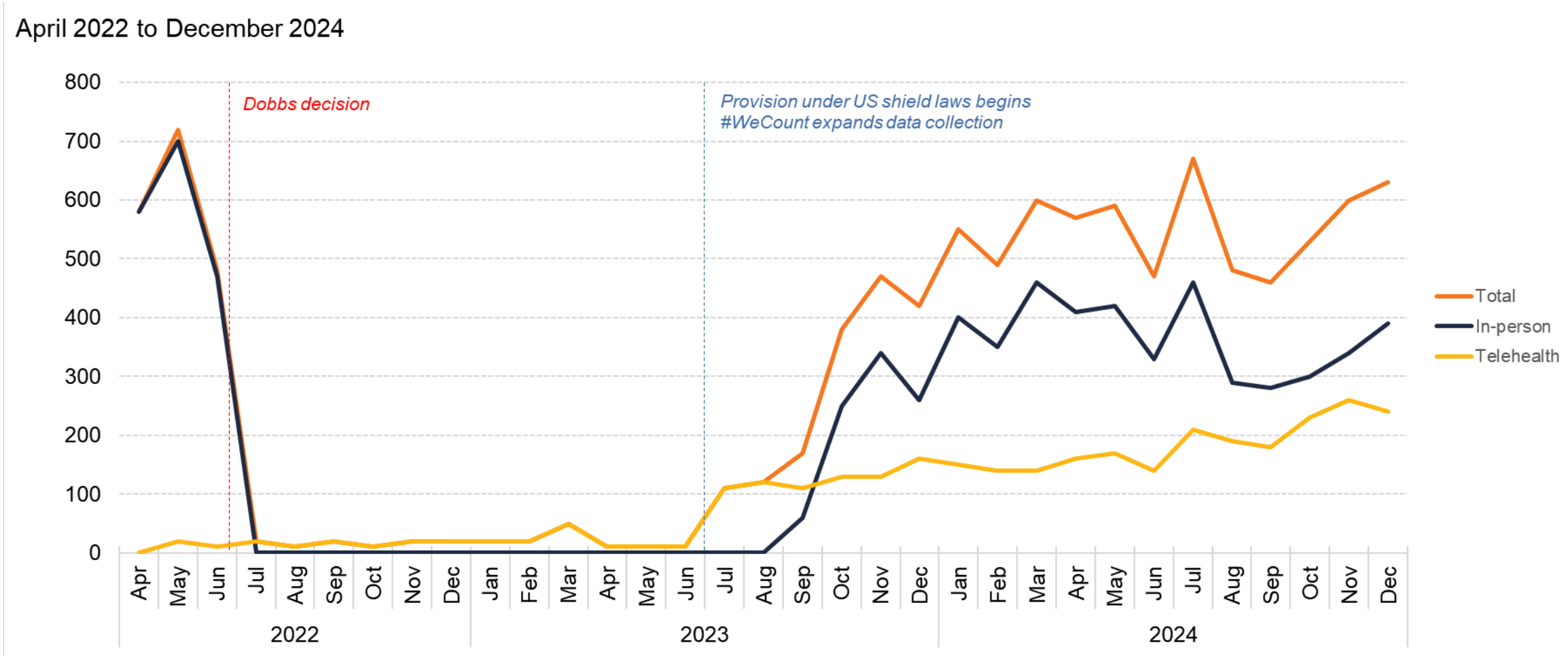
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West Virginia



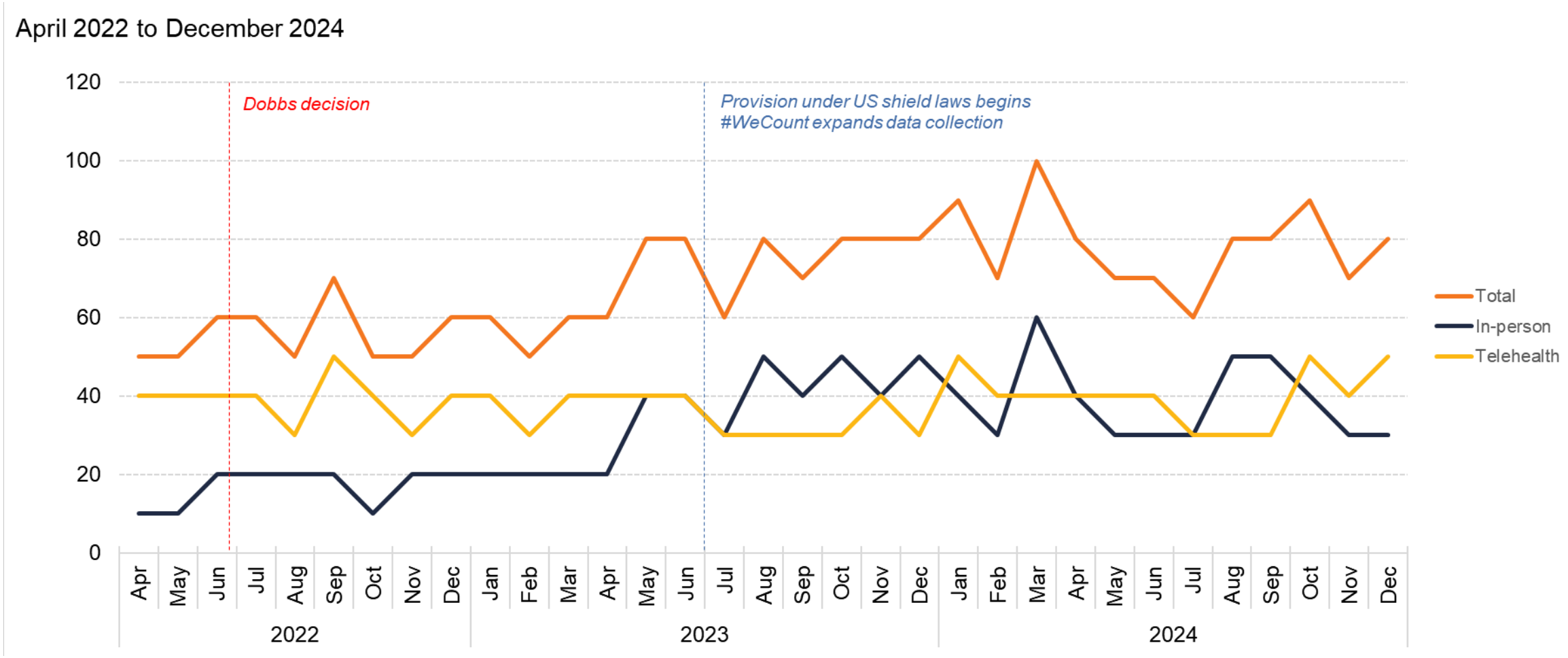
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Wisconsin



Source: Society of Family Planning, June 2025

Wyoming



Source: Society of Family Planning, June 2025

EXHIBIT 3

2021 FDA Letter to ACOG and SMFM
About Mifepristone REMS
(Apr. 12, 2021)



April 12, 2021

Maureen G. Phipps, MD, MPH, FACOG
Chief Executive Officer
American College of Obstetricians and Gynecologists
c/o Rachel Tetlow, Federal Affairs Director
rtetlow@acog.org

Skye Perryman, General Counsel
sperryman@acog.org

William Grobman, MD, MBA
President
Society for Maternal-Fetal Medicine
w-grobman@northwestern.edu

Dear Drs. Phipps and Grobman,

In your letter of April 20, 2020, to former Commissioner Stephen Hahn, you expressed concerns about the in-person dispensing requirements for certain prescription drugs during the current public health emergency. In my letter to you of March 19, 2021, I indicated that staff in the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) were evaluating the issues you raised.

Following up on my March 19, 2021, letter I am writing to report the results of CDER's review and analysis.

CDER conducted a literature search for studies pertinent to the in-person dispensing requirement in the Mifepristone REMS Program during the COVID-19 pandemic. Based on this literature search, CDER identified four publications that included relevant clinical outcome data.[1] CDER

[1] Chong E, et al. Expansion of a Direct-to-Patient Telemedicine Abortion Service in the United States and Experience during the COVID-19 Pandemic. Contraception 2021 (accepted manuscript). https://www.sciencedirect.com/science/article/pii/S0010782421000913; Kerestes C, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. Contraception 2021 (accepted manuscript). https://doi.org/10.1016/j.contraception.2021.03.025; Aiken A et al. Effectiveness, Safety and Acceptability of No-test Medical Abortion Provided Via Telemedicine: a National Cohort Study. British J Obstet Gynecol 2021. https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.16668; Reynolds-Wright JJ et al. Telemedicine medical abortion at home under 12 weeks' gestation: a prospective observational cohort study during the COVID-19 pandemic. BMJ Sex Reprod Health 2021. https://srh.bmj.com/content/early/2021/02/04/bmjsrh-2020-200976

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

found that although there are limitations to the study designs, the overall findings from these studies do not appear to show increases in serious safety concerns (such as hemorrhage, ectopic pregnancy, or surgical interventions) occurring with medical abortion as a result of modifying the in-person dispensing requirement during the COVID-19 pandemic.

CDER also reviewed postmarketing adverse events that reportedly occurred from January 27, 2020 - January 12, 2021, with mifepristone use for medical termination of early pregnancy, along with available information about deviations or noncompliance events associated with the Mifepristone REMS Program.[2] CDER found that the small number of adverse events reported to FDA during the COVID-19 public health emergency (PHE) provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to the reported adverse events.

In summary, provided the other requirements of the Mifepristone REMS Program are met, and given that the in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare personnel because it may involve a clinic visit solely for this purpose, CDER intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form. Further, to the extent all of the other requirements of the Mifepristone REMS Program are met, CDER intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

CDER is communicating this decision to the approved application holders subject to the Mifepristone REMS Program.

Sincerely yours,



Janet Woodcock, M.D.
Acting Commissioner of Food and Drugs

[2] See Mifepristone REMS Program at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390. CDER's analysis covers both products that are subject to the Mifepristone REMS Program (Mifeprex and the approved generic, Mifepristone Tablets, 200 mg).

EXHIBIT 4

Dr. Margaret Carpenter indictment

Clerk of Court Demographic Information Report for

Judicial District:	18th
DA Name:	Tony Clayton
Judge:	
Parish:	West Baton Rouge
Defendant Name:	Dr. Margaret D Carpenter, and Nightingale Medical, PC
DOB:	12/17/1969
Race:	
Sex:	
Date of Arrest:	
Arr. Agency:	Attorney Generals Office
SID:	
US Citizen:	
Drivers License #:	
Drivers License State:	
City:	New Paltz
State:	NY
Deputy Clerk:	Sharon Saul
Minute Clerk:	Kelli Arnold
Charge:	14:87.9.B(1)
Plea:	
Date Filed:	JAN 31 2025
Date Arraigned:	

THE EIGHTEENTH JUDICIAL DISTRICT COURT
FOR THE PARISH OF WEST BATON ROUGE

STATE OF LOUISIANA

STATE OF LOUISIANA

FILED: January 31, 2025
Sharon Paul
Deputy Clerk of Court

VERSUS

DR. MARGARET D. CARPENTER AND NIGHTINGALE MEDICAL, PC
[redacted]

NO. 250187

A TRUE BILL
Foreman
Date: 1-31-2025

BILL OF INDICTMENT

The GRAND JURY OF THE STATE OF LOUISIANA, *duly impaneled sworn and charge in and for the body of the Parish of West Baton Rouge, in the name and by authority of said State, upon their oath, PRESENT: that one DR. MARGARET D. CARPENTER AND NIGHTINGALE MEDICAL, PC, late of the State of New York, County of Ulster, with force and arms, in the Parish of West Baton Rouge, State of Louisiana, aforesaid, and within the jurisdiction of the Eighteenth Judicial District Court in and for the Parish of West Baton Rouge charges that* :

LA R.S. 14:87.9 (A) AND (B)(1) CRIMINAL ABORTION BY MEANS OF ABORTION-INDUCING DRUGS, Dr. Margaret D Carpenter, and Nightingale Medical, PC, on or about April 5, 2024, did knowingly cause an abortion to occur by means of delivering, dispensing, distributing, or providing a pregnant women with an abortion-inducing drug.

Contrary to the law of the State of Louisiana and against the peace and dignity of the same.

TONY CLAYTON
DISTRICT ATTORNEY

BY: Tony Clayton #21191
Assistant District Attorney
Eighteenth Judicial District
State of Louisiana

EXHIBIT 5

Center for Drug Evaluation and Research, Application Number: 20-687 Medical Review(s)
(Jan. 27, 2000)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-687

MEDICAL REVIEW(S)

JAN 27 2000

MEDICAL OFFICER'S REVIEW OF AMENDMENTS 024 AND 033
FINAL REPORTS FOR THE U.S. CLINICAL TRIALS INDUCING ABORTION UP TO 63 DAYS GESTATIONAL AGE AND COMPLETE RESPONSES REGARDING DISTRIBUTION SYSTEM AND PHASE 4 COMMITMENTS

NDA Number: 20-687

Applicant: Population Council
One Dag Hammarskjold Plaza
New York, New York 10017

Dates of Submission: June 3, 1999 and August 18, 1999

Dates Submissions Received: June 4, 1999 and August 19,1999

Date Review Completed: October 28, 1999

Date Review Revised: November 19, 1999

Date Review Finalized: November 22,1999

I. General Information:

A. Name of Drug:
1. Established Name: Mifepristone
2. Trade Name: None designated as yet.

3. Laboratory Code Name: RU 38486 (RU-486).

B. Pharmacologic Category: Antiprogestational and antiglucocorticoid agent.

C. Proposed Indication: Medical termination of intrauterine pregnancy through 49 days' pregnancy.

D. Dosage Form and Route of Administration: Tablet for oral administration.

E. Strength: Each tablet contains 200 mg of mifepristone.

F. Dosage: Three 200 mg tablets (600 mg) of mifepristone are taken as a single oral dose. Unless abortion has occurred, the patient takes two 200 μg tablets (400 μg) of misoprostol orally two days after ingesting mifepristone.

G. Related Drugs: None marketed.

H. Table of Contents:

1. General Information 1
2. Manufacturing Controls Reference 2
3. Pharmacology and Pharmacodynamics Reference 2
4. Clinical Background 2
5. Regulatory Background 3
6. Statistical Consultation Reference 6
7. Clinical Studies 6
8. Reviewer's Comments, Evaluation, and Conclusions 15
9. Labeling Evaluation Reference 20
10. Conclusion 20
11. Recommended Phase 4 Studies 20
12. Consideration of Advisory Committee Member's Comments . . 21
13. Recommendation 29

II. Manufacturing Controls: Please refer to chemist's review for details.

III. Pharmacology and Pharmacodynamics: Please refer to pharmacologist's review for details.

IV. Clinical Background:

Mifepristone is a synthetic steroid that was approved for the termination of pregnancy in France in December 1988 (launched September 1989), in Sweden in 1992, in the United Kingdom in 1991, and in China in 1988. (It should be noted that mifepristone used in China is not manufactured by Roussel Uclaf but by domestic companies). When administered alone in total doses of 1400-1600 mg over 1-10 days, the success rate was 64-85%. Subsequent studies demonstrated that the administration of mifepristone followed by a synthetic prostaglandin analog increases the success rate to over 95%. In a preliminary study of 100 women, the success rate of 600 mg mifepristone and 0.2 mg misoprostol was 95% for pregnancies of no more than 49 days of amenorrhea. Misoprostol is a synthetic prostaglandin E_1 analog

In the misoprostol

Nine phase 2 clinical studies to determine the most effective dose and dosage regimen for mifepristone used alone for the interruption of pregnancy were conducted in France between 1983 and 1986. Patients in these studies were entered with a target gestational age of less than or equal to 41 days of amenorrhea. One thousand patients were exposed to doses ranging from 100 mg for one to four days to 800 mg for one day.

Following completion of the phase 2 studies, nine phase 3 clinical trials employing a single 600 mg dose of mifepristone were conducted to evaluate the efficacy and the

safety of this dose. The target population was patients with pregnancies having a gestational age ≤42 days of amenorrhea. A total of 2,459 patients were studied.

The advantage of combining mifepristone 600 mg with a prostaglandin (sulprostone 250μg I.M. 36-48 hours later) for pregnancy interruption was demonstrated in 1985. A series of ten clinical trials were conducted between 1987 and 1991 to confirm and extend these initial observations. In addition to sulprostone, other prostaglandins including gemeprost, 15MePGF 2a, and prostine E_2 were evaluated. During the ten studies, a total of 19,947 patients were exposed to mifepristone administered as a single 600 mg dose. One of these studies enrolled over 16,000 patients. Very rare cases of hypotension and one myocardial infarction were reported. Successful termination of early pregnancy was achieved in 82.6 to 100% of the patients enrolled in these studies and the safety of mifepristone was confirmed.

The efficacy and safety of mifepristone given as a single 600 mg oral dose in combination with misoprostol 0.4 mg orally administered approximately 36 to 48 hours after mifepristone for termination of pregnancy was evaluated in two historically controlled, pivotal clinical trials conducted in France. The first study included women with intrauterine pregnancies of ≤ 49 days and the second study included women with intrauterine pregnancies of ≤63 days. In the second study, a second dose of 200 μg of misoprostal was given 3 hours after the first dose if complete abortion had not occurred. In the first study of 1205 evaluable patients, the complete abortion rate was 95.4% and in the second study of 1104 evaluable patients, the complete abortion rate was 92.8%. These two studies were evaluated in the review of a new drug application that was submitted March 16, 1996.

V. Regulatory Background:

2 **Page(s) Redacted**

Deliberative Process

VI. Statistical Consultation: None required

VII. Clinical Studies:

The efficacy and safety of mifepristone was evaluated in two prospective, open-label, multicenter clinical trials in the United States according to two identical protocols (166A and 166B) at 17 centers (University hospitals, Planned Parenthood clinics, and free-standing clinics). The studies were conducted at centers that could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures. The studies included patients in three gestational age groups:

Group 1: amenorrhea of ≤49 days
Group 2: amenorrhea of 50-56 days
Group 3: amenorrhea of 57-63 days

Data from the two studies were combined in the following evaluation.

A. Investigators:

Dr. Paul Blumenthal	Baltimore, Maryland
Dr. Lynn Borgatta	White Plains, New York
Dr. Mitchell Crenin	Pittsburgh, Pennsylvania
Dr. Catherine Dean	St. Louis, Missouri
Dr. Susan Haskell	Des Moines, Iowa
Dr. Tyrone Mallory	Atlanta, Georgia
Dr. Daniel Mishell, Jr.	Los Angeles, California
Dr. Mark Nichols	Portland, Oregon
Dr. Alfred Poindexter	Houston, Texas
Dr. Suzanne Poppema	Seattle, Washington

Dr. Eugene Rothenberg	Shrewsbury, New Jersey
Dr. Katherine Sheehan	San Diego, California
Dr. Laszlo Sogor	Cleveland, Ohio
Dr. Judith Tyson	Burlington, Vermont
Dr. Peter Vargas	Aurora, Colorado
Dr. Carolyn Westhoff	New York, New York

B. Objectives of the Study:

The study was conducted to evaluate the effectiveness, safety, acceptability, and feasibility of using mifepristone and misoprotol in a variety of clinical settings within the United States health care system for the induction of abortion in women whose duration of amenorrhea was no more than 63 days.

C. Rationale for the Study:

Extensive experience has been gained outside the United States with the use of mifepristone and various prostaglandin analogs, including misoprostol, for the termination of pregnancies up to 63 days, with complete abortion rates ranging from 92.7% to 99%. The applicant wished to confirm the efficacy and safety of the regimen in the United States.

D. Method of Assignment to Treatment:

Eligible patients fulfilling all of the inclusion criteria and none of the exclusion criteria were assigned to one of the three treatment groups, based on gestational age.

E. Number of Subjects:

A total of 2,121 patients were enrolled including 859 patients in groups 1,722 patients in group 2, and 540 patients in group 3.

F. Duration of Clinical Trial:

Patients were to receive mifepristone on day 1 and misoprostol on day 3 and were to be observed in the clinical setting for at least 4 hours after misoprostol administration. Patients were to return for evaluation on day 15.

G. Inclusion Criteria:

1. Was at least 18 years of age and in good general health.

2. Requested a voluntary termination of pregnancy.

3. Had a positive urine pregnancy test.

4. Had an intrauterine pregnancy with a duration of amenorrhea of ≤63 days (from the first day of her last menstrual period) that was confirmed by uterine size on pelvic examination and by vaginal ultrasound evaluation.

5. Agreed to have a surgical termination of pregnancy if the study procedures failed to terminate her pregnancy.

6. Was a resident of the United States.

7. Gave written informed consent to participate in the study and was willing and able to participate.

H. Exclusion Criteria:

1. Had evidence of any disorder which represented a contraindication to the use of mifepristone (such as adrenal disease or a condition requiring chronic corticosteroid administration) or misoprostol (such as asthma, glaucoma, mitral stenosis, arterial hypotension, sickle cell anemia, or a known allergy to prostaglandins).

2. Had a history of severe liver, respiratory, or renal disease or thromboembolism.

3. Had a cardiovascular disease, e.g. angina, valve disease, arrhythmia, cardiac failure, or insulin dependent diabetes.

4. Had hypertension that was being treated on a chronic basis or had blood pressure of greater than 140/90mmHg.

5. Was anemic (hemoglobin < 10 g/dL or hematocrit < 30%).

6. Had a known clotting defect or was receiving anticoagulants.

7. Had an IUD *in situ*.

8. Was breastfeeding.

9. Had adnexal masses or tenderness on pelvic examination that suggested pelvic inflammatory disease.

10. Had an ectopic pregnancy or threatened abortion.

11. Was over 35 years of age and smoked more than 10 cigarettes per day, and

had another risk factor for cardiovascular disease such as diabetes mellitus, hyperlipidemia, hypertension, or a family history of ischemic heart disease.

12. Was unlikely to understand and comply with the requirements of the study.

13. Lived or worked more than one hour from the emergency care facility that served the abortion center.

I. Trial Period:

September 13, 1994 to September 12, 1995

J. Dosage and Mode of Administration:

Patients were not to eat during the one hour before and after the administration of mifepristone. In the presence of the investigator, each patient was administered three 200 mg mifepristone tablets by mouth with no more than 240 mL of water. Patients were informed that they should not smoke during the 48 hours following mifepristone administration and on the day misoprostol was to be administered. Unless the investigator could verify unequivocally that complete abortion had occurred, patients were administered two 200 μg misoprostol tablets by mouth with no more than 240 mL of water in the presence of the investigator 36 to 60 hours after the administration of mifepristone.

K. Efficacy Assessments:

Pelvic examinations were performed before mifepristone administration at visit 1, before misoprostol administration at visit 2, during the 4 hour observation period after misoprostol administration, and at the visit 3 evaluation. At visit 1, patients also had transvaginal ultrasound examinations and quantitative hCG β subunit pregnancy tests performed. At visits 2 and 3, ultrasound examinations were performed at the discretion of the investigator.

The outcome of treatment was classified as follows:

1. Complete abortion: pregnancy termination and complete expulsion of the products of conception without the need of surgical intervention.

2. Incomplete abortion: pregnancy termination with either partial expulsion or nonexpulsion of the products of conception diagnosed at visit 3 or at study end if later than visit 3 with surgery required.

3. Ongoing pregnancy: a viable pregnancy diagnosed at visit 3 based on fetal heartbeat and/or fetal growth indicating gestations that are

two weeks older than at visit 1; surgery required.

4. Medical intervention: before visit 3, the investigator judged that a surgical intervention was medically indicated.

5. Patient request: before visit 3, the patient chose not to proceed with the medical method of abortion and requested surgical intervention.

In the analyses of treatment outcome, complete abortion only was classified as a treatment success. All other categories resulted in a surgical procedure and , therefore, were classified as treatment failures.

L. Safety Assessments:

Adverse events were summarized and evaluated.

M. Disposition of Patients:

A total of 2121 patients were enrolled. Of these, 2015 (95.0%) were included in the efficacy analyses. There were 106 patients excluded from the efficacy analyses because of failure to show up for visit 3, thus preventing confirmation of a final outcome. For 92 of these patients, there was some information suggesting a successful outcome. For one excluded patient, there was evidence that suggested failure. The remaining 13 women were lost to followup; 5 had continuing pregnancies when last seen at visit 2. All 2121 patients were evaluable for safety. A total of 827 patients in Group 1, 678 patients in Group 2, and 510 patients in Group 3 were included in the efficacy evaluation.

N. Demographic Characteristics:

Most patients were Caucasian (71%), 20-29 years of age (61%; mean age of 26.9 years), of normal body mass index (71%), nulliparous (55%) and had a previous elective abortion (51%). The differences among the three gestational age groups in race distribution and mean age, weight, and body mass index were small and not of clinical significance.

O. Results:

1. Efficacy:

Success and failure rates are summarized in Table 1.

Table 1
(Sponsor's Table 4.1)
Treatment Outcomes by Gestational Age (Evaluable Patients)

Treatment Outcomes	Group 1 ≤ 49 days N = 827	Group 2 50-56 days N = 678	Group 3 57-63 days N = 510
Total Successes	762 (92%)	563 (83%)	395 (77%)
RU-486 alone	40 (5%)	12 (2%)	4 (< 1%)
Plus misoprostol	722 (87%)	551 (81%)	391 (77%)
Total Failures	65 (8%)	115 (17%)	115 (23%)
Med intervention	13 (2%)	26 (4%)	21 (4%)
Patient request	5 (< 1%)	13 (2%)	12 (2%)
Incomplete ab	39 (5%)	51 (8%)	36 (7%)
Ongoing preg	8 (< 1%)	25 (4%)	46 (9%)

Failures are discussed in this review in the "Safety" section of "Results."

Complete abortion rates according to time of occurrence are displayed in Table 2 as confirmed by the investigators.

Table 2
(Sponsor's Table 5.1)
Time to Occurrence of Complete Abortion

Occurrence Time	Group 1 ≤ 49 days N =827	Group 2 50-56 days N=678	Group 3 57-63 days N=510
Mifepristone alone	40 (4.8%)	12 (1.8%)	4 (0.8%)
≤ 4h after misoprostol	376 (45.5%)	312 (46.0%)	178 (34.9%)
> 4h & < end of day 4	178 (21.5%)	118 (17.4%)	118 (23.1%)
After day 4	168 (20.3%)	121 (17.8%)	95 (18.6%)
Surgical intervention	65 (7.9%)	115 (17.0%)	115 (22.5%)

2. Safety:

Adverse events, regardless of causality, were reported for at least 99% of the patients in each gestational age group. More than one adverse event was reported for most patients. The majority of adverse events were of mild or moderate severity. Approximately 23% of the adverse events in each gestational age group were judged to be severe. The most common adverse event was abdominal pain, including uterine cramping. This was to be expected since the treatment procedure is designed to induce the uterine cramping (and bleeding) necessary to produce an abortion.

Other commonly reported adverse events were nausea, vomiting, headache, diarrhea, and dizziness. No serious adverse events were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. Table 3 shows that the rates of most, but not all, adverse events that occurred in patients whose gestational age was ≤ 49 days were not significantly different from the rates across all gestational age groups.

Table 3

Most Commonly Reported Adverse Events

Adverse Event	Group 1 ≤ 49 days N=859 Percentage	Groups 1, 2, and 3 ≤ 63 days N=2121 Percentage
Abdominal pain (cramping)	96	97
Nausea	61	67
Headache	31	32
Vomiting	26	34
Diarrhea	20	23
Dizziness	12	12
Fatigue	10	9
Back pain	9	9
Uterine hemorrhage	5	7
Fever	4	4
Viral infections	4	4
Vaginitis	3	4
Rigors (chills/shaking)	3	3
Dyspepsia	3	3
Insomnia	3	2
Asthenia	2	2
Leg pain	2	2
Anxiety	2	2
Anemia	2	2
Leukorrhea	2	2
Sinusitis	2	2
Syncope	1	2

Table 4 shows the rates of adverse events in any gestational age group which were significantly different across gestational age groups.

Table 4
Adverse Events Significantly Different Across Gestational Age Groups

Adverse Event	Group 1 ≤ 49 days Percentage	Group 2 50-56 days Percentage	Group 3 57-63 days Percentage
Nausea	61	71	72
Vomiting	26	38	41
Diarrhea	20	23	26
Uterine hemorrhage	5	8	10

No patient was discontinued from the study because of an adverse event and there were no deaths.

The median bleeding duration for group 1 was 14 days and 15 days for groups 2 and 3.

The proportions of patients who received any medications for bleeding increased with increasing gestational age form 5.7% in group 1 to 10.7% in group 3. A total of 146 patients (6.9%) received uterotonics (ergot-type medications or oxytocin) for bleeding.

Fourteen patients (0.7%) were hospitalized for an adverse event. Of these patients, 2 of 4 in the ≤ 49 days group, 3 of 5 in the 50-56 days group, and 3 of 5 in the 56-63 days group had adverse events (severe excessive bleeding) which were considered to be study drug related. The other patients were hospitalized for reasons unrelated to study treatment (pneumonia, meningitis, automobile accident, depression, shooting injury, endometritis).

Nineteen patients (0.9%) had emergency room visits that did not result in hospitalization. Sixteen of these 19 patients had excessive bleeding (2, ≤ 49 days; 7, 50-56 days; 7, 57-63 days). The other three visits were for chest pain, nausea and vomiting, and cramping.

Four patients received blood transfusions (1, ≤ 49 days; 2, 50-56 days; 1, 57-63 days). Three of these patients were hospitalized.

IV fluids were administered for various reasons to 9 (1.0%) patients in the ≤ 49 days group, 19 (2.6%) in the 50-56 days group, and 18 (3.3%) in the 57-63 days group.

The following five potentially serious adverse events occurred:

A 34 year old patient with a 20 year history of seizures and a pregnancy of

46 days gestational age had a mild seizure (convulsion) on the day of mifepristone administration and received 250 mg of dilantin. In the opinion of the investigator, the patient's seizure was not related to treatment with mifepristone and she received misoprostol 47 hours after the mifepristone.

A 28 year old of 54 days gestational age with a negative gastrointestinal history reported possible blood in her stool a month after misoprostol administration. In the opinion of the investigator, the patient's melena was not related to study treatment.

A 23 year old of 57 days gestational age developed moderate purpura (body bruises) that lasted for one day without treatment ten days after receiving misoprostol. In the opinion of the investigator, the patient's purpura was not related to study treatment.

A 21 year old of 57 days gestational age developed severe viral meningitis 6 days after receiving misoprostol and was hospitalized. In the opinion of the investigator, the patient's meningitis was not related to study treatment.

A 27 year old of 60 days gestational age with a negative gastrointestinal history reported blood in her stool 3 days after receiving misoprostol. At the time of last contact with the patient three weeks later, no further incidents of melena had been reported. In the opinion of the investigator, the patient's melena was not related to study treatment.

The proportions of patients with a decrease in hemoglobin or hematocrit of more than 20% from their pre-mifepristone administration levels increased significantly with increasing gestational age, from 3.1% in the ≤ 49 days group to 8.0% in the 57-63 days group.

Of the 1028 patients with hemoglobin measurements before and after misoprostol administration, 131 had a decrease of at least 2mg/dL (7.8%, ≤49 days; 15.0%, 50-60 days; 17.4% 57-63 days).

Hypotension after administration of misoprostol occurred in 0.3% - 1.4% of all treated patients.

Hypertension after administration of misoprostol occurred in 1.5% - 1.7% of all treated patients.

Decrease in heart rate by > 20% after administration of misoprostol occurred in 18.2% - 21.3% of all patients.

Increase in heart rate by >20% after administration of misoprostol occurred in 11.8% - 14.1% of all patients.

For the subgroup of patients with a full panel of laboratory tests, the median changes were small and not of clinical significance.

Failure of the mifepristone - misoprostol procedure required surgical intervention which is an additional safety concern, albeit small. A total of 295 patients were classified as having failed medical abortion. Of these patients, 79 (27%) had ongoing pregnancies, 126 (43%) had incomplete abortions, 30 (10%) requested and had surgical terminations, and the remaining 60 (20%) patients had surgical terminations performed because of medical indications directly related to the medical procedure. In group 1 (≤ 49 days gestation), of the 65 failures, 8 (12%) patients had ongoing pregnancies, 39 (60%) patients had incomplete abortions, 5 (8%) requested and had surgical terminations performed, and the remaining 13 (20%) patients had surgical terminations directly related to the medical procedure. The failure rates for medical intervention, patient request, incomplete abortion, and ongoing pregnancy were significantly higher in groups 2 and 3 than in group 1.

For each gestational age group, the adverse event rates were highest at Planned Parenthood clinics and lowest at Free-Standing clinics, with university hospital clinics in the middle.

VIII. Reviewer's Comments, Evaluation, and Conclusions:

Two studies were conducted according to two identical protocols at 17 centers to evaluate a mifepristone - misoprostol regimen for the termination of pregnancies in the United States health care system. The studies included patients in three gestational age groups:

Group 1: amenorrhea of ≤ 49 days
Group 2: amenorrhea of 50-56 days
Group 3: amenorrhea of 57-63 days

The studies included women who requested a voluntary termination of pregnancy, had a positive pregnancy test, and a documented intrauterine pregnancy. Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more than ten cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had intrauterine devices, were breast-feeding, were receiving anticoagulation or long-term glucocorticoid therapy, had adrenal masses, had

ectopic pregnancies, or had signs or symptoms suggesting that they might abort spontaneously. All the women agreed to undergo surgical termination of pregnancy if the medical method failed. A total of 2,121 women were enrolled in the two studies including 859 women who were in the ≤ 49 days group, which is the gestational age which is the subject of this application.

Pregnancy was measured from the first day of the last menstrual period according to menstrual history, pelvic examination, and vaginal ultrasonography and women were assigned to the appropriate gestational age group.

Three clinic visits were scheduled. At visit 1 (day 1), the women were assessed clinically and took three 200 mg tablets of mifepristone orally in the presence of the investigator. Patients did not eat for one hour before and after the consumption of the mifepristone. At visit 2 (day 3), they took 400 μg of misoprostol orally unless a complete abortion had already occurred. Patients did not smoke during the 48 hours following mifepristone consumption and on the day misoprostol was administered. Patients then remained at the clinics under observation for at least four hours. Adverse events such as nausea, vomiting, diarrhea, abdominal pain, and vaginal bleeding were rated by the women and recorded. Blood pressure and heart rate were measured at least hourly. Vaginal bleeding was recorded on a diary card and rated by each woman on days 1 through 15 as "spotting", "normal", or "heavy." During this period, the women were also monitored for the expulsion of the conceptus. At visit 3 (day 15), the treatment outcome was assessed.

Efficacy was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure. The need for a vacuum aspiration or dilatation and curettage constituted a failure. A surgical procedure was performed at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion.

A total of 106 women were excluded from the efficacy analysis because they did not return for visit 3. Evidence suggesting a successful outcome was available for 92 of these women, and evidence of failure for 1. The remaining 13 women were lost to followup; 5 had continuing pregnancies when last seen at visit 2. The efficacy analysis, therefore, included 2015 women. No additional information is available on the outcomes of the 5 women with continuing pregnancies who were lost to followup. All other women with continuing pregnancies were aborted surgically.

Efficacy was 92% in the ≤ 49 days group with a lower 95% confidence interval of 90%. This is somewhat less than the 95.5% efficacy with a lower 95% C.I. of 94.2% reported in the pivotal French studies upon which approval of this application was recommended.

Efficacy was 83% in the 50-56 days group with a lower 95% confidence interval of 80%. Efficacy was 77% in the 57-63 days group with a lower 95% confidence interval of 74%.

The 92% success rate in the ≤ 49 days group is an acceptable one.

The median duration of bleeding in the ≤ 49 days group was 14 days. The average duration of bleeding was 16 days. This is considerably longer than the average duration of 9 days reported in the French studies upon which approval of this application was recommended, but is an acceptable duration.

Excessive bleeding necessitated blood transfusion in only 1 patient in the ≤ 49 days group and required hospitalization of only 2 patients in the ≤ 49 days group. An additional 2 patients in the ≤ 49 days group were treated in the emergency room for excessive bleeding. Thirteen (2%) patients in the ≤ 49 days group required surgical intervention because of excessive bleeding. Bleeding was managed by the administration of uterotonic agents such as oxytocin, methylergonovine or vasopressin in 5% of patients in the≤ 49 days group.

The adverse event rates were higher in these studies than those in the pivotal French studies upon which approval of this application was recommended. This is shown in Table 5.

Table 5

Frequent Adverse Events (≤ 49 days) in French and U.S. Trials

Adverse Event	French Trials	U.S. Trials
Abdominal pain (cramping)	83%	96%
Nausea	43%	61%
Headache	2%	31%
Vomiting	18%	26%
Diarrhea	12%	20%
Dizziness	1%	12%

The majority of adverse events were of mild or moderate severity. The difference in the frequency of common adverse events noted above is acceptable.

In the pivotal French trials, 5.5% of subjects had a decrease in hemoglobin of greater than 2g/dL while in the U.S. trials, 7.8 % of patients in the ≤ 49 days group had such a decrease. This difference is an acceptable one.

The U.S. clinical trials confirmed the findings of the pivotal French trials that mifepristone and misoprostol are safe and effective in terminating pregnancies of up to 49 days gestation even though the success rate in the U.S. trials was lower

than that of the French trials. This lower success rate might be related to the lack of experience of most of the U.S. investigators with medical abortion. The lower success rate might also be attributable somewhat to the fact that in the U.S. trials, a woman's request for a surgical termination any time after receiving mifepristone was honored and classified as a failure rather than being excluded form the efficacy analysis. However, in the ≤ 49 days group, less than 8% of the failures (5 patients) were because of patient requests.

The success of medical termination of pregnancy decreased with advancing gestational age and the incidence of adverse events increased with advancing gestational age. The majority of surgical interventions were for incomplete abortion and excessive bleeding.

This method of pregnancy termination is of limited value because of the relatively short window of opportunity, in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.

Another disadvantage of this method of pregnancy termination is the need for at least three visits to the medical facility including at least a four hours stay after the administration of the misoprostol.

In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects).

In the U.S. clinical trials, an increase in the incidence of some adverse events (vomiting, nausea, diarrhea, uterine hemorrhage) occurred in the 50-56 and 57-63 days gestational age groups compared to the ≤ 49 days group. The safety profile of the ≤ 49 days group in the U.S. study did not differ significantly from the pivotal French studies, even though the incidence of common adverse events in the U.S. clinical trials was higher than that of the French trials in the ≤ 49 days group. The percentage of patients in the U.S. studies and the French studies requiring hospitalization, requiring blood transfusion and experiencing heavy bleeding was about the same. However, about 1.6% of the patients in the ≤ 49 days group in the U.S. study had surgical intervention because of heavy bleeding compared to less than 1% of patients in the French studies. The average duration of bleeding was 16 days in the U.S. studies compared to 9 days in the French studies.

While the U.S. clinical trials confirm the safety and efficacy of mifepristone and misoprostol found in the pivotal French studies for women seeking medical

abortions with gestations of 49 days duration or less, they demonstrate that with longer durations of gestation (50-56 days and 57-63 days), the treatment regimen is less effective and the incidence of adverse events is higher.

A comparison of medical termination of pregnancy with surgical termination is of interest in a polulation of women who are given a choice to select between medical and surgical termination of early pregnancy. Such a comparative clinical trial was conducted according to a uniform protocol from 1991 to 1993 in urban clinics in China, Cuba, and India, three countries where abortion is legal and available. A total of 1373 women with amenorrhea ≤ 56 days were given a choice of surgical abortion or mifepristone and misoprostol in the same dosage regimen as used in the U.S. studies. The results of this study were published in 1997. The medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion (8.6% versus 0.4% in China, 16.0% versus 4.0% in Cuba, and 5.2% versus 0% in India). In each site failure rates of medical abortion increased with gestational age. Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients. The only serious complication was excessive bleeding in medical abortion patients, which is a reason for surgical intervention and for dissatisfaction among medical abortion patients. Three patients (all medical abortions) received blood transfusions. This is a serious potential disadvantage of the medical method. On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients. Slightly higher proportions of medical than surgical patients were dissatisfied (8.8% versus 3.8%). Despite the bleeding pattern and the failure rate of the medical abortion method, particularly in China, medical abortion by the mifepristone and misoprostol regimen was said by the authors of this published study to be safe, efficacious, and highly desired by and acceptable to women in developing countries.

The results of a smaller study published in 1999 comparing mifepristone to surgical abortion in U.S. women are consistent with the findings of the larger comparative clinical trial done in China, Cuba, and India. The study was a nonconcurrent, prospective, cohort analysis of 178 mifepristone - misoprostol and 199 suction curettage abortion subjects with intrauterine pregnancies ≤ 63 days gestational age. The medical abortion cohort represents all of the subjects enrolled at one U.S. clinical site for the mifepristone clinical trial between December, 1994 and August, 1995. The surgical abortion cohort was enrolled prospectively at the same clinical site between November, 1995 and December, 1996. Overall, 18.3% of medical and 4.7% surgical patients failed their primary procedure and received an unanticipated suction curettage (R.R. 3.93; 95% CI 1.87,8.29). The risk of failure demonstrated a statistically significant upward trend from 3.3 to 4.4 with advancing gestational age. Four mifepristone patients required curettage for acute bleeding while no surgical patients did. Nine

mifepristone patients required curettage to manage ongoing pregnancy while no surgical patients did. Five mifepristone patients required suction curettage because of incomplete abortion while no surgical patients did. Fourteen mifepristone and eight surgical patients required suction curettage for persistent bleeding. The median time delay for therapeutic curettage was significantly longer in the mifepristone group than in the surgical group (35 days versus 8 days). Mifepristone patients experienced significantly longer postprocedure bleeding than did surgical patients. The mean difference in bleeding days between cohorts was 9.6 days (95% CI, 6.8, 12.4). Mifepristone patients reported significantly longer bleeding in all three gestational age groups. Overall, mifepristone abortion patients reported significantly higher levels of pain, nausea, vomiting, and diarrhea during the actual abortion than did surgical patients. The use of antiemetic agents during the abortion procedure was significantly more common in mifepristone patients than surgical patients (31.1% versus 1%). Mifepristone patients were routinely offered oral narcotics for expulsion-related pain, and 78.5% used them. Mifepristone patients reported more problems during the follow-up interval than did surgical patients. Post-abortion pain occurred in 77.1% of mifepristone patients compared with only 10.5% of surgical patients (RR 7.4, 95% CI 4.7, 11.5). Nausea or vomiting in the follow-up interval was common in the mifepristone group (68.6%), but rare among surgical patients (0.6%) (RR 117.9, 95% CI 16.7, 834.7).

Although the mifepristone and surgical abortion techniques are both safe and effective, the abortion and post-abortion experiences differ significantly as reported in the two published studies above that permit direct comparison of the two techniques in a prospective manner.

IX. Labeling Evaluation:

Comments regarding labeling revisions were transmitted to the sponsor in a letter dated September 18, 1996. Revised draft labeling was submitted by the sponsor June 25, 1999 and currently is under review.

X. Conclusion:

The results of the U.S. studies do not adversely differ significantly from the results of the two pivotal French clinical trials which were the basis for the approvable letter to the sponsor September 18, 1996.

XI. Recommended Phase 4 Studies:

The medical officer, in his revised original NDA review, recommended that phase 4 studies with the following objectives be conducted:

A. To monitor the adequacy of the distribution and credentialing

system.

B. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

C. To assess the long-term effects of multiple use of the regimen.

D. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

E. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.

F. To ascertain the effect of the regimen on children born after treatment failure.

The phase 4 recommendations were included in the approvable letter to the sponsor dated September 18, 1999.

XII. Consideration of Advisory Committee Members' Comments:

Part of the review process for this application included seeking expert advice from members of the FDA Reproductive Health Drugs Advisory Committee at a public meeting July 19, 1996. The committee voted 6-0 (with two abstentions) that the pivotal studies (French studies) presented at that time showed that the benefits of a mifepristone and misoprostol regimen for terminating early pregnancies outweighed its risks. The studies presented to the committee involved women treated within 49 days of the beginning of their last menstrual period.

Preliminary safety data from recently completed U.S. trials were also presented.

The committee recommended some phase 4 studies and individual committee members offered some individual comments for consideration by the FDA staff, particularly comments regarding labeling and the drug distribution system. All comments were carefully and fully considered and, to the extent possible, implemented.

The applicant was asked September 18, 1996 to submit a comprehensive description of the proposed distribution system. The following complete response from the applicant was submitted to FDA August 18, 1999 regarding the distribution system:

"The details of the distribution system for the product are in the process of being worked out with the proposed distributor. However, the following key principles will be adhered to in the final distribution arrangements:

- Product will only be available from one or two distributors nationwide and not through retail pharmacies or direct to physicians from the manufacturer.
- Each physician interested in obtaining the product must request the product from the distributors, register with them and open an account.
- Access to the distributors will be through the distributors' general order system and through a specially established toll free telephone number with product ordering as an option.
- Aside from standard credit checks run by the distributors to open a new account, each requesting physician will be required to register by providing their BNDD # and their state Medical License #, and signing a letter that they have the following:
  - The ability to accurately confirm the duration of pregnancy
  - The ability to determine blood Rh factor
  - Access to medical facilities equipped to provide emergency care should that become necessary.

In this same letter they will also be asked to indicate their agreement to:

- Obtain signed acknowledgment from the patient that they have been provided with the product label, that they have read and understood the patient information, have had the procedure, its risks and benefits explained to them, and that they agree to follow the treatment procedure.
- Place the dose # on the acknowlegement and in the patient record.
- Maintain complete records for each patient including blood tests, ultrasound examinations and progress noted.
- Fill out and return AE (Adverse Event) cards to the distributor, identifying patient by dose # only.
- Use every effort to ensure patients return for their follow up visit 14-20 days after taking the product.

- Provide the distributor with as much information as possible if there is an ongoing pregnancy following completion of the treatment procedure and this pregnancy is not terminated.

In addition, the toll free telephone number will enable providers to request training materials and information, and speak to an experienced medical consultant about either a non-emergency patient issue or an urgent medical problem or possible complication. Through a separate routing on the toll free telephone number, patients will have access to general information about the product, a provider location near them and web page addresses for more information.

The final distribution system will be more fully developed in the next few months but will always attempt to insure that the drug is only supplied to qualified physician/hospitals who register with the distributor, that the patient is given access to the product label and that the product # is placed on the acknowledgment in the patient's file and that the anonymity of the patient is maintained.

Market launch will not occur until the distribution system is finalized and there are adequate systems in place to track shipment and use."

FDA requested six phase 4 studies of the applicant's August 22, 1996 (and reminded them of their commitment to perform them in the approvable letter dated September 18, 1996). The requested studies are listed below:

1. To monitor the adequacy of the distribution and credentialing system.

2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

3. To assess the long-term effects of multiple use of the regimen.

4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.

6. To ascertain the effect of the regimen on children born after treatment failure.

The applicant's complete response was submitted to FDA August 18, 1999 regarding the requested phase 4 studies as follows:
"We are mindful of our Phase 4 commitments as outlined in the Population Council's letter to FDA dated September 16, 1996. We plan to discuss in more detail and develop a consensus with the FDA post-NDA approval.

1. The Council recognizes the need for additional information about our proposed distribution and credentialing system and the necessity for making certain that it is designed to result in safe and efficacious abortions for women and in properly controlled access to the product. We will provide the FDA with a detailed product distribution and provider credentialing plan that describes our own monitoring indicators, and we would welcome additional discussion with the Agency at that time. We intend to monitor the distribution and credentialing system but we do not believe that the frequency of post-surgical complications will necessarily be a meaningful indicator of its effectiveness.

2. Although the Council cannot commit to a study that follows all women who have surgical abortions following failed mifepristone abortion, we would propose to investigate treatment failures among a representative sample of providers for a mutually agreeable period of time, for instance six months or one year. In such an investigation, we would classify women undergoing medical abortion according to whether they 1) completed their abortions successfully; 2) had a failed medical abortion and required a surgical abortion; 3) required surgical intervention for other reasons; or 4) were lost to follow-up.

   We are not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing this, as it could violate women's privacy.

3. A prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome, might result in an invasion of women's privacy and would not likely produce a meaningful scientific result for decades. However, the Council has been informed that central registries of mifeprostone users exist in Europe. We will examine these data sources to determine what can be learned about multiple use. In addition, in future studies of the regimen carried out by the Council in the U.S., we will attempt to develop a cohort of women who report more than one use of the regimen and agree to be followed.

4. We are willing to supply treatment failure data from a sample of providers for a mutually agreeable period to time, for instance six months or one

year, bearing in mind that such data will not include women lost to follow-up.

5. The Council agrees that it is desirable to have additional information on users of the regimen who are under age 18, or over age 35 or who are smokers. From the French and United States clinical trials, we do have some data on women who were more than 35 years old and on women who smoked. The French trials also included some subjects who were under age 18 years of age. We will submit an analysis of our safety and efficacy data on these subgroups. In addition, data on women under 18 or over 35 years of age and those who smoke will be collected in the sample of women we have agreed to study, as described in item Number 2 and 4 above.

6. Since live births are extraordinarily rare as outcomes of treatment with mifepristone (e.g. approximately 19 out of more than 250,000 in the French database) this issue is best approached by reporting through providers who utilize the regimen. We will instruct our distributor to include materials for providers that ask them to report to the distributor any treatment failure in which the woman decides to continue her pregnancy. The provider will ascertain which of these women agree to be followed to document the health of any children born of such pregnancies. In addition, any spontaneous reports of live births of children exposed to mifepristone *in utero* will be investigated."

Other issues raised by individual advisory committee members are addressed below:

While the DOSAGE AND ADMINISTRATION section of the labeling states that mifepristone may be administered by or under the supervision of a physician trained in abortion, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies, and with access to emergency medical facilities, the applicant has not mentioned anything about conducting training seminars for use of mifepristone, without financial incentive to physicians, and distributing the drug only to those physicians who completed the training. Perhaps the applicant will address this point when the details of the distribution system are submitted to FDA.

The applicant should be able to assess compliance with return visits of patients in the phase 4 studies to be performed.

A surgical termination, if needed, should be provided at no additional cost to the patient. It should be part of the mifepristone-misoprostol method of abortion.

Reasonable attempts to contact patients who do not return to confirm the abortion should be made by the physician.

The applicant intends to monitor the distribution system to ensure that only qualified physicians are treating patients.

The applicant will monitor the number of failed medical terminations and any resulting surgical complication.

The applicant will examine central registries of mifepristone users in Europe to determine what can be learned about multiple use. In addition, the applicant proposes to attempt to develop a cohort of women in future studies in the United States who report more than one use of the regimen and agree to be followed.

The applicant has some data on women who were more than 35 years of age, on women who smoked, and on women under 18 years of age. They will submit an analysis of safety and efficacy data on these subgroups. In addition, data on these subgroups will be collected during the phase 4 studies.

The outcomes of pregnancies not terminated by medical or surgical abortion should be followed up and reported by the physician. This should be part of the credentialing and distribution system.

Conditions of exclusions in the clinical trials are in the labeling.

There is no age restriction in the labeling. Women under 18 years of age or over 35 years of age were arbitrarily excluded from the clinical trials, but there is no biologic reason to think that the efficacy and safety of drug administration to these age groups is any different from that of women 18-35 years of age.

The labeling states that misoprostol should be taken two days after ingesting mifepristone.

Women who smoked at least 10 cigarettes per day were excluded from the French studies. Women in the French studies were informed that they should neither smoke nor drink alcohol during the 48 hours following mifepristone administration and on the day misoprostol was to be administered.

Women in the U.S. studies were informed that they should not smoke during the 48 hours following mifepristone administration and on the day misoprostol was to be administered. Women were excluded from the U.S.

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studies if they were over 35 years of age, smoked more than 10 cigarettes per day, and had another risk factor for cardiovascular disease. The labeling contains a cautionary statement that women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone. The labeling does not contain a statement that alcohol and/or tobacco should be avoided during treatment. Myocardial infarction has been associated with the administration of an intramuscularly administered prostaglandin, sulprostone, but no such association has been reported with the administration of misoprostol. The labeling for misoprostol does not contain any statement regarding avoiding smoking.

Several comments regarding labeling were made by individual advisory committee members and have been throughly considered.

Overall, I do not think that the labeling imparts an impression to the physician or patient that the treatment regimen is "free of adverse effects and free of actually serious side effects."

The use of mifepristone and misoprostol extends the options available to women for the elective termination of early pregnancy, but it is inappropriate to directly compare this regimen with surgical termination in terms of adverse events. For example, bleeding and cramping are to be expected with mifepristone and misoprostol and not generally expected with surgical termination. The two methods are usually appropriate for abortion at different gestational ages. Medical abortions are done usually during the fifth to seventh weeks of gestation. Surgical terminations are usually not done before the sixth week of gestation.

Reference to drugs known to cause enzyme induction has been deleted.

The risk of malformation occurring if pregnancy is not terminated after drug administration appears in table 2 of the labeling.

The labeling states that a surgical termination must be recommended for patients who have an ongoing pregnancy because of the risk of fetal malformation resulting from the treatment procedure.

The physician labeling mentions that although specific drug interactions have not been studied, it is possible that interactions could occur with drugs like aspirin or other non-steroidal anti-inflammatory agents that modify or inhibit prostaglandin synthesis and metabolism. The only available study, however, found no evidence that non-steroidal antinflamatory drugs inhibit the ability of misoprostol to induce uterine

contractions and expulsions. In the patient labeling, the patient is instructed to advise her medical provider of all the medications she is taking and not to take any of them or any other medications during the treatment procedure without first telling her medical provider.

The mifepristone labeling states that since the effects of mifepristone on infants are unknown, and it is not known if misoprostol or its active metabolite is excreted in human milk, breast feeding women should consult with their medical provider to decide if they should discard their breastmilk for a few days following administration of the medications.

The labeling for misoprostol states that it is not known if the active metabolite (misoprostol acid) is excreted in human milk, and therefore, misoprostol should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants.

Two days is the optimal time to administer misoprostol after the administration of mifepristone because mifepristone requires 36-48 hours to sensitize the uterine muscle to prostaglandins. This information could be added to the labeling.

We do not know if, or to what extent, effectiveness decreases if administration of misoprostol is delayed past two days after the administration of mifepristone. We do know that administration of misoprostol 36-48 hours after the administration of mifepristone is well founded, based on the mechanism of action. The labeling does state that misoprostol should be administered two days after administration of the mifepristone.

Most of the data available are from women 18 years of age or older. However, the drug regimen is expected to be as safe and effective for pregnant women under the age of 18 years as it is for those over the age of 18 years.

Consideration should be given to including a statement under PRECAUTIONS in the physician labeling that the regimen is less effective and the incidence of adverse events is higher in women seeking abortion with pregnancies of greater than 49 days.

Consideration should also be given to including a statement in the patient labeling under "Are there any reasons that I should not have the treatment procedure?" that the regimen is less effective and the incidence of adverse events is higher in women seeking abortion with pregnancies greater than 49 days. This could follow the statements in the patient labeling that state,

"You should not have the treatment procedure if your medical provider determines that the duration of your pregnancy is more than 49 days. For many women this means that the first day of your last period was more than 49 days ago."

The physician labeling contains a PATIENT INFORMATION section that includes the statement, "Before giving you any medication, your medical provider will ask you to sign a statement that you have decided to terminate your pregnancy, and that you have read and understood this information." An ACKNOWLEGEMENT is included in the PATIENT INFORMATION section for the patient and medical provider to sign. Consideration should be given to adding the statement, "My medical provider has confirmed that I am pregnant and that the pregnancy is not greater than 49 days" and a statement that, " My medical provider has discussed with me alternatives to medical abortion including surgical abortion and continuation of this pregnancy."

Everyone who was a member of the advisory committee when mifepristone was presented and who is still a special government employee was sent the results of the U.S. studies in the form of a copy of the article, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States" by members of the Population Council published in the April 30, 1998 issue of the New England Journal of Medicine. The article accurately and succinctly summarizes the results of the studies.

XIII. Recommendation:

Approval of this application is recommended provided that the labeling is satisfactorily revised and the complete details of the distribution system which are yet to be submitted are acceptable.

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APPEARS THIS WAY
ON ORIGINAL

SEP 13 2000

September 12, 2000

Mifepristone Tablets, 200mg
NDA 20-687

Population Council
Safety Update Report #3

Medical Officer's Review of Safety Update No. 3 Dated March 31, 2000

This NDA Safety Update Report summarizes the body of information which has been obtained by the Population Council since the cut-off date for the previous NDA Safety Update Report submitted August 3, 1999. The primary source of new information for this report is the Periodic Safety Update Report #9 prepared by the manufacturer of mifepristone, as well as from foreign clinical studies sponsored by the Population Council and from the literature. The cut-off date for this third report is February 29, 2000.

The report from presents information from investigational and marketing experience with the product received by that company from worldwide sources. As stated in that report, there have been no specific actions taken with respect to the product for safety reasons such as rejection, withdrawal or suspension of marketing authorization, restrictions to distribution, suspension of clinical trials, modifications of dosage formulation, or changes in target population or indications. It is stated that in connection with new product approvals by European Union member countries via the mutual recognition procedure, some new textual changes were made to product labeling to reflect common usage practice and for purposes of accuracy and explanation.

One new area of safety concern is apparent in the new information presented in this NDA Safety Update Report. Following queries concerning the use of mifepristone in patients with acute hereditary hepatic porphyrias, conducted an experiment at The chick embryo liver in ovo is a validated model system and currently used to identify "inducing" effects of drugs by measuring increases in hepatic delta amino levulinate synthetase, a rate controlling enzyme, resulting in overproduction of porphyrin and cytochrome P 450. Mifepristone crystalline powder was tested on that model and appeared to be highly toxic on the chick embryo liver. Therefore, concluded that the drug should be contraindicated in patients with inherited porphyrias. This contraindication has been added to the updated Master Data Sheet dated December 1999 by It should be considered for inclusion in the labeling for Mifeprex as a contraindication, but since the contraindication would be based upon the results of a single nonclinical safety study, I am of the opinion that it does not warrant being in the labeling unless further confirmatory data becomes available.

The known number of subjects exposed to mifepristone in clinical studies for various indications is 32,439. Over patients have received mifepristone in commercial distribution since its initial marketing in France in 1989. No clinical studies were conducted in the U.S. by the Population Council during the period covered by this NDA

Safety Update Report.

Protocol 171 (not conducted under an IND) has recently been completed in India for pregnancy termination in 900 women. There were no hospitalizations and no unexpected adverse events. Losses to follow-up were 3.5% and 4.4%.

Protocol [redacted] not conducted under an IND) is ongoing [redacted]

Records have been maintained by [redacted] of ongoing pregnancies following administration of mifepristone and a prostoglandin for medical termination of the pregnancies. There are now reports of 107 ongoing pregnancies. Nine cases of fetal abnormalities have been reported as having occurred in association with these pregnancies. Eight of these occurred with the use of mifepristone and gemeprost. One occurred with the use of mifepristone alone.

Mifepristone is now approved for marketing in 21 countries.

The information contained in this Safety Update Report is consistent with the cumulative experience gained to date on mifepristone and does not reveal any unexpected, unanticipated safety issues that would change the benefit to risk ratio.

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NDA 20-687
Population Council

Mifepristone 200 mg Oral Tablets
Review completed November 19, 1999

Medical Officer's Review of Safety Update Report No. 2 Dated August 3, 1999

This second NDA Safety Update Report includes accumulated information relative to the safety of mifepristone which has been obtained by the Population Council since Many 25, 1996, the cut-off date for the first Safety Update Report submitted on June 20, 1996. The cut-off for this second report is June 30, 1999.

Information in the report includes that obtained from recently completed and ongoing clinical trials with the product sponsored by the Population Council and by the manufacturers, Roussel Uclaf Additionally, the report contains Periodic Safety Update Reports prepared by the French manufacturers to summarize the worldwide safety experience with the product, updated information on international regulatory approvals and new information obtained from the literature. The report also contains a Clinical Expert Report on mifepristone which was prepared by and which summarizes the accumulated clinical documentation on the efficacy and safety of the product.

Five periodic safety update reports are submitted covering the period December 1, 1995 - August 31, 1998. An estimated patients received mifepristone under marketing conditions during this period.

In addition to the periodic safety update reports, international reports of adverse reactions have been submitted in two other formats: 1) two quarterly safety line listings of safety reports from clinical trials and of the drug during the period of April 1, 1996 - September 30, 1996 when Roussel Uclaf was responsible for the drug and 2) five individual safety reports (and one follow-up report) received form Roussel Uclaf that were reported to IND

The periodic safety update reports provide a comprehensive summary of the safety information received by Roussel Uclaf from worldwide sources during the covered time periods. Three of the five individual safety reports are also included in the periodic safety update reports. A total of 67 reports were received during a 32 month period when patients received mifepristone. This is one report per patients treated. A total of 28 of these adverse events were assessed as serious. This is one serious report per patients treated. Five of these adverse events were some sort of urticaria or allergic reaction. One instance of disseminated intravascular coagulation was reported from the United Kingdom. Five

of the reports were of fetal abnormalities. The other reports were diverse. No unexpected safety issues are raised by this safety update report. Overall safety results are similar to those seen in the pivotal French studies and in the U.S. studies.

In the period since 1987, Roussel Uclaf have received information on continuing pregnancies after administration of mifepristone or mifepristone and prostaglandins for medical termination of the pregnancies. A report, updated through June 1999, includes 87 reports of ongoing pregnancies, of which 26 followed the use of mifepristone alone and the remainder followed the use of mifepristone and a prostaglandin (or unknown). Nine reports of fetal anomalies have been received. Mifepristone alone was used in one report and mifepristone and gemeprost was used in eight reports. The one report of a fetal anomaly in a patient who received mifepristone alone resulted in a therapeutic termination of pregnancy with cleft palate and sirenomelia which was believed not to be drug related because of embryogenesis considerations. Of the nine reports of fetal anomalies, three occurred in babies at term. One had bilateral talipes (club foot), one had fingernail defect 3, and the third had a heart malformation. Fifteen of the 87 ongoing pregnancies were lost to followup.

A total of 33 normal babies have been born to women who received mifepristone alone (10), mifepristone plus misoprostol (11), or mifepristone plus some other prostaglandin (12). Data are too limited to determine whether mifepristone is a human teratogen.

Ninety articles published between 1996 and 1999 are submitted. These studies report the use of mifepristone in different clinical conditions, variable dosages, and for variable time durations. There is nothing reported in any of these articles that would change the safety profile of mifepristone for early abortion.

In the reports of early pregnancy termination, adverse events and efficacy reported are similar to that reported in the pivotal French studies and in the U.S. studies.

Unrelated to pregnancy termination, but of interest, are two reports where mild elevations in hepatic transaminases were noted in some subjects. Kettel reported 7 subjects with endometriosis treated with mifeprisone, 5 mg daily for six months. Subjects with liver function abnormalities were excluded from treatment. One of the 7 subjects experienced a mild increase in liver transaminases. Perrault reported 28 subjects with untreated metastatic breast carcinoma treated with mifepristone, 200 mg daily. Mild elevations of AST were reported in 6 of the 28 subjects. (Six subjects had metastatic liver disease. It is not known how many, if any, of these subjects with metastatic liver disease were among the six reports of elevated AST.) These mild elevations in hepatic transaminases are of interest because some such changes were noted very early in abortion dose finding studies. However, 248 subjects in the U.S. studies had a full panel of laboratory tests at baseline and at visit 3 including alkaline phosphatase, AST, ALT, and LDH. The median changes noted were small and not of clinical significance.

The Clinical Expert Report on Mifepristone in Termination of Pregnancy is a review of the clinical documentation forming the basis for approval, key results from the published trials, and post-marketing surveillance data. It contains no new information.

We are informed that mifepristone was approved in eight countries (including Germany) July 6, 1999 under the mutual recognition procedure of the European Union.

No new areas of safety concern are apparent. Information contained in this safety update report is consistent with the cumulative experience gained to date from the pivotal French studies and the U.S. studies. The risk-benefit assessment remains unchanged.

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NDA 20-687
Mifepristone

The Population Council
August 28, 1996

Medical Officer's Summary of Safety Update Dated
June 20, 1996

Included in the Safety Update Report received June 27, 1996 are two new clinical study reports as well as new information regarding study reports previously submitted.

The first new clinical study report is entitled, "The Efficacy and Safety of Mifepristone 600 mg in a Single Dose in Combination with Intravenously Administered Sulprostone (Nalador) in Therapeutic Termination of Second Trimester Pregnancy". The second new clinical report is entitled "Role of Cortisol in the Thermal Response to Alimentation: Effect of Mifepristone" and consisted of twelve healthy, male volunteers, six of whom received a single 600 mg tablet and six of whom received a placebo.

Neither of the two new clinical study reports reveal any additional safety concerns not identified in the two pivotal clinical studies.

Newly completed clinical trials include three studies of labor induction, two studies of breast cancer, and the United States clinical trials of early pregnancy termination. Laboratory data from these completed studies have not yet been analyzed and, therefore, no information on laboratory data are reported in this safety update. Final data analysis and study reports for these six studies have not been completed. The results for termination of pregnancy studies conducted in the United States are expected to be in full agreement with the two pivotal clinical studies. No unanticipated safety issues were raised in these studies. Preliminary examination of information from the United States studies as it was forwarded weekly from the clinics directly to the sponsor during the course of the trials indicates that the final, analyzed results will be similar to those obtained in similar clinical trials of the same medical regimen.

The literature update includes eleven articles published in 1995 and one article published in 1996. Three articles are of particular interest. One is the publication of one of the pivotal clinical studies (FF/92/486/24) by Aubeny et.al. The second is entitled "A Comparative Analysis of Fall in Hemoglobin Following Abortions Conducted By Mifepristone (600 mg) and Vacuum Aspiration" by Thonneau et. Al. The investigators found significant blood loss in the two weeks following abortions by the mifepristone/sulprostone protocol while hemoglobin concentrations remained stable in women who had vacuum aspiration. Women who took mifepristone experienced a mean fall of 0.7 g/dl in hemoglobin two weeks after the abortion. The third article entitled "Clinical, Hormonal, and Sonographic Predictors of Successful RU-486-Induced Abortions" was by Menashe et.al. A small hematoma, seen as a localized detachment of the gestational sac, was observed in the decidua capsularis in women who aborted successfully. A significant decrease in plasma levels of estradiol and progesterone and significantly increased cortisol levels in the plasma of the patients who aborted were observed by the seventh day following treatment.

Table four of the Safety Update Report contains adverse reactions from all sources reported to Roussel Uclaf which were summarized in the quarterly line listings covering July 1, 1995 to September 30, 1995; October 1, 1995 to December 31, 1995; January 1, 1996 to March 31, 1996 and reported in the Periodic Safety Update No. 3 dated January 1996 for the period June 1, 1995 to November 30, 1995.

Of a total of forty eight patient reports of adverse experiences listed in Table 4, twenty-eight were reported from patients enrolled in the United States studies (protocols 166A and B). Of these twenty-eight reports, nineteen were metrorrhagia, three were abdominal pain, two were dehydration, and there were one each of depression, viral meningitis, vomiting, and syncope. Vacuum aspiration or D&C was performed in twelve cases of metrorrhagia and a blood transfusion was given in one case of metrorrhagia. Concomitant hypotension was also reported in four patients with severe metrorrhagia. The patient with syncope presented with a marked vasovagal reaction fifteen minutes after misoprostol administration.

In the section of the Safety Update Report entitled "Tolerance of RU 486 During United States Studies" there is Table 1 which was submitted to the sponsor by Russell Uclaf June 7,1995 which indicates that there were forty-seven serious adverse events plus 8 non serious adverse events in the United States studies (protocols 166 A and B). Table 2 indicates that of the forty-seven serious adverse events forty-one were related to bleeding, two to hypotension, and one each to vomiting, chest pain, infection, and accidental injury.

[redacted]

Also included is a half page document entitled "Notifications Report to Roussel Uclaf from Study English PMS" which lists seven reactions occurring in five patients. There were three reports of uterine hemorrhage, one incomplete abortion with bleeding, one convulsion, one congenital nail disorder, and one report of lack of efficacy.

Also included is a section entitled "New Foreign Marketing Information" which consists only of a core product information document from the product manufacturer revised in March 1995.

Since the start of the use of mifepristone until November 30, 1995, Roussel Uclaf has recorded fifty-three cases of continued pregnancy after the intake of mifepristone for early pregnancy termination (alone or associated with a postaglandin analog).

Among these fifty-three cases:

Nineteen pregnancies were delivered at term (or close to it):
Fifteen were uneventful pregnancies with children normal at birth.
One was normal but born prematurely (33-34 weeks) from caesarean section
One was normal except for common slight bilateral talipes.
One case involves unilateral fingernail defects.
One child was reported as strictly normal at birth but it was known that when she was three months old, the infant was diagnosed as having an autoimmune disorder with chronic giant cell hepatitis and immunohemolytic anemia and later died of severe infectious pneumonia likely exacerbated by immuno-suppressive drugs. The reporting physician's opinion (an expert in teratogenicity) was that the onset of the autoimmune disorder was coincidental and that the role of mifepristone could be reasonably excluded.

In fifteen cases information on further condition of the fetus was made available, mainly in the cases where pregnancy is known to have been terminated later:

In nine cases, termination was performed voluntarily and information either from histologic examination or from ultrasound was that the fetus was normal.

In one case, at therapeutic termination the fetus was noted to have sirenomelia associated with other fetal malformations. The opinion of the consulting embryologists to whom the case was submitted by Roussel Uclaf was that the role of mifepristone was very unlikely. This case has been published (Pons J.C. and all : Lancet, 1991, 328: 763).

In five cases of ongoing pregnancy, the latest available information during second trimester examination indicated normal pregnancy and fetus development.

In six cases, no information on the fetus could be obtained but pregnancy was known to have been terminated later.

In thirteen cases, no further information was made available; in most cases patients were lost to follow-up, and in some cases pregnancy is still ongoing.

Comment: This Safety Update does not reveal any unexpected, unanticipated safety issues that were not made known in the original submission of the NDA.

/S/

Concur: /S/ 9/11/96

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687
Mifepristone

The Population Council
August 29, 1996

Medical Officer's Review of Safety Update Including a Summary Of International Post-Marketing Surveillance Data Dated July 25, 1996.

Submission dated July 25, 1996 contains summaries of all the safety information available to the sponsor from Roussel Uclaf International (France, Sweden, United Kingdom) post-marketing surveillance reports, starting from 1989, the first year mifepristone was on the market in France.

Spontaneous notification of suspected adverse events reported in post-marketing surveillance of mifepristone from June 1989 to June 1995 are listed in Table 7 of the submission. Causality by mifepristone is judged to be "unlikely", "unrelated", "not assessable", "insufficient data", "misuse", or "rumor" in the vast majority of cases. Adverse events that were possibly or probably related to drug use were usually expected events such as metrorrhagia. The most commonly used prostaglandin analogue during this period was sulprostone, given by injection.

The Mifepristone Safety Report covering the period January 1, 1991 through December 31, 1992 covers the first eighteen months since the launching of mifepristone in the United Kingdom. It also includes the period of discontinuation of sulprostone and the introduction in France of misoprostol as a possible alternative prostaglandin analogue. The report also contains the entire safety information available since [redacted] early pregnancy termination. In July, 1992, two new indications of mifepristone were approved in France, "therapeutic termination of second trimester pregnancy" and "labor induction in utero fetal death". [redacted]

The International Safety Report Periodic Update from January 1, 1993 to May 31, 1995 contains no unexpected or unanticipated reports of adverse reactions that were not already known. There were no post-marketing phase IV or surveillance studies reported in final form during this period. There is mention of about three thousand four hundred and thirty-five patients enrolled in the post-marketing surveillance program conducted by Roussel Uclaf in the United Kingdom during the period of this report, but no additional information is available.

Periodic Safety Update Report No. 3 from June 1, 1995 to November 30, 1995 has been reviewed previously by the Food And Drug Administration Medical Officer and his comments are in his Safety Update Review dated August 28, 1996. No unexpected or unanticipated adverse reactions were found in this periodic report.

Comment: From the cumulative experience to date, no new special areas of concern have been identified. The assessment of the risk-benefit ratio of mifepristone is unaltered by the data included in this Safety Update Report.

/S/

Concur: /S/ 9/9/96

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687
Mifepristone

The Population Council
August 29,1996

Medical Officer's Review of United States Safety Data Dated July 14, 1996

Submission dated July 14, 1996 is a summary report of the serious adverse events from Protocols 166 A and B during the United States clinical trials. All of these reports have been submitted previously in IND

A total of fifty-two subjects had at least one SAE. There was more than one adverse event reported for most subjects. The most frequently reported SAE was hemorrhage (41 reports). This was followed by fainting/dizziness (20 reports) which includes all of the following events: fainting, feeling faint or lightheaded, dizziness, syncope, vasovagal reaction and passing out. Other serious adverse events that were reported by at least four subjects are listed in the summary below.

Total No. of Patients	Total No. of Clinics	Total No. of Adverse Events	Total Number of Treatments				Total No. Hospitalized
			D&C/ Asp.	Meth./ oxy.	IV Fluids	Transfusion	
52	13	Hemorrhage 41 Faint/Dizziness 20 Cramping 14 Vomiting 06 Hypotension 05 Tachycardia 04	34	15	28	04	26

These serious adverse events resulted in the hospitalization of twenty-six subjects. Four subjects received transfusions. A total of twenty-eight subjects received IV fluids (including 3 of the subjects that also had transfusions). A total of thirty-four subjects received a D&C or aspiration. All but two of the subjects who had a D&C or aspiration reported hemorrhage. Fifteen subjects recieved methergine or oxytocin for treatment of bleeding, although eleven of these subjects eventually had a surgical procedure.

It is not possible to make a complete comparison of the serious adverse events reported in the United States trial and the pivotal French studies in the NDA, due to different definitions of SAEs and different adverse event reporting requirements in the two countries. Also, the safety analysis of the United States trials has not been conducted, since the good clinical practice audit of the clinics is currently being completed. Therefore, t this time comparisons between the United States and NDA pivotal studies can only be made with the serious adverse events

reported from these fifty-two United States subjects, rather than other less serious adverse events that will be uncovered during the safety analysis of the entire United States database. However, some general comparisons can be made. The total number of subjects enrolled in United States Protocol 166A/B was 2,121. This is slightly less than the number of subjects (2480) enrolled in the pivotal French trials in the NDA. The number of transfusions is identical (4) in both studies and the number of hospitalizations is similar (26 in the United States trials and 21 in the pivotal trials). The number of reported cases of hemorrhage, metrorrhagia or excessive bleeding was similar in the two studies. Hemorrhage was reported by forty-one subjects in the United States studies. In the NDA pivotal studies, fifty-two subjects reported metrorrhagia or excessive bleeding, which was categorized as severe in twenty-one subjects. However, the manner in which the bleeding was treated differed in the two studies. In the Unites States trials, thirty-two of the thirty-four surgical interventions (D&C or aspiration) were performed on subjects experiencing hemorrhage. In the NDA pivotal trials, a total of fifteen subjects received surgical interventions for bleeding. The greater number of surgical interventions by United States investigators is not unexpected, due to their initial lack of experience in the control of bleeding during medical abortion. This was the first clinical trial of medical abortion in the United States, but medical abortion had been available in France for several years prior to the conduct of the French studies of mifepristone and misoprostol. The United States investigators have noted that as they gained experience with the bleeding that occurs during medical abortion, they were less likely to surgically intervene.

There were five cases of hypotension, in the United States trials, although blood pressure readings were given for only two of these subjects. There were seven cases of clinically relevant hypotension, one rated as severe, in the NDA pivotal trials. There were also a similar number of reports of tachycardia for United States subjects and in the pivotal trials (4 and 5 reports, respectively).

The incidence of other adverse events reported in the United States subjects, such as cramping or vomiting, cannot at this time be fairly compared to the numbers of these adverse events reported from all subjects in the NDA pivotal studies. This comparison must await the safety analysis of the United states database.

Conclusion:

The SAEs reported during the United States trial do not appear to differ significantly from those reported in the pivotal NDA trails, although a full comparison is not possible at this time. The higher incidence of surgical intervention in the United States trials may be explained by the initial inexperience of United States clinicians in providing medical abortion. Investigators in the United States trials have indicated that there was a learning curve associated with the treatment of bleeding during the trial. The incidence of other events such as hemorrhage, transfusions, and hospitalizations were similar in the two studies.

In summary, the current comparison of SAEs between the United States trial and the NDA pivotal trials indicated that medical abortion can be safely delivered in a wide variety of United States settings.

/S/

Concur: /S/ 9/9/96

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT 6

Blake M. Autry & Roopma Wadhwa,
Mifepristone, StatPearls
(Feb. 28, 2024)

NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-.

Mifepristone

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Last Update: February 28, 2024.

Continuing Education Activity

Mifepristone, also called RU-486, is a synthetic steroid with dual FDA-approved applications. Firstly, it is utilized in combination with misoprostol for pregnancy termination up to 10 weeks of gestation, offering a medical alternative to surgical procedures for induced abortions. Secondly, mifepristone is employed in managing and treating hyperglycemia associated with Cushing syndrome. As a low-dose competitive binder, mifepristone obstructs progesterone action by binding to its intracellular receptor. Higher doses impede cortisol activity at the glucocorticoid receptor, concurrently elevating circulating cortisol levels to regulate hyperglycemia in individuals with Cushing syndrome. Apart from its predominant use in medically induced abortions, mifepristone proves valuable in addressing Cushing syndrome and uterine leiomyomas.

This activity focuses on elucidating the mechanism of action, adverse event profile, and other crucial aspects, such as dosing, pharmacodynamics, pharmacokinetics, monitoring, and relevant interactions of mifepristone. Healthcare professionals treating patients with mifepristone gain insights into its multifaceted roles, facilitating informed decision-making within the healthcare team. Noteworthy adverse reactions associated with mifepristone include bacterial infections and prolonged, heavy menstrual bleeding, underscoring the importance of comprehensive understanding and vigilance in its clinical use.

Objectives:

- Identify appropriate indications for mifepristone use in elective abortion procedures and other medical conditions.
- Screen patients to assess their eligibility for mifepristone therapy, considering medical history, contraindications, and potential drug interactions.
- Assess patient response to mifepristone treatment and monitor for adverse reactions or complications.
- Develop effective communication with patients, providing clear instructions and addressing their concerns regarding mifepristone treatment.

Access free multiple choice questions on this topic.

Indications

FDA-Approved Indications

Mifepristone, also known as RU-486, has 2 main FDA-approved indications. These are pregnancy termination combined with misoprostol through 10 weeks gestation and the management and treatment of hyperglycemia in patients exhibiting signs of Cushing syndrome.[1][2][3]

Off-Label Uses

In addition to the above indications, mifepristone has shown efficacy with off-label uses for postcoital emergency contraception, cervical maturation, and adjunct therapy for uterine leiomyomas.[2][4][5][6]

Mechanism of Action

Mifepristone works by antagonism of glucocorticoid and progesterone receptors. At low doses, mifepristone works by being a selective antagonist of progesterone. The drug does so by binding to the intracellular progesterone receptor. At high doses, mifepristone blocks cortisol at the glucocorticoid receptor. This action causes an effect on the hypothalamic-pituitary-adrenal axis, leading to an increase in circulating cortisol, thus controlling hyperglycemia in some patients. Mifepristone has a higher affinity for the glucocorticoid II receptor than the glucocorticoid I receptor.

For use in pregnancy termination, mifepristone works by interrupting progesterone. Progesterone is the primary hormone in preparing the endometrium for implantation and sensitizing the body to the effects of prostaglandins by increasing their synthesis and decreasing their metabolism. It causes the release of endogenous prostaglandins and an increase in the sensitivity of the myometrium to the contractile effects of prostaglandins. The increase in prostaglandins results in menstrual bleeding, disruption of the endometrium, and then termination.[1][7]

Pharmacokinetics

Absorption: Mifepristone is rapidly absorbed, and peak plasma concentrations are attained 90 minutes after administration.

Distribution: Mifepristone has high plasma protein binding (approximately 98%); it binds to albumin and alpha-1-acid glycoprotein. Mifepristone can cross the blood-brain barrier.[8]

Metabolism: Mifepristone is metabolized by CYP3A4, CY2C8, CYP2C9, and CYP2B6; it forms pharmacologically active metabolites.[9][10]

Elimination: The average elimination half-life of mifepristone is 18 hours (single dose). The primary route of elimination is through feces.[11][12]

Administration

Available Dosage Forms

Mifepristone is generally available as an oral tablet in 200 mg and 300 mg preparations.

Adult Dosing

Clinicians should be enrolled in the REMS program. According to the American College of Obstetricians and Gynecologists (ACOG) guidelines for medication abortion, mifepristone can be used in the first 70 days (10 weeks) of gestation; clinicians should confirm pregnancy and estimate gestational age. Any intrauterine device present must be removed before initiating mifepristone. The regimen for termination of pregnancy involves a single mifepristone dose of 200 mg orally and misoprostol 800 µg buccally.

Initially, a 200 mg tablet of mifepristone is administered in a single oral dose. On days 2 or 3, misoprostol should be placed in the buccal pouch as 4 200 µg tablets (total 800 µg). Misoprostol should be taken within 24 to 48 hours after taking mifepristone. Misoprostol should be kept in cheek pouches for at least 30 minutes. The efficacy decreases when misoprostol is administered <24 hours or >48 hours after the administration of mifepristone.[13]

To manage and treat hyperglycemia in patients with Cushing syndrome, an initial dose of 300 mg should be given orally once daily with a meal. That dose may be increased by 300 mg every 2 to 4 weeks up to a maximum of 1200

mg daily. According to the Endocrine Society Guidelines, the quick onset of action of mifepristone is helpful in life-threatening hypercortisolism.[14][15]

For emergent postcoital contraception, 600 mg should be given orally in a single dose within 72 hours of intercourse. For uterine leiomyomas, 25 to 50 mg once daily by mouth can help reduce the size of the fibroids.[1][3]

Specific Patient Populations

Hepatic impairment: In patients with hyperglycemia with Cushing syndrome, the maximum dose of mifepristone is 600 mg daily for mild to moderate hepatic impairment; use is not recommended in severe hepatic impairment. According to product labeling, no studies have been conducted for mifepristone in hepatic impairment for termination of intrauterine pregnancy; caution is advised.

Renal impairment: In patients with hyperglycemia with Cushing syndrome, the maximum dose is 600 mg daily. According to product labeling, no studies have been conducted for mifepristone in renal impairment for termination of intrauterine pregnancy; caution is advised.

Pregnancy considerations: Mifepristone use for hypercortisolism is contraindicated in pregnancy due to the risk of abortion. As mifepristone is the standard medication in abortion regimens, clinicians must be aware of potential associated teratogenicity (limb defects and Moebius syndrome).[13]

Breastfeeding considerations: Mifepristone is distributed in human milk. Available medical information suggests that breastfeeding need not be discontinued after a single dose of mifepristone, as in medical abortion. However, long-term breastfeeding should be avoided during long-term therapy for hyperglycemia in patients with Cushing syndrome. Product labeling indicates that the decision should be based on a risk-benefit evaluation of the infant and mother.[16]

Pediatric patients: The safety and effectiveness of mifepristone for the termination of intrauterine pregnancy have been demonstrated in pediatric patients.

Older patients: Clinical trials of mifepristone for endogenous Cushing syndrome did not have a sufficient sample size to detect a statistically significant difference.

Adverse Effects

Severe reactions include fetal death, anaphylactic reactions, toxic epidermal necrolysis, angioedema, and teratogenesis.

Moderate reactions may present as hypokalemia, peripheral edema, hypertension, dyspnea, constipation, hypoglycemia, vaginal bleeding, uterine contractions, stomatitis, hot flashes, endometrial hyperplasia, anemia, adrenocortical insufficiency, palpations, and hypotension.[17][4]

Mild reactions include nausea, abdominal pain, fever, vomiting, fatigue, headache, diarrhea, dizziness, sinusitis, pharyngitis, GERD, malaise, insomnia, maculopapular rash, pruritis, pelvic pain, chills, menstrual irregularity, emotional lability, and syncope.[3][18][19]

Drug-Drug Interactions

- **CYP3A4 inhibitors:** Strong inhibitors of CYP3A, such as itraconazole, ketoconazole, ritonavir, atazanavir, clarithromycin, conivaptan, saquinavir, telithromycin, and voriconazole can increase the concentration of mifepristone.[20][21] The maximum dose of mifepristone should not exceed 600 mg per day.

- **CYP3A4 inducers:** Strong CYP3A4 inducers such as carbamazepine, phenytoin, rifampin, phenobarbital, and St. John's wort can reduce concentrations of mifepristone. Concurrent use with mifepristone should be avoided.[22]

- **Drugs metabolized by CYP2C8/CYP2C9:** Fluvastatin, warfarin, and repaglinide are metabolized by CYP2C8/CYP2C9. Use the lowest dose possible during concurrent administration with mifepristone.[23][24]

- **Drugs metabolized by CYP2B6:** Mifepristone is an inhibitor of CYP2B6 and may increase the concentration of drugs metabolized by CYP2B6, such as bupropion and efavirenz. Use with caution.[10][25]

Contraindications

When using mifepristone to terminate a pregnancy or conception, caution is necessary to test out the patient populations with contraindications to mifepristone. Patients who have previously had a hypersensitivity reaction to mifepristone or prostaglandin therapy should not have mifepristone therapy. Hypersensitivity reactions include symptoms of anaphylaxis, angioedema, rash, hives, and pruritus. Additional contraindications include inherited porphyria, bleeding disorders, and adrenal failure. Clinicians must exclude ectopic pregnancy according to product labeling.[26]

The use of mifepristone in patients with Cushing syndrome is contraindicated with concurrent administration of simvastatin, lovastatin, and CYP3A substrates (ie, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus, and tacrolimus).[27][28]

Additionally, mifepristone is contraindicated in patients who are pregnant for the control of hyperglycemia. If the patient has a history of unexplained vaginal bleeding, endometrial cancer, or endometrial hyperplasia with signs of atypia, they should not receive mifepristone. Physicians need to be watchful for symptoms of abdominal pain, infection, sepsis, and vaginal bleeding after starting mifepristone. If these symptoms develop, the clinician should stop mifepristone immediately.[4][5]

Boxed Warning:

Termination of pregnancy (mifepristone for Cushing syndrome-related hyperglycemia)

Clinicians should exclude pregnancy before stating mifepristone or if treatment is interrupted for >14 days in females of reproductive potential. Clinicians should advise patients to use non-hormonal contraceptives; no contraception is required if the patient has surgical sterilization.

Risk of severe infections and bleeding (mifepristone for medical termination of pregnancy)

Infection: After administering mifepristone, several adverse reactions require monitoring, including severe bacterial infections post-medical abortion or post-dilatation and curettage procedure where the use of mifepristone was indicated. There is no causal relationship between the drug and developing an infection, but they can occur. Before prescribing mifepristone, the patient should understand the risks, signs to look for, and a plan of action if they need help. Signs to look out for include sustained fever, severe abdominal pain, heavy bleeding, syncope, or general malaise lasting more than 24 hours after taking the medication. If a bacterial infection occurs, there is a high possibility that the pathogen is *Clostridium sordellii*, which can present atypically.[29]

Bleeding: Prolonged, heavy bleeding after taking mifepristone is a possibility based on the drug's mechanism of action. Mifepristone promotes endometrial proliferation, leading to endometrial thickening and heavier vaginal bleeding. Bleeding is expected on average for 9 to 16 days post-pregnancy termination. The manufacturer describes excessive bleeding as soaking through 2 thick pads every hour. If excessive bleeding occurs, it could point to an incomplete abortion or other complications. In these instances, monitoring for hypovolemic shock becomes important.[30][26]

Monitoring

When using mifepristone in managing patients with Cushing syndrome, clinicians must consider the effects on the HPA axis. This treatment can lead to adrenal insufficiency due to persistently elevated cortisol levels. Due to this, cortisol levels should not serve as a monitoring parameter. Clinically, watch for signs of fatigue, hypoglycemia, hypotension, nausea, or weakness. If the clinician observes these, discontinue mifepristone and administer high-dose steroids. Once resolved, mifepristone may be restarted at a lower dose.

Hypokalemia needs to be monitored in these patients as well. A pre-treatment potassium level of 4.0 mEq/L is suggested to reduce the risk of hypokalemia. If the potassium is <4.0 mEq/L, consider potassium repletion.[31] Patients receiving Cushing syndrome treatment are at higher risk for developing opportunistic infections such as *Pneumocystis jirovecii* pneumonia.[4][5][32] Mifepristone can prolong the QTc interval and its use merits caution in combination with other drugs that also prolong the QT interval.[33]

According to ACOG, clinicians should evaluate patients after the administration of mifepristone for termination of pregnancy. This monitoring is crucial to ensure the complete termination of pregnancy. Termination can be confirmed by medical history, physical examination, human chorionic gonadotropin (hCG), and ultrasonography.[34]

Toxicity

Mifepristone is metabolized in the liver by CYP3A4; thus, medications that are CYP3A4 inhibitors can result in higher concentrations of mifepristone in the patient. For patients taking multiple doses of mifepristone in managing hyperglycemia in Cushing syndrome, the medication's half-life is reportedly around 85 hours. During this time, the significant symptoms to watch for are cardiogenic. Hypokalemia is very common due to the effects of cortisol on unopposed mineralocorticoid receptors.[4]

Patients should be observed closely for signs and symptoms of adrenal insufficiency.[4] Hypokalemia and hypertension can be due to Cushing syndrome and may not always suggest excess glucocorticoid receptor antagonism due to mifepristone. Persistent and difficult-to-treat hypertension and hypokalemia may indicate excess glucocorticoid receptor antagonism, requiring discontinuation of mifepristone and rescue treatment with steroids.[31]

To avoid problems with mifepristone toxicity and adverse effects, the suggestion is to titrate the dosage gradually. Following up and monitoring the patient during the dosage escalation process is essential. Mifepristone is included in the US National Institute for Occupational Safety and Health (NIOSH) hazardous drugs list. Healthcare providers should take appropriate precautions, such as wearing gloves and safe dispensing.[35]

Enhancing Healthcare Team Outcomes

Due to ongoing controversies, clinicians should be up-to-date with medicolegal aspects when prescribing mifepristone.[36] Mifepristone is available through the REMS (Risk Evaluation and Mitigation Strategies) program, which incorporates Ensuring Elements To Assure Safe Use (ETASU).[30] The mifepristone REMS Program was revised in January 2023.[37]

- Mifepristone can only be prescribed by a healthcare provider certified under the Mifepristone REMS Program.
- Healthcare providers need to complete a prescriber agreement form to prescribe mifepristone.
- The patient agreement form must be discussed and signed by the health care provider and patient; counseling regarding the risks of the mifepristone regimen is required.
- The patient must be given a copy of the patient agreement form and FDA-approved mifepristone medication guide.
- Mifepristone may only be dispensed by a certified pharmacy that has completed the pharmacy agreement form.

- Certified pharmacies must be competent in shipping, tracking, and delivering mifepristone to the patient on time.

The patient will receive optimal care if the interprofessional healthcare team works together in an integrated fashion with open communication channels. Collaboration and shared decision-making are the keys to a good outcome. Depending on the indication of mifepristone, patients will be treated in various locations. Healthcare providers must be aware of red flag symptoms if the patient experiences an adverse reaction. For instance, clinicians, nursing staff, lab technicians, and pharmacists should work together to ensure the patient's hemodynamic stability in cases of heavy bleeding. If the patient develops a bacterial infection, an infectious disease specialist should be consulted to provide evidence-based care. Endocrinologists should be consulted for the management of endogenous hypercortisolism-related hyperglycemia. Gynecologists should ensure the termination of pregnancy.

The entire team must work together to support the patient from all angles; this can be especially important for females after losing a pregnancy. Social work support can be crucial in this case. Patients may require both pre and post-elective abortion counseling. An interprofessional team approach and open communication between physicians, advanced practice practitioners, specialists, pharmacists, nurses, and social workers can ensure the optimum use of mifepristone in their patients.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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EXHIBIT 7

The Facts on Mifepristone,
Planned Parenthood

The Facts on Mifepristone

What is Mifepristone?

Mifepristone is the first of two medications used in a medication abortion (also known as the "abortion pill"). Mifepristone has been safe and legal in the United States since the U.S. Food and Drug Administration (FDA) approved the brand name Mifeprex nearly 20 years ago. In April 2019, the FDA approved the first generic form of mifepristone, following a review of the evidence that medication abortion is a safe, effective way to end an early pregnancy – with a safety record of over 99%.

What Happens in a Medication Abortion?

The "abortion pill" is the common name in the United States for using two different medications – mifepristone and misoprostol – to end an early pregnancy. In general, it is used up to 70 days, or 10 weeks, after the first day of your last menstrual period.

1. **Mifepristone** works by blocking the hormone progesterone. Without progesterone, the lining of the uterus breaks down and the pregnancy cannot continue.

2. **Misoprostol**, the second medication, is taken either right away or up to 48 hours later and causes the uterus to empty. It's like having a heavy, crampy period and is very similar to an early miscarriage.

Medication abortion is extremely effective in ending an early pregnancy, working approximately 95-99% of the time, and gives patients the option to end their pregnancy at home or in another setting in which they feel comfortable, while still providing them with the medical support and information they need.

A growing number of patients in the United States are choosing to end their pregnancy with medication abortion. In fact, in 2014, nearly one in three people seeking abortion outside of a hospital used medication abortion.

The World Health Organization has concluded that misoprostol, taken in certain doses, can be used safely and effectively to end an early pregnancy in situations where using the combination of both mifepristone and misoprostol is not available – although taking only misoprostol is less effective than the combined mifepristone/misoprostol regimen. In the United States, the FDA-approved regimen is for patients to take both mifepristone and misoprostol.

What Else is Mifepristone Used for?

Mifepristone is also used for evidence-based indications in (1) medical management of miscarriage, (2) cervical preparation for later 2nd trimester abortion, and (3) management of 2nd and 3rd trimester pregnancies when the fetus has died before birth.

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Use in Miscarriage Care

Mifepristone, in combination with misoprostol, offers the most effective medication regimen for managing an early miscarriage. A 2018 study published in the New England Journal of Medicine found that adding mifepristone to the medication misoprostol was more effective for the management of early miscarriage than taking misoprostol alone and reduced the likelihood of patients needing an additional procedure.

Claims of "Abortion Reversal"

There is no medical evidence to support the assertion that a medication abortion can be "reversed" if someone is given a high dose of progesterone after taking mifepristone. This claim is primarily led by Dr. George Delgado, an acknowledged anti-abortion activist. In recent years, his unproven concept of "abortion reversal" has been introduced into legislatures across the country by those opposed to legal abortion. In 2015, Arizona was the first state to pass a law requiring providers to tell their patients that their medication abortions could be "reversed." A number of other states have since followed suit, despite the lack of evidence.

Planned Parenthood continually reviews available research and medical evidence to inform our Medical Standards & Guidelines and patient education materials. The treatment that Delgado has proposed, as well as the legislative efforts requiring health care providers to inform people seeking abortion of that treatment, are not evidence-based. Experts such as the American College of Obstetricians and Gynecologists reject these claims, as they have not been proven in reliable medical studies. In 2019, a study testing the claim of "abortion reversal" was halted early due to patient safety concerns.

Medically Unnecessary Restrictions on Mifepristone

Currently in the United States, patients cannot access mifepristone through a pharmacy. It remains out-of-reach for many people across the country, particularly those living in remote or rural areas, due to the FDA's Risk Evaluation and Mitigation Strategy (REMS) restrictions. **The REMS restrictions on mifepristone are not supported by research and create medically unnecessary barriers for patients accessing both medication abortion and the best method of managing a miscarriage.**

- REMS restrictions on mifepristone require that patients must be given the medication at a doctor's office, hospital, or health center from a health care provider who has pre-registered with the drug manufacturer and arranged to stock the medication at their facility (or is under the supervision of another health care provider who has).

- These unnecessary restrictions limit the number of health care providers who prescribe mifepristone and severely limit patients' access to this option, since patients aren't able to fill a prescription for the medication at a pharmacy, as they could with any other equally safe medication.

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- The REMS restrictions on mifepristone are not supported by research and are yet another example of reproductive health care – especially abortion – being treated differently than other kinds of health care in ways that only make things harder for patients.

- Because they're not supported by medical science, leading medical associations – including the American College of Obstetricians and Gynecologists and American Academy of Family Physicians – support removing REMS restrictions on mifepristone entirely.

A number of states have additional laws further regulating the administration of medication abortion. For example, there are currently 18 states that effectively ban providing medication abortion via telemedicine, even though there is no scientific basis for these bans.

Planned Parenthood believes that everyone should be able to have a safe and legal abortion, if and when they make that decision. Planned Parenthood health centers in 14 states currently use health-center-to-health-center telemedicine to provide patients with access to medication abortion. Providing medication abortion via telemedicine is just as safe and effective as when the health care provider is in the same health center as the patient. This is just one part of the work we do to ensure that all people get the reproductive health care they need, no matter where they live.

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EXHIBIT 8

Medication Abortion: Your Questions Answered,
Yale Med. (Sept. 11, 2023)

1-877-YALEMDS

Medication Abortion: Your Questions Answered

SEPTEMBER 11, 2023



Medication abortion, which involves taking two medications (mifepristone and misoprostol) at specific times over a couple of days, was used for more than half of all abortions in the United States in 2020. Yale Medicine answers common questions about the medications.

Credit: Getty Images

Editor's note: Information in this article was accurate at the time of original publication. Because information about abortion medication is changing rapidly, we encourage you to review your state laws for the latest information and consult with your doctor or health care provider for medical advice relating to the use of medication abortion.

Since the Supreme Court overturned *Roe v. Wade* in June 2022, making it possible for states to ban abortion, there has been a heightened focus on medication abortion, often known as the "abortion pill." Medication abortion was used for more than half of all abortions in the United States in 2020.

Medication abortion involves taking two medications—mifepristone and misoprostol—at specific times over a couple of days. These medications must be prescribed by an authorized health care provider.

State law bans or restrictions on surgical or procedural abortion may also apply to medication abortion. As the legal landscape of medication abortion is changing rapidly, individuals should consult their state law to determine the legality of medication abortion as it applies to them.

Below, we answer common questions about medication abortion.

How does medication abortion work?

For medication abortion, an individual takes mifepristone, followed by misoprostol up to 48 hours later.

Mifepristone is a medication that blocks progesterone activity in a female's body. Progesterone is a critical hormone for supporting an early pregnancy. The second medication, misoprostol, causes contractions and expels the pregnancy tissue. It typically takes 12 to 24 hours to pass the tissue.

Mifepristone, in the above described regimen with misoprostol, is currently approved by the U.S. Food and Drug Administration (FDA) to end a pregnancy through 10 weeks gestation (70 days or less since the first day of the last menstrual period).

What does medication abortion feel like?

After individuals take mifepristone, they likely will not feel anything. After taking the second pill, misoprostol, bleeding and cramps typically arise after a couple of hours. It may feel like a very crampy period with heavy bleeding or an early miscarriage. The further along the pregnancy is, the more discomfort individuals may experience. The cramping and bleeding may be accompanied by chills, nausea, and fever, which are side effects of misoprostol. If nausea, vomiting, fever, or diarrhea persists more than 24 hours after taking the second set of pills, individuals should call their doctor. These symptoms may be a sign of infection.

In most cases, the worst of the bleeding and cramping typically lasts up to 24 hours. It is common to feel tired for one to two days after taking misoprostol, but most people are able to go back to normal activities after the bleeding and cramping have stopped. If there is no bleeding within 24 hours of taking misoprostol, individuals should call their health care provider.

How do you know if the pregnancy has been terminated?

A person can confirm whether the medication abortion was successful by having an ultrasound or a blood test about a week after taking the medications. Because it takes time for pregnancy hormones to subside, an at home, urine based pregnancy test takes about a month after the medication abortion to show a negative result.

How early in the pregnancy can you have a medication abortion?

If abortion is permitted under state law, a medication abortion can be started as soon as pregnancy is confirmed. Individuals seeking medication abortion should visit their doctor or health care provider, who will

take a medical history.

An ultrasound to confirm that the pregnancy is intrauterine, meaning in the uterus, may also be performed and is required in some states. Notably, a medication abortion will not treat an ectopic pregnancy, in which a fertilized egg implants outside the uterus; rather, prompt medical or surgical intervention for an ectopic pregnancy is necessary.

Individuals should check with their doctor or health care provider to determine whether an ultrasound is required or recommended.

How effective is a medication abortion?

Medication abortion is highly effective, although the risk of its failure does increase as the pregnancy progresses. People seeking this treatment are advised to discuss all options, as well as effectiveness rates and risks, with their medical provider.

If medication abortion does not terminate a pregnancy, a procedural (surgical) abortion* may be recommended.

Or, if the pregnancy is no longer continuing to develop but the tissue has not passed, an individual could decide, in consultation with their medical provider, to either have a procedural abortion or take additional misoprostol*.

As for effectiveness rates, when taken before 64 days of gestation, medication abortion is reported to terminate a pregnancy between 91.6% and 99.7% of the time, depending on how misoprostol is administered, the interval between the dose of mifepristone and misoprostol, and gestational age. Medication abortion is generally more effective earlier in the pregnancy. A second dose of misoprostol* may be prescribed and administered starting at 64 days of gestation to increase effectiveness.

* *The procedures and/or steps mentioned above may be recommended by a medical provider only if it is legal in the state in which the person resides or is present. States differ on time periods in which abortion is a legal option and whether and the extent to which there are any exceptions.*

What are the risks of medication abortion?

Medication abortion is considered a safe procedure. Complications are rare, but they can include, but are not limited to, pregnancy tissue being left in the uterus, blood clots in the uterus, bleeding too much or for too long, infection, or an ongoing pregnancy. These issues can often be addressed with medication or other treatments.

There is less than a 0.4% risk of serious complications, according to a 2013 review article published in *Contraception*. From 2000 to June 2022, there have been 28 deaths out of 5.6 million women who have taken mifepristone, according to the FDA. However, “these events can not with certainty be causally attributed to mifepristone” for various reasons, the FDA says.

Still, individuals should watch out for an allergic reaction to either medication (rash, hives, itching, swollen or blistered skin with or without a fever, wheezing, and trouble swallowing, among others), excessive bleeding

(saturating two pads per hour for more than two hours), severe stomach pain, severe diarrhea, serious vaginal irritation, pelvic pain, and a fast heartbeat. Individuals experiencing these symptoms should consult with their doctor.

Outside of any rare or serious complications, medication abortion, according to studies, does not affect future pregnancies or overall health.

How does medication abortion affect the menstrual cycle?

It's normal to have some vaginal bleeding and spotting for a few weeks after medication abortion. Typically, the menstrual period will return four to eight weeks later.

Individuals can have sex after a medication abortion as soon as they feel ready. Because it's possible to remain pregnant after a medication abortion, a doctor should be consulted before using birth control pills or a device.

This article was medically reviewed by Yale Medicine obstetrician gynecologist Tessa Madden, MD.

Information provided in Yale Medicine articles is for general informational purposes only. No content in this article should be used as a substitute for medical advice or medical care from your doctor or health care provider. No content in this article should be construed as advice on the legality of medical abortion in the state in which you are located. Always seek the individual advice of your doctor or health care provider with any questions you have regarding a medical condition.

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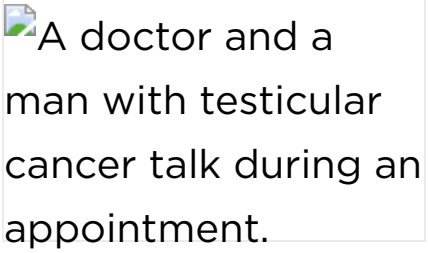
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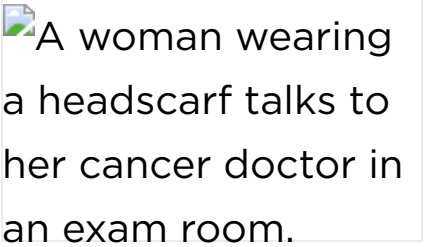
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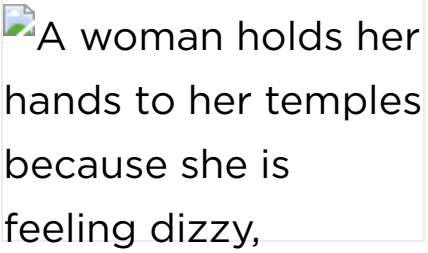
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A woman wearing a headscarf talks to her cancer doctor in an exam room.

A Transient Ischemic Attack (TIA) is as Urge…



A woman holds her hands to her temples because she is feeling dizzy, possibly from a transient ischemic attack (TIA).

EXHIBIT 9

FDA-Approved Label for Mifepristone
(Mifeprex) (Jan. 2023)
("Mifeprex 2023 Label")

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MIFEPREX safely and effectively. See full prescribing information for MIFEPREX.

MIFEPREX® (mifepristone) tablets, for oral use
Initial U.S. Approval: 2000

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

See full prescribing information for complete boxed warning.

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use.

- **Atypical Presentation of Infection. Patients with serious bacterial infections and sepsis can present without fever, bacteremia or significant findings on pelvic examination. A high index of suspicion is needed to rule out serious infection and sepsis. (5.1)**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. (5.2)**

MIFEPREX is only available through a restricted program called the mifepristone REMS Program (5.3).
Before prescribing MIFEPREX, inform the patient about these risks. Ensure the patient knows whom to call and what to do if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort or general malaise for more than 24 hours after taking misoprostol.

----------INDICATIONS AND USAGE----------

MIFEPREX is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. (1)

----------DOSAGE AND ADMINISTRATION----------

- 200 mg MIFEPREX on Day 1, followed 24-48 hours after MIFEPREX dosing by 800 mcg buccal misoprostol. (2.1)
- Instruct the patient what to do if significant adverse reactions occur. (2.2)
- Follow-up is needed to confirm complete termination of pregnancy. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card (3)

----------CONTRAINDICATIONS----------

- Confirmed/suspected ectopic pregnancy or undiagnosed adnexal mass (4)
- Chronic adrenal failure (4)
- Concurrent long-term corticosteroid therapy (4)
- History of allergy to mifepristone, misoprostol, or other prostaglandins (4)
- Hemorrhagic disorders or concurrent anticoagulant therapy (4)
- Inherited porphyria (4)
- Intrauterine device (IUD) in place (4)

----------WARNINGS AND PRECAUTIONS----------

- Ectopic pregnancy: Exclude before treatment. (5.4)
- Rhesus immunization: Prevention needed as for surgical abortion. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>15%) are nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Danco Laboratories, LLC at 1-877-432-7596 or medicaldirector@earlyoptionpill.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- CYP3A4 inducers can lower mifepristone concentrations. (7.1)
- CYP3A4 inhibitors can increase mifepristone concentrations. Use with caution. (7.2)
- CYP3A4 substrate concentrations can be increased. Caution with coadministration of substrates with narrow therapeutic margin. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Risk of fetal malformations in ongoing pregnancy if not terminated is unknown. (8.1)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Dosing Regimen
2.2 Patient Management Following Misoprostol Administration
2.3 Post-treatment Assessment: Day 7 to 14
2.4 Contact for Consultation
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Infections and Sepsis
5.2 Uterine Bleeding
5.3 Mifepristone REMS Program
5.4 Ectopic Pregnancy
5.5 Rhesus Immunization
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)
7.2 Drugs that May Increase Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)
7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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For current labeling information, please visit https://www.fda.gov/drugsatfda

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND SOMETIMES FATAL INFECTIONS OR BLEEDING

Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.

- **Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis *[see Warnings and Precautions (5.1)]*.**
- **Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding *[see Warnings and Precautions (5.2)]*.**

Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the mifepristone REMS Program *[see Warnings and Precautions (5.3)]*.

Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if they experience sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if they experience abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting, or diarrhea) for more than 24 hours after taking misoprostol.

1 INDICATIONS AND USAGE

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Regimen

For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period. The duration of pregnancy may be determined from menstrual history and clinical examination. Assess the pregnancy by ultrasonographic scan if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected.

Remove any intrauterine device (“IUD”) before treatment with MIFEPREX begins [*see Contraindications (4)*].

The dosing regimen for MIFEPREX and misoprostol is:

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Case 2:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 206 of 525 PageID 17236

- MIFEPREX 200 mg orally + misoprostol 800 mcg buccally
  - *Day One:* MIFEPREX Administration
    One 200 mg tablet of MIFEPREX is taken in a single oral dose.
  - *Day Two or Three:* Misoprostol Administration (minimum 24-hour interval between MIFEPREX and misoprostol)
    Four 200 mcg tablets (total dose 800 mcg) of misoprostol are taken by the buccal route.

    Tell the patient to place two 200 mcg misoprostol tablets in each cheek pouch (the area between the cheek and gums) for 30 minutes and then swallow any remnants with water or another liquid (see Figure 1).

    Figure 1

    2 pills between cheek and gum on left side + 2 pills between cheek and gum on right side

Patients taking MIFEPREX must take misoprostol within 24 to 48 hours after taking MIFEPREX. The effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours or more than 48 hours after mifepristone administration.

Because most women will expel the pregnancy within 2 to 24 hours of taking misoprostol *[see Clinical Studies (14)]*, discuss with the patient an appropriate location for them to be when taking the misoprostol, taking into account that expulsion could begin within 2 hours of administration.

2.2 Patient Management Following Misoprostol Administration

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms *[see Adverse Reactions (6)].*

Give the patient:

- Instructions on what to do if significant discomfort, excessive vaginal bleeding or other adverse reactions occur
- A phone number to call if the patient has questions following the administration of the misoprostol
- The name and phone number of the healthcare provider who will be handling emergencies.

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Case 2:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 207 of 525 PageID 17237

2.3 Post-treatment Assessment: Day 7 to 14

Patients should follow-up with their healthcare provider approximately 7 to 14 days after the administration of MIFEPREX. This assessment is very important to confirm that complete termination of pregnancy has occurred and to evaluate the degree of bleeding. Termination can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan. Lack of bleeding following treatment usually indicates failure; however, prolonged or heavy bleeding is not proof of a complete abortion.

The existence of debris in the uterus (e.g., if seen on ultrasonography) following the treatment procedure will not necessarily require surgery for its removal.

Patients should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at the time of follow-up, however, could indicate an incomplete abortion.

If complete expulsion has not occurred, but the pregnancy is not ongoing, patients may be treated with another dose of misoprostol 800 mcg buccally. There have been rare reports of uterine rupture in women who took MIFEPREX and misoprostol, including women with prior uterine rupture or uterine scar and women who received multiple doses of misoprostol within 24 hours. Patients who choose to use a repeat dose of misoprostol should have a follow-up visit with their healthcare provider in approximately 7 days to assess for complete termination.

Surgical evacuation is recommended to manage ongoing pregnancies after medical abortion *[see Use in Specific Populations (8.1)]*. Advise the patient whether you will provide such care or will refer them to another provider as part of counseling prior to prescribing MIFEPREX.

2.4 Contact for Consultation

For consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

3 DOSAGE FORMS AND STRENGTHS

Tablets containing 200 mg of mifepristone each, supplied as 1 tablet on one blister card. MIFEPREX tablets are light yellow, cylindrical, and bi-convex tablets, approximately 11 mm in diameter and imprinted on one side with “MF.”

4 CONTRAINDICATIONS

- Administration of MIFEPREX and misoprostol for the termination of pregnancy (the “treatment procedure”) is contraindicated in patients with any of the following conditions:
  - Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy) *[see Warnings and Precautions (5.4)]*
  - Chronic adrenal failure (risk of acute adrenal insufficiency)
  - Concurrent long-term corticosteroid therapy (risk of acute adrenal insufficiency)
  - History of allergy to mifepristone, misoprostol, or other prostaglandins (allergic reactions including anaphylaxis, angioedema, rash, hives, and itching have been reported *[see Adverse Reactions (6.2)]*)
  - Hemorrhagic disorders or concurrent anticoagulant therapy (risk of heavy bleeding)

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- Inherited porphyrias (risk of worsening or of precipitation of attacks)

- Use of MIFEPREX and misoprostol for termination of intrauterine pregnancy is contraindicated in patients with an intrauterine device ("IUD") in place (the IUD might interfere with pregnancy termination). If the IUD is removed, MIFEPREX may be used.

5 WARNINGS AND PRECAUTIONS

5.1 Infection and Sepsis

As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX *[see Boxed Warning]*. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.

A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting, or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

5.2 Uterine Bleeding

Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications, and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion *[see Boxed Warning]*.

Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.

Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in patients who bleed heavily.

Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfusions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to ≤ 0.1% of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

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5.3 Mifepristone REMS Program

MIFEPREX is available only through a restricted program under a REMS called the mifepristone REMS Program, because of the risks of serious complications *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the mifepristone REMS Program include the following:

- Prescribers must be certified with the program by completing the Prescriber Agreement Form.
- Patients must sign a Patient Agreement Form.
- MIFEPREX must only be dispensed to patients by or under the supervision of a certified prescriber, or by certified pharmacies on prescriptions issued by certified prescribers.

Further information is available at 1-877-4 Early Option (1-877-432-7596).

5.4 Ectopic Pregnancy

MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies *[see Contraindications (4)]*. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.

Patients who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

5.5 Rhesus Immunization

The use of MIFEPREX is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Infection and sepsis *[see Warnings and Precautions (5.1)]*
- Uterine bleeding *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Information presented on common adverse reactions relies solely on data from U.S. studies, because rates reported in non-U.S. studies were markedly lower and are not likely generalizable to the U.S. population. In three U.S. clinical studies totaling 1,248 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally, women reported adverse reactions in diaries and in interviews at the follow-up visit. These studies enrolled generally healthy women of reproductive age without contraindications to mifepristone or misoprostol use according to the MIFEPREX product label. Gestational age was assessed prior to study enrollment using the date of the woman's last menstrual period, clinical evaluation, and/or ultrasound examination.

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Case 2:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 210 of 525 PageID 17240

About 85% of patients report at least one adverse reaction following administration of MIFEPREX and misoprostol, and many can be expected to report more than one such reaction. The most commonly reported adverse reactions (>15%) were nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness (see Table 1). The frequency of adverse reactions varies between studies and may be dependent on many factors, including the patient population and gestational age.

Abdominal pain/cramping is expected in all medical abortion patients and its incidence is not reported in clinical studies. Treatment with MIFEPREX and misoprostol is designed to induce uterine bleeding and cramping to cause termination of an intrauterine pregnancy. Uterine bleeding and cramping are expected consequences of the action of MIFEPREX and misoprostol as used in the treatment procedure. Most patients can expect bleeding more heavily than they do during a heavy menstrual period *[see Warnings and Precautions (5.2)]*.

Table 1 lists the adverse reactions reported in U.S. clinical studies with incidence >15% of women.

Table 1
Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. Clinical Studies

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

One study provided gestational-age stratified adverse reaction rates for women who were 57-63 and 64-70 days; there was little difference in frequency of the reported common adverse reactions by gestational age.

Information on serious adverse reactions was reported in six U.S. and four non-U.S. clinical studies, totaling 30,966 women through 70 days gestation who used mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally. Serious adverse reaction rates were similar between U.S. and non-U.S. studies, so rates from both U.S. and non-U.S. studies are presented. In the U.S. studies, one studied women through 56 days gestation, four through 63 days gestation, and one through 70 days gestation, while in the non-U.S. studies, two studied women through 63 days gestation, and two through 70 days gestation. Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2.

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For current labeling information, please visit https://www.fda.gov/drugsatfda
Case 2:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 211 of 525 PageID 17241

Table 2
Serious Adverse Reactions Reported in Women Following Administration of Mifepristone (oral) and Misoprostol (buccal) in U.S. and Non-U.S. Clinical Studies

Adverse Reaction	U.S.			Non-U.S.		
	# of studies	Number of Evaluable Women	Range of frequency (%)	# of studies	Number of Evaluable Women	Range of frequency (%)
Transfusion	4	17,774	0.03-0.5%	3	12,134	0-0.1%
Sepsis	1	629	0.2%	1	11,155	<0.01%*
ER visit	2	1,043	2.9-4.6%	1	95	0
Hospitalization Related to Medical Abortion	3	14,339	0.04-0.6%	3	1,286	0-0.7%
Infection without sepsis	1	216	0	1	11,155	0.2%
Hemorrhage	NR	NR	NR	1	11,155	0.1%

NR= Not reported
* This outcome represents a single patient who experienced death related to sepsis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MIFEPREX and misoprostol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: post-abortal infection (including endometritis, endomyometritis, parametritis, pelvic infection, pelvic inflammatory disease, salpingitis)
Blood and the lymphatic system disorders: anemia
Immune system disorders: allergic reaction (including anaphylaxis, angioedema, hives, rash, itching)
Psychiatric disorders: anxiety
Cardiac disorders: tachycardia (including racing pulse, heart palpitations, heart pounding)
Vascular disorders: syncope, fainting, loss of consciousness, hypotension (including orthostatic), light-headedness
Respiratory, thoracic and mediastinal disorders: shortness of breath
Gastrointestinal disorders: dyspepsia
Musculoskeletal, connective tissue and bone disorders: back pain, leg pain
Reproductive system and breast disorders: uterine rupture, ruptured ectopic pregnancy, hematometra, leukorrhea
General disorders and administration site conditions: pain

7 DRUG INTERACTIONS

7.1 Drugs that May Reduce MIFEPREX Exposure (Effect of CYP 3A4 Inducers on MIFEPREX)

CYP450 3A4 is primarily responsible for the metabolism of mifepristone. CYP3A4 inducers such as rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum concentrations of mifepristone). Whether this action has an impact on the efficacy of the dose

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For current labeling information, please visit https://www.fda.gov/drugsatfda
Case 2:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 212 of 525 PageID 17242

regimen is unknown. Refer to the follow-up assessment *[see Dosage and Administration (2.3)]* to verify that treatment has been successful.

7.2 Drugs that May Increase MIFEPREX Exposure (Effect of CYP 3A4 Inhibitors on MIFEPREX)

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum concentrations of mifepristone). MIFEPREX should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.

7.3 Effects of MIFEPREX on Other Drugs (Effect of MIFEPREX on CYP 3A4 Substrates)

Based on *in vitro* inhibition information, coadministration of mifepristone may lead to an increase in serum concentrations of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MIFEPREX is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Risks to pregnant patients are discussed throughout the labeling.

Refer to misoprostol labeling for risks to pregnant patients with the use of misoprostol.

The risk of adverse developmental outcomes with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol is unknown; however, the process of a failed pregnancy termination could disrupt normal embryo-fetal development and result in adverse developmental effects. Birth defects have been reported with a continued pregnancy after a failed pregnancy termination with MIFEPREX in a regimen with misoprostol. In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

Data

Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone,fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

8.2 Lactation

MIFEPREX is present in human milk. Limited data demonstrate undetectable to low levels of the drug in human milk with the relative (weight-adjusted) infant dose 0.5% or less as compared to maternal dosing. There is no information on the effects of MIFEPREX in a regimen with

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Case 2:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 213 of 525 PageID 17243

misoprostol in a breastfed infant or on milk production. Refer to misoprostol labeling for lactation information with the use of misoprostol. The developmental and health benefits of breast-feeding should be considered along with any potential adverse effects on the breast-fed child from MIFEPREX in a regimen with misoprostol.

8.4 Pediatric Use

Safety and efficacy of MIFEPREX have been established in pregnant females. Data from a clinical study of MIFEPREX that included a subset of 322 females under age 17 demonstrated a safety and efficacy profile similar to that observed in adults.

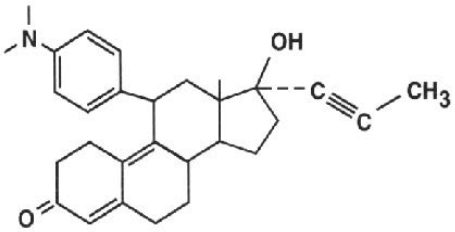
10 OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than 1800 mg (ninefold the recommended dose for medical abortion). If a patient ingests a massive overdose, the patient should be observed closely for signs of adrenal failure.

11 DESCRIPTION

MIFEPREX tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical, and bi-convex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:



The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 192-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone, resulting in effects on the uterus and cervix that, when combined with misoprostol, result in termination of an intrauterine pregnancy.

During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity

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For current labeling information, please visit https://www.fda.gov/drugsatfda
Case 2:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 214 of 525 PageID 17244

of prostaglandins.

12.2 Pharmacodynamics

Use of MIFEPREX in a regimen with misoprostol disrupts pregnancy by causing decidual necrosis, myometrial contractions, and cervical softening, leading to the expulsion of the products of conception.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women.

Antiglucocorticoid and antiandrogenic activity: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

12.3 Pharmacokinetics

Mifepristone is rapidly absorbed after oral ingestion with non-linear pharmacokinetics for Cmax after single oral doses of 200 mg and 600 mg in healthy subjects.

Absorption

The absolute bioavailability of a 20 mg mifepristone oral dose in females of childbearing age is 69%. Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 ± 1.0 mg/L occurring approximately 90 minutes after ingestion.

Following oral administration of a single dose of 200 mg in healthy men (n=8), mean Cmax was 1.77 ± 0.7 mg/L occurring approximately 45 minutes after ingestion. Mean $AUC_{0-\infty}$ was 25.8 ± 6.2 mg*hr/L.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin, and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance.

Elimination

Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum concentrations are undetectable by 11 days.

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Case 2:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 215 of 525 PageID 17245

Specific Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed.

Mutagenesis

Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

14 CLINICAL STUDIES

Safety and efficacy data from clinical studies of mifepristone 200 mg orally followed 24-48 hours later by misoprostol 800 mcg buccally through 70 days gestation are reported below. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure based on 22 worldwide clinical studies (including 7 U.S. studies) appear in Table 3.

The demographics of women who participated in the U.S. clinical studies varied depending on study location and represent the racial and ethnic variety of American females. Females of all reproductive ages were represented, including females less than 18 and more than 40 years of age; most were 27 years or younger.

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Case 2:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 216 of 525 PageID 17246

Table 3
Outcome Following Treatment with Mifepristone (oral) and Misoprostol (buccal) Through 70 Days Gestation

	U.S. Trials	Non-U.S. Trials
N	16,794	18,425
Complete Medical Abortion	97.4%	96.2%
Surgical Intervention*	2.6%	3.8%
Ongoing Pregnancy**	0.7%	0.9%

* Reasons for surgical intervention include ongoing pregnancy, medical necessity, persistent or heavy bleeding after treatment, patient request, or incomplete expulsion.
** Ongoing pregnancy is a subcategory of surgical intervention, indicating the percent of women who have surgical intervention due to an ongoing pregnancy.

The results for clinical studies that reported outcomes, including failure rates for ongoing pregnancy, by gestational age are presented in Table 4.

Table 4
Outcome by Gestational Age Following Treatment with Mifepristone and Misoprostol (buccal) for U.S. and Non-U.S. Clinical Studies

	≤49 days			50-56 days			57-63 days			64-70 days		
	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies	N	%	Number of Evaluable Studies
Complete medical abortion	12,046	98.1	10	3,941	96.8	7	2,294	94.7	9	479	92.7	4
Surgical intervention for ongoing pregnancy	10,272	0.3	6	3,788	0.8	6	2,211	2	8	453	3.1	3

One clinical study asked subjects through 70 days gestation to estimate when they expelled the pregnancy, with 70% providing data. Of these, 23-38% reported expulsion within 3 hours and over 90% within 24 hours of using misoprostol.

16 HOW SUPPLIED/STORAGE AND HANDLING

is only available through a restricted program called the Mifepristone REMS Program *[see Warnings and Precautions (5.3)].*

MIFEPREX is supplied as light yellow, cylindrical, and bi-convex tablets imprinted on one side with “MF.” Each tablet contains 200 mg of mifepristone. One tablet is individually blistered on one blister card that is packaged in an individual package (National Drug Code 64875-001-01).

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

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Case 2:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 217 of 525 PageID 17247

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide), included with each package of MIFEPREX. Additional copies of the Medication Guide are available by contacting Danco Laboratories at 1-877-4 Early Option (1-877-432-7596) or from www.earlyoptionpill.com.

Serious Infections and Bleeding

- Inform the patient that uterine bleeding and uterine cramping will occur [*see Warnings and Precautions (5.2)*].
- Advise the patient that serious and sometimes fatal infections and bleeding can occur very rarely [*see Warnings and Precautions (5.1, 5.2)*].
- MIFEPREX is only available through a restricted program called the Mifepristone REMS Program [*see Warnings and Precautions (5.3)*]. Under the mifepristone REMS Program:
    - Patients must sign a Patient Agreement Form.
    - MIFEPREX is only dispensed by or under the supervision of certified prescribers or by certified pharmacies on prescriptions issued by certified prescribers.

Provider Contacts and Actions in Case of Complications

- Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, or if the patient experiences complications including prolonged heavy bleeding, severe abdominal pain, or sustained fever *[see Boxed Warning]*.
-

Compliance with Treatment Schedule and Follow-up Assessment

- Advise the patient that it is necessary to complete the treatment schedule, including a follow-up assessment approximately 7 to14 days after taking MIFEPREX *[see Dosage and Administration (2.3)]*.
- Explain that
    - prolonged heavy vaginal bleeding is not proof of a complete abortion,
    - if the treatment fails and the pregnancy continues, the risk of fetal malformation is unknown,
    - it is recommended that ongoing pregnancy be managed by surgical termination *[see Dosage and Administration (2.3)]*. Advise the patient whether you will provide such care or will refer them to another provider.

Subsequent Fertility

- Inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses.
- Inform the patient that contraception can be initiated as soon as pregnancy expulsion has been confirmed, or before resuming sexual intercourse.

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Manufactured for:
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www.earlyoptionpill.com

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MEDICATION GUIDE

Mifeprex (MIF-eh-prex) (mifepristone tablets, for oral use

Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your healthcare provider.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Seeking medical attention as soon as possible is needed in these circumstances. Serious infection has resulted in death in a very small number of cases. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your healthcare provider. You can write down your healthcare provider's telephone number here _____.

Be sure to contact your healthcare provider promptly if you have any of the following:

- **Heavy Bleeding.** Contact your healthcare provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).
- **Abdominal Pain or "Feeling Sick."** If you have abdominal pain or discomfort, or you are "feeling sick," including weakness, nausea, vomiting, or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your healthcare provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).
- **Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your healthcare provider right away. Fever may be a symptom of a serious infection or another problem.

If you cannot reach your healthcare provider, go to the nearest hospital emergency room.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy. In many cases, this surgical procedure can be done in the office/clinic. The chance of birth defects if the pregnancy is not ended is unknown.

Talk with your healthcare provider. Before you take Mifeprex, you should read this Medication Guide and you and your healthcare provider should discuss the benefits and risks of your using Mifeprex.

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What is Mifeprex?

Mifeprex is used in a regimen with another prescription medicine called misoprostol, to end an early pregnancy. Early pregnancy means it is 70 days (10 weeks) or less since your last menstrual period began. Mifeprex is not approved for ending pregnancies that are further along. Mifeprex blocks a hormone needed for your pregnancy to continue. When you use Mifeprex on Day 1, you also need to take another medicine called misoprostol 24 to 48 hours after you take Mifeprex, to cause the pregnancy to be passed from your uterus.

The pregnancy is likely to be passed from your uterus within 2 to 24 hours after taking Mifeprex and misoprostol. When the pregnancy is passed from the uterus, you will have bleeding and cramping that will likely be heavier than your usual period. About 2 to 7 out of 100 women taking Mifeprex will need a surgical procedure because the pregnancy did not completely pass from the uterus or to stop bleeding.

Who should not take Mifeprex?

Some patients should not take Mifeprex. Do not take Mifeprex if you:

- Have a pregnancy that is more than 70 days (10 weeks). Your healthcare provider may do a clinical examination, an ultrasound examination, or other testing to determine how far along you are in pregnancy.
- Are using an IUD (intrauterine device or system). It must be taken out before you take Mifeprex.
- Have been told by your healthcare provider that you have a pregnancy outside the uterus (ectopic pregnancy).
- Have problems with your adrenal glands (chronic adrenal failure).
- Take a medicine to thin your blood.
- Have a bleeding problem.
- Have porphyria.
- Take certain steroid medicines.
- Are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Ask your healthcare provider if you are not sure about all your medical conditions before taking this medicine to find out if you can take Mifeprex.

What should I tell my healthcare provider before taking Mifeprex?

Before you take Mifeprex, tell your healthcare provider if you:

- cannot follow-up within approximately 7 to 14 days of your first visit
- are breastfeeding. Mifeprex can pass into your breast milk. The effect of the Mifeprex and misoprostol regimen on the breastfed infant or on milk production is unknown.
- are taking medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
  Mifeprex and certain other medicines may affect each other if they are used together. This can cause side effects.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

How should I take Mifeprex?

- Mifeprex will be given to you by a healthcare provider or pharmacy.
- You and your healthcare provider will plan the most appropriate location for you to take the misoprostol, because it may cause bleeding, cramps, nausea, diarrhea, and other symptoms that usually begin within 2 to 24 hours after taking it.
- Most women will pass the pregnancy within 2 to 24 hours after taking the misoprostol tablets.

Follow the instruction below on how to take Mifeprex and misoprostol:

Mifeprex (1 tablet) orally + misoprostol (4 tablets) buccally

Day 1:

- Take 1 Mifeprex tablet by mouth.

24 to 48 hours after taking Mifeprex:

- Take 4 misoprostol tablets by placing 2 tablets in each cheek pouch (the area between your teeth and cheek - see Figure A) for 30 minutes and then swallow anything left over with a drink of water or another liquid.
- The medicines may not work as well if you take misoprostol sooner than 24 hours after Mifeprex or later than 48 hours after Mifeprex.
- Misoprostol often causes cramps, nausea, diarrhea, and other symptoms. Your healthcare provider may send you home with medicines for these symptoms.



Figure A (2 tablets between your left cheek and gum and 2 tablets between your right cheek and gum).

Follow-up Assessment at Day 7 to 14:

- This follow-up assessment is very important. You must follow-up with your healthcare provider about 7 to 14 days after you have taken Mifeprex to be sure you are well and that you have had bleeding and the pregnancy has passed from your uterus.
- Your healthcare provider will assess whether your pregnancy has passed from your uterus. If your pregnancy continues, the chance that there may be birth defects is unknown. If you are still pregnant, your healthcare provider will talk with you about a surgical procedure to end your pregnancy.
- If your pregnancy has ended, but has not yet completely passed from your uterus, your provider will talk with you about other choices you have, including waiting, taking another dose of misoprostol, or having a surgical procedure to empty your uterus.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda
Case 2:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 222 of 525 PageID 17252

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or over-the-counter medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your healthcare provider about them because they may interfere with the treatment. Ask your healthcare provider about what medicines you can take for pain and other side effects.

What are the possible side effects of Mifeprex and misoprostol?

Mifeprex may cause serious side effects. See "What is the most important information I should know about Mifeprex?"

Cramping and bleeding. Cramping and vaginal bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must follow-up with your healthcare provider approximately 7 to 14 days after taking Mifeprex. See "How should I take Mifeprex?" for more information on your follow-up assessment. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take 24 to 48 hours after Mifeprex. Bleeding or spotting can be expected for an average of 9 to16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of passing the pregnancy.

The most common side effects of Mifeprex treatment include: nausea, weakness, fever/chills, vomiting, headache, diarrhea and dizziness. Your provider will tell you how to manage any pain or other side effects. These are not all the possible side effects of Mifeprex.

Call your healthcare provider for medical advice about any side effects that bother you or do not go away. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Mifeprex.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Mifeprex. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider for information about Mifeprex that is written for healthcare professionals.

For more information about Mifeprex, go to www.earlyoptionpill.com or call 1-877-4 Early Option (1-877-432-7596).

Manufactured for: *Danco Laboratories, LLC*
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596) www.earlyoptionpill.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. Approval 01/2023

EXHIBIT 10

2021 FDA Letter to AAPLOG and Am. Coll. of Pediatricians denying in part and granting in part 2016 Citizen Petition, Docket No. FDA-2019-P-1534 (Dec. 16, 2021)



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December 16, 2021

Re: Docket No. FDA-2019-P-1534

Dear Drs. Harrison and Van Meter:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on March 29, 2019, on behalf of the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians (Petition). In the Petition, you request that FDA: (1) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (2) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

Specifically, in your Petition you request that the Agency:

(1) Restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to include the following:

- Indications and Usage - Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days gestation.

- Dosage and Administration:
  - Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

  - The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

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- Contraindications - Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

- Adverse Event Reporting - Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

- Additional studies - The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

(2) Retain the Mifeprex REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

We have carefully considered the information submitted in your Petition and other relevant data available to the Agency. Based on our review of this information, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Mifeprex

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (new drug application (NDA) 020687). The application was approved under part 314, subpart H (21 CFR part 314, subpart H), "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.[1]

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.[2] Accordingly, in June 2011, we approved a REMS for Mifeprex, consisting of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Elements to assure safe use included: (1) prescriber certification (ETASU A); (2) that Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber

[1] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf.
[2] 73 FR 16313 (Mar. 27, 2008).

(ETASU C); and (3) that Mifeprex is dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

On March 29, 2016, we approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex submitted by the applicant Danco Laboratories, LLC (S-020 efficacy supplement). The approval included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol (including the dose of misoprostol and a change in the route of misoprostol administration from oral to buccal (in the cheek pouch); the interval between taking Mifeprex and misoprostol; and the location at which the patient may take misoprostol). The approval also modified the gestational age up to which Mifeprex has been shown to be safe and effective, as well as the process for follow-up after administration of the drug.

Specifically, the following changes, among others, were made as part of the 2016 approval:[3]

- Revised the dosing regimen to consist of 200 mg of Mifeprex taken by mouth, followed in 24-48 hours by 800 mcg of misoprostol taken buccally (in the cheek pouch). This differs from the originally approved dosing regimen of 600 mg of oral Mifeprex followed 48 hours later by 400 mcg of oral misoprostol.

- Revised the indication for use of Mifeprex, in a regimen with misoprostol, to extend the maximum gestational age for the medical termination of intrauterine pregnancy from 49 days to 70 days.

- Reduced the number of office visits by the patient under the approved regimen from three to one.

- Replaced the term "physician" with the term "healthcare provider."

In addition, after reviewing the data and information submitted by the applicant in the S-020 efficacy supplement, and after taking into consideration the safety data that had become available since the initial approval of Mifeprex in 2000, we determined the Mifeprex REMS continued to be necessary to ensure the benefits of the product outweigh the risks. However, we approved modifications to the Mifeprex REMS that reflected the changes approved in the efficacy supplement. These changes to the REMS included, among others:[4]

- Updating the Prescriber Agreement Form to reflect the revised indication and dosing regimen.

- Removing the Medication Guide as a REMS element (but retaining the Medication Guide as labeling).

[3] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[4] See https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf.

- Removing the requirement that certified prescribers report certain enumerated adverse events to the applicant (specifically, any hospitalization, transfusion or other serious adverse events), but retaining the requirement that certified prescribers report all deaths to the sponsor.

Under the March 2016 approval, the Mifeprex REMS also continued to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.[5]

B. Generic Version of Mifeprex

On April 11, 2019, we approved GenBioPro, Inc.'s generic version of Mifeprex, Mifepristone Tablets, 200 mg (abbreviated new drug application (ANDA) 091178). This action took place after this Petition was submitted to the Agency. As required by 21 CFR 314.94(a)(8), GenBioPro's approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, has the same labeling (with certain permissible differences) as the brand product it references, Mifeprex. Accordingly, although we refer to the Mifeprex labeling in several sections of this response, our discussions in this response apply equally to both the NDA and the generic product labeling, unless otherwise specifically noted.[6]

GenBioPro's generic version of Mifeprex is subject to the same ETASU as its listed drug (21 U.S.C. -1(i)). At the time we approved GenBioPro's generic version of Mifeprex, that ANDA product was required to use a single, shared system for the ETASU with the brand drug product, Mifeprex, unless the requirement was waived by FDA (21 U.S.C. 355-1(i)). FDA did not waive this requirement. Accordingly, at the same time that FDA approved GenBioPro's generic version of Mifeprex in 2019, FDA approved a supplemental new drug application (sNDA) for Mifeprex, approving modifications to the existing, approved REMS for Mifeprex to establish a single, shared system REMS for mifepristone products for the medical termination of intrauterine pregnancy through 70 days gestation (referred to as the Mifepristone REMS Program). In establishing the single, shared system REMS in 2019, no substantive changes were made to the ETASU in the March 2016 Mifeprex REMS. References to the REMS in this response refer to the Mifepristone REMS Program established in 2019, unless otherwise noted.

C. In-Person Dispensing Requirement During the COVID-19 PHE

[5] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf.

[6] We note that Korlym and the generic version of Korlym (Mifepristone Tablets, 300 mg) contain the same active ingredient – mifepristone - as Mifeprex and the generic version of Mifeprex (Mifepristone Tablets, 200 mg). Although these drug products contain the same active ingredient, their intended uses target different receptors, and the products have different strengths and use different dosing regimens. Korlym and the generic version of Korlym are approved for the control of hyperglycemia (high blood sugar levels) due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance, and have failed surgery or are not candidates for surgery. References to mifepristone in this response refer to the use of mifepristone for the medical termination of intrauterine pregnancy through 70 days gestation, unless otherwise noted.

FDA has recognized that during the COVID-19[7] public health emergency (PHE),[8] certain REMS requirements for various products may be difficult to comply with because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. The Agency has also received queries concerning products with REMS that have ETASUs, including REMS with ETASUs that restrict distribution, and the impact of such ETASUs on patient access when patients self-isolate or are subject to quarantine.

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 PHE regarding the requirement in the Mifepristone REMS Program that mifepristone used for medical termination of intrauterine pregnancy through 70 days gestation be dispensed to patients by or under the supervision of a certified prescriber only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement").

Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020 to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.[9]

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

FDA's intent to exercise enforcement discretion with respect to these requirements during the COVID-19 PHE was the result of a thorough scientific review by experts within FDA's Center for Drug Evaluation and Research (CDER), who evaluated relevant information, including available clinical outcomes data and adverse event reports.

D. Minor Modification

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[7] The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19).

[8] Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[9] *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

In response to a request submitted by the applicants, FDA approved a minor modification to the Mifepristone REMS Program on May 14, 2021. This minor modification revised the Patient Agreement Form to use gender neutral language. Specifically, the pronouns "she" and "her" in the Patient Agreement Form were replaced with "the patient." The minor modification also included revisions to the REMS document to be consistent with the revisions to the Patient Agreement Form. These changes did not affect the substance of the Patient Agreement Form, the REMS document, or the Mifepristone REMS Program.

E. Review of the Mifepristone REMS Program

In 2021, FDA also undertook a full review of the Mifepristone REMS Program.[10] In conducting this review, FDA reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation, as well as information submitted by the sponsors of the NDA and the ANDA (together, the Applicants). As discussed in more detail below, based on our review of this information, FDA has determined that certain elements of the Mifepristone REMS Program remain necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation; and therefore, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risk. Specifically, we find that the healthcare provider certification and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions continue to be necessary components of the REMS to ensure the benefits of mifepristone outweigh the risks for this indication.

We also find that the in-person dispensing requirement is no longer necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation. We have concluded that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added.[11] Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Accordingly, today we are sending a REMS Modification Notification letter to both Applicants in the Mifepristone REMS Program. As stated in that letter, FDA has concluded that a modification is necessary and must include the following changes:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

[10] We note that the Agency is in litigation regarding the Mifepristone REMS Program and committed to conducting a full review of the Mifepristone REMS Program, including reviewing any relevant data and evidence submitted to the Agency by the Plaintiffs in that litigation (*Chelius et al v. Becerra*, Joint Mot. to Stay Case Pending Agency Review, ECF No. 148, May 7, 2021, Civ. No. 1:17-00493 (D. Haw.)).

[11] Although we have determined that the Mifepristone REMS Program must be modified to add a requirement for pharmacy certification, this was not raised in your Petition and therefore is not discussed further in this response.

- Adding a requirement that pharmacies that dispense the drug be specially certified.

II. DISCUSSION OF ISSUES RAISED

A. Mifeprex Regimen

1. Indications and Usage

In the Petition, you ask FDA to restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to limit Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, to 49 days gestation (Petition at 1 and 3). For the reasons explained below, we deny this request.

Citing to a 2011 study and a practice bulletin issued by the American College of Obstetricians and Gynecologists (ACOG), you state that medical abortion[12] regimens demonstrate an increase in complications and failures, including serious risks of hemorrhage, infection, and ongoing pregnancy, after 49 days gestation (Petition at 3-4).

Our review of the S-020 efficacy supplement in 2016 concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.[13] Complete medical abortion rates from the pivotal clinical trials relied on for the initial approval of Mifeprex (with an indication for medical termination of intrauterine pregnancy through 49 days gestation) were 92.1 percent and 95.5 percent in the United States and French trials, respectively.[14] The studies reviewed in support of the 2016 approval for Mifeprex (with an indication for medical termination of intrauterine pregnancy through 70 days gestation) showed comparable efficacy. The 2016 Clinical Review of the S-020 efficacy supplement summarized clinical outcomes and adverse effects from 22 studies (7 in the United States and 15 from outside the United States) through 70 days gestation, using the currently approved regimen of 200 mg oral mifepristone with 800 mcg buccal misoprostol. The ranges of complete medical abortion rates calculated by the clinical reviewer were 93.2 percent to 98.7 percent in the United States studies, and 92 percent to 98 percent in the non-United States studies.[15]

Serious adverse events associated with the use of mifepristone through 70 days gestational age are rare. Per the current mifepristone labeling, the rates of serious adverse events are low: transfusions are 0-0.1 percent, sepsis is less than 0.01 percent, hospitalization related to medical abortion is 0-0.7 percent, and hemorrhage is 0.1 percent.[16] As discussed

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[12] In this response, the terms "medical abortion" and "medication abortion" both refer to the use of mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy.
[13] See 2016 Clinical Review available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf, at 32-38 and 47-47.
[14] See 1999 Medical Officer's Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf, at 11 (Table 1) and 16.
[15] See 2016 Clinical Review, supra n. 13, at 28-31.
[16] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

throughout this response, the benefit/risk assessment supported our 2016 conclusion that the product is safe and effective through 70 days gestation.

In support of your assertion that medical abortion demonstrates an increase in complications after 49 days gestation, you cite to Mentula, et al.,[17] a register-based, retrospective cohort study that included 18,248 women in Finland who underwent medical abortion between January 1, 2003, and December 31, 2006 (Petition at 3). As an initial matter, we note that the Mentula study was primarily designed to assess the immediate adverse events following medical abortion in the second trimester (13 to 24 gestational weeks as defined by the authors) and then compare those events to those identified with medical abortion in the first trimester (up to 12 gestational weeks as defined by the authors). The study was not designed to compare rates of complications across gestational weeks within the first trimester. It is true that the Mentula publication includes information on the percentages of women who had surgical evacuation following medical abortion and the percentages of women who had infection following medical abortion, based on weekly gestational age, from 5 weeks to 20 weeks gestation.[18] However, the data in the Mentula study are relatively old (2003-2006); in our 2016 review of the S-020 efficacy supplement, we conducted an extensive review of more recent data[19] and concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.

You also cite to ACOG Practice Bulletin No. 143, which states: "the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days."[20] This statement is based on a 1998 publication which evaluated patients undergoing medical abortion with mifepristone 600 mg and then oral misoprostol 400 mcg two days later.[21] The regimen studied in this 1998 publication is not the currently approved regimen for mifepristone in the United States. Further, ACOG Practice Bulletin No. 143 has been withdrawn and replaced by Practice Bulletin No. 225, which was published in October 2020 and no longer contains this statement.[22]

You also state that the failure rate of the approved regimen (which you refer to as the "buccal misoprostol regimen") increases as the gestational age increases, especially at

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[17] Mentula MJ, Niinimake M, Suhonen S, et al. Immediate Adverse Events After Second Trimester Medical Termination of Pregnancy: Results of a nationwide registry study, Human Reproduction. 2011;26(4):927-932.
[18] Id. at Fig. 2 and Fig. 3. Surgical intervention after medical abortion and infection after medical abortion are two distinct adverse events. The calculation of abortion completion rates accounts for the need for surgical intervention. In clinical studies we reviewed, success of medical abortion was defined as the complete expulsion of the products of conception without the need for surgical intervention.
[19] See 2016 Cross-Discipline Team Leader Review, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf, at 37 (Table 4).
[20] Petition at 3. See Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.
[21] Spitz I, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United Sates, NEJM. 1998;338 (18):1241-1247.
[22] See ACOG Practice Bulletin No. 225. Medication Abortion Up to 70 Days of Gestation. Obstetrics and Gynecology 2020; 136(4); e31 to e47.

gestational ages greater than 49 days, relying on a 2015 meta-analysis,[23] and that the gestational limit should not have been increased (Petition at 3-4). We agree that the failure rate of medical abortion regimens, including the currently approved regimen, generally increases with increasing gestational age. However, the increase in failure rate with each incremental week of gestation, as described in approved mifepristone labeling and in this 2015 meta-analysis, is small, and we believe that the benefit/risk profile for medical termination of intrauterine pregnancy between 49 and 70 days gestation remains acceptable.

For these reasons, we deny your request that FDA limit mifepristone, in a regimen with misoprostol for the termination of intrauterine pregnancy, to 49 days gestation.

2. Dosage and Administration

a. Prescriber Qualifications

You state that FDA should limit the "ability" to prescribe and dispense Mifeprex to qualified, licensed physicians, rather than permitting non-physicians to apply to be certified prescribers, because of the regimen's serious risks and because physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age (Petition at 4). We do not agree.

Healthcare providers who are licensed to prescribe can become certified in REMS programs if they are able to meet the applicable REMS requirements. To become certified to prescribe mifepristone under the Mifepristone REMS Program, the prescriber must review the prescribing information for mifepristone and complete a Prescriber Agreement Form. By signing the form, the prescriber agrees that they meet certain qualifications, including the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also: (1) be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care; or (2) be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.[24]

In our review of the S-020 efficacy supplement in 2016, we determined that available data support that Mifeprex is safe and effective when prescribed by midlevel providers, such as physician assistants and nurse practitioners, as well as by physicians.[25] Our 2016 review included four studies that evaluated the safety and efficacy of medical abortion when performed by non-physician healthcare providers. Two trials evaluated the currently

[23] Petition at 4, fn. 6 (citing Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet. Gynecol 126 (1) July 2015 12-21).
[24] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf; see also https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.
[25] See 2016 Clinical Review, supra n. 13, at 79; see also 2016 Cross-Discipline Team Leader Review, supra n. 19, at 17-18. We also note that in most states, midlevel clinicians, such as physician assistants and nurse practitioners, are licensed to prescribe medications.

approved Mifeprex and buccal misoprostol regimen (Olavarrieta and Kopp Kallner);[26,27] one trial studied a regimen using vaginal misoprostol (Warringer);[28] a fourth study did not specify the route of misoprostol administered (Puri).[29] Olavarrieta reported a completion rate of 97.9 percent when medical abortion was provided by nurses as compared with 98.4 percent with physicians. Kopp Kallner reported a completion rate of 99 percent with certified nurse midwives versus 97.4 percent with physicians. Warriner reported an abortion completion rate of 97.4 percent with nurses as compared with 96.3 percent with physicians. Puri reported an abortion completion rate of 96.8 percent when the service was provided by nurse-midwives as compared with 97.4 percent in the "standard care" group.[30] Our 2016 review also included a systematic review of six controlled clinical studies by Renner;[31] the authors concluded that the evidence "indicates that trained mid-level providers may effectively and safely provide first trimester surgical and medical termination of pregnancy services." Additionally, Barnard et al., in a Cochrane systematic review, assessed the safety and effectiveness of abortion procedures administered by mid-level providers (nurse practitioners, midwives, other non-physician healthcare providers) compared to doctors.[32] The authors concluded, based in part on two of the studies that we had reviewed in 2016,[33] that there was no statistically significant difference in the risk of failure for medical abortions performed by mid-level providers compared with doctors.

We also believe that the identification of patients for whom the use of mifepristone is contraindicated can be done by mid-level healthcare providers, as well as physicians. Mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation is contraindicated in patients with any of the following conditions:[34]

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass

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[26] Olavarrieta CD, Ganatra B, Sorhaindo A, et al. Nurse versus Physician-provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial. Bull World Health Organ. 2015;93:249-258.

[27] Kopp Kallner H, Gomperts R, Salomonsson E, et al. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. BJOG. 2015; 122: 510-517.

[28] Warriner IK, Wang D, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet. 2011; 377: 1155-61.

[29] Puri M, Tamang A, Shrestha P, et al. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. Reproductive Health Matters. 2015; 22(44) 94-103.

[30] 2016 Clinical Review, supra n. 13, at 43.

[31] Renner RM, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care? A systematic review. BJOG 2013 Jan;120(1):23-31.

[32] Barnard S, Kim C, Park MN, Ngo TD. Doctors or mid-level providers for abortion (Review). Cochran Database of Systematic Reviews. 2015, Issue 7.

[33] Of the medical abortion studies reviewed by Barnard et al (Id.), two were reviewed by the Agency as part of the review of the S-020 supplement in 2016. See Warriner et al (supra n. 28) and Kopp Kallner et al (supra n. 27). The third used a different dose of misoprostol than the currently approved regimen. See Jejeebhoy SJ, Kalyanwalaa S, Zaviera AJF, Kumara R, Mundleb S, Tankc J, et al. Feasibility of expanding the medication abortion provider based in India to include avurvedic physicians and nurses. International Perspectives on Sexual and Reproductive Health 2012;38(3)133-42)

[34] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

- An intrauterine device in place
- Chronic adrenal failure
- Concurrent long-term corticosteroid therapy
- History of allergy to mifepristone, misoprostol, or other prostaglandins
- Hemorrhagic disorder or concurrent anticoagulant therapy
- Inherited porphyrias

These contraindications can be assessed by trained healthcare providers who prescribe mifepristone by obtaining a medical history, from medical records, and/or from physical examination or ultrasound if appropriate. We continue to believe that available data support the conclusion that mid-level healthcare providers, as well as physicians, possess the clinical and counseling skills necessary to provide medical abortion. We note this is consistent with ACOG's statement in its current practice bulletin that "[i]n addition to physicians, advanced practice clinicians, such as nurse-midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medical abortion."[35] Further, if necessary, ultrasound training and certification is available to nurse practitioners and physician assistants, as well as physicians.[36] In sum, available information supports that mid-level healthcare providers as well as physicians can determine whether mifepristone is an appropriate treatment for a particular patient and dispense it.

You also assert that FDA should strengthen the requirement that providers accurately assess the duration of the pregnancy by mandating that gestational age be assessed by ultrasound (Petition at 5). We refer you to FDA's 2016 Response to the citizen petition submitted to Docket No. FDA-2002-P-0364 (the "2016 CP Response"), where FDA stated that the determination of gestational age does not always require an ultrasound. In the 2016 CP Response, FDA stated it had "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS [transvaginal ultrasound]) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider."[37]

In the Petition, you reference the Prescriber Agreement Form, in which the provider must attest they have the ability to: (1) accurately assess the duration of the pregnancy; (2) diagnose ectopic pregnancies; and (3) provide surgical intervention if needed (or have made plans to provide such care through others), and you state that a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional

[35] ACOG Practice Bulletin No. 225, supra n. 22.
[36] American Institute of Ultrasound in Medicine. Accessed November 26, 2021. https://www.aium.org/officialStatements/70.
[37] FDA's citizen petition response dated March 29, 2016, to the citizen petition submitted by the American Association of Pro-Life Obstetricians and Gynecologists, the Christian Medical and Dental Association, and Concerned Women for America on August 20, 2002, Docket No. FDA-2002-P-0364 at 18. See https://www.regulations.gov/document/FDA-2002-P-0364-0002.

contraindications (Petition at 5-6). You state that FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex (Petition at 4).

Certified prescribers do not have to be physically present with the patient as long as they have confirmed the patient's gestational age and intrauterine pregnancy. As noted above, in the 2016 CP response, FDA "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy."[38] Moreover, the evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber and can be done in different types of healthcare settings. A certified prescriber can also review the Patient Agreement Form[39] with the patient, fully explain the risks of the mifepristone treatment regimen, and answer any questions, as in any consent process, without physical proximity. See also section II.B.1.c (ETASU C – In-person Dispensing).

With respect to providing surgical intervention in cases of incomplete abortion or severe bleeding and assuring patient access to medical facilities equipped to provide blood transfusions and resuscitation (if necessary), the Prescriber Agreement Form does not reflect a requirement that the certified prescriber must provide such care personally; rather, the prescriber must agree that they have the ability to provide such care or that they have made plans to provide such care through others, and that they have the ability to assure the patient has access to appropriate medical facilities. It is common practice for healthcare providers to provide emergency care coverage for other healthcare providers' patients, and in many places, hospitals employ "hospitalists" to provide care to all hospitalized patients. We also note ACOG's statement that "[i]n rare cases, a patient who undergoes a medication abortion may need to obtain an additional intervention, such as uterine aspiration. If the prescribing clinician does not perform the intervention, it is medically appropriate to provide a referral."[40]

For these reasons, we deny your request that FDA limit the "ability" to prescribe and dispense mifepristone to licensed physicians, and we deny your request that FDA require certified providers to physically meet with and examine the patient.

b. Office Visits and Administration of Mifepristone/Misoprostol

In the Petition, you state that the use of mifepristone and misoprostol should require three office visits by the patient (Petition at 7). In support of this position, you state the following:

- Drug-induced abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 10).

[38] Id.
[39] See https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.
[40] ACOG Practice Bulletin Number 225 supra n. 22.

- Abortion complications are more frequent when women abort at home and more healthcare oversight is needed (Petition at 8).

- Home administration of misoprostol does not permit healthcare providers to control when their patients take misoprostol and without monitoring:

    - a patient may take buccal misoprostol before the minimum 24-hour period after taking Mifeprex, which leads to a significantly increased failure rate (Petition at 7).

    - a patient may swallow misoprostol rather than administer it buccally, and oral administration is not as effective as buccal administration in ending the pregnancy (Petition at 7).

- Because providers may now "confirm" that a patient's drug-induced abortion was successful without a clinic visit, this increases the threat that Rh-negative patients will not receive Rhogam, which is necessary to prevent serious risks in subsequent pregnancies (Petition at 7 and 9).

We address each of these points below.

i. Follow-up Care

The safe use of mifepristone when used in the approved regimen with misoprostol is not contingent on a specific number of office visits being made by the patient undergoing a medical termination of pregnancy. The 2016 labeling change for Mifeprex regarding post-treatment assessment, including the change to the approved regimen to reduce the number of offices visits from three to one, was based on evidence reviewed in the S-020 efficacy supplement. We concluded, upon reviewing the data, that three office visits were not necessary to assure the safe use of Mifeprex.[41]

In your Petition, you point to statements by ACOG that medical abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 8, 10). The ACOG statements you point to are from ACOG Practice Bulletin No. 143, which has been withdrawn and replaced by Practice Bulletin No. 225.[42] Neither of the statements from the withdrawn Practice Bulletin nor Practice Bulletin No. 225 contraindicate medical abortion in women who are not available for an in-clinic follow-up visit. The current ACOG recommendations indicate that for medical abortion, "[f]ollow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility."[43] The patient and their healthcare provider should determine the best option for follow-up as part of the consultation and consent process.[44] As reflected in ACOG's guidance, appropriate follow-

[41] See 2016 Clinical Review, supra n. 13, at 44 and 64-67.
[42] ACOG Practice Bulletin Number 225, supra n. 22.
[43] Id.
[44] Id.

up after medical termination of a pregnancy may be accomplished in multiple ways and not all require an in-clinic visit.

You also question findings in multiple studies that evaluated the effectiveness of semiquantitative urine pregnancy tests (multi-level pregnancy tests, or MLPT) and low sensitivity urine pregnancy tests (LSPT) to rule out on-going pregnancies and assessed the ability of patients to self-administer these tests and interpret the test results (Petition at 9-10). Overall, these studies concluded that in the majority of women, it is feasible to use a simplified test to determine if further follow-up is necessary. A recent systematic review and meta-analysis by Baiju assessed the effectiveness and safety of self-assessment of the outcome of medical abortion completed at home versus routine clinic follow-up after medical abortion, concluding self-assessment was not inferior to routine clinic follow-up.[45] We note that this is consistent with current ACOG recommendations, which state that "follow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility."[46]

You also assert that it is important for a patient to be under observation after taking misoprostol to ensure that they are appropriately monitored and provided sufficient pain medication (Petition at 8). You cite the World Health Organization (WHO)'s statement in guidance that up to 90 percent of women will abort within 4-6 hours after taking misoprostol; you further state that the 2000 regimen permitted patients to be in the clinic during this time period (Petition at 8). Your reference to the WHO guidance document[47] appears to be out of context. The WHO guidance takes no position on whether women should return to and remain in the clinic during a follow-up visit for purposes of taking misoprostol; in fact, it explicitly recognizes that post-abortion care may not require a follow-up visit if the patient is adequately counseled.[48] In the United States, and as reflected in the approved labeling, medical termination of pregnancy usually involves patients terminating the pregnancy at home, with appropriate follow-up that may not include a return visit.

ii. At Home Medical Abortion and Healthcare Oversight

In addition, you cite a 2018 study to support your statement that abortion complications are more frequent when women abort at home (Petition at 8). The study evaluated complications following medical abortion (both less than 12 weeks and more than 12 weeks gestation) as well as following surgical abortion, at one hospital in Sweden between 2008 and 2015.[49] For the years 2008 to 2010, data were collected retrospectively; for the years

[45] Baiju, N, Acharya, G, D'Antonio, F, et al. 2019. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. BJOG; 126:1536-1544.
[46] ACOG Practice Bulletin Number 225, supra n. 22.
[47] World Health Organization, Safe Abortion: technical and policy guidance for health systems – 2nd edition. 2012. Page 45 and Section 2.2.2.1 Medication for pain.
[48] Id. at Section 2.3 Post-abortion care and follow-up, at 52.
[49] Carlsson I, Breding K, Larsson PG, 2018, Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study, BMC Women's Health 18:158.

2011 to 2015, data were collected prospectively. In this study, medical abortions after 12 gestational weeks all occurred at the hospital. The authors report that, among medical abortions less than 12 weeks, the complication frequency increased from 5.4 percent (2008 to 2010) to 8.2 percent (2015). However, the authors also compared the complications related to medical abortions that occurred at less than 12 gestational weeks between "at home" abortions (managed as an outpatient) and "at the hospital" abortions, in 2015 and found no statistically significant difference (8.2 percent "at home" versus 8.0 percent at the hospital). For pregnancies less than or equal to 9 gestational weeks, the rates are similar for the "at home" group (10.0 percent) and the "at the hospital" group (9.3 percent). Notably, as part of our review and approval of the S-020 efficacy supplement in 2016, we assessed serious adverse events by gestational age, including hospitalizations, serious infection requiring hospitalization or intravenous antibiotics, bleeding requiring transfusion, and ectopic pregnancy, as reported in the literature submitted by the Applicant. We concluded that these serious adverse events are rarely reported in the literature and that the regimen of mifepristone 200 mg followed by buccal misoprostol 800 mcg in 24-48 hours is safe to approve for use through 70 days gestation.[50]

You also state that medical abortion is a longer process than surgical abortion and that it requires more attention and care from healthcare providers (Petition at 10). We agree that medical abortion can be a longer process than surgical abortion,[51] but we disagree that medical abortion always requires in-person follow-up with a healthcare provider. Not all of the complications associated with medical abortion necessarily require more intensive management from healthcare providers during a follow-up visit. The question of whether to include an in-person follow-up visit should be discussed by the healthcare provider and the patient. We have concluded that medical abortions are safe and effective for patients who are appropriate candidates and reducing the number of clinic visits does not compromise patient safety.

The current approved labeling for mifepristone for medical termination of pregnancy states that complete pregnancy termination "can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan." Not all these modalities require an in-clinic assessment during a follow-up visit. Our review of the S-020 efficacy supplement concluded that "available data support … that there are a variety of follow-up modalities that can adequately identify the need for additional intervention."[52] We note that these findings are also consistent with ACOG guidelines, which state that "[r]outine in-person follow-up is not necessary after uncomplicated medication abortion" and recommend several methods for post-treatment follow-up, as appropriate, including serial serum hCG testing alone or telephone follow-up at one week after treatment followed by urine pregnancy testing at four weeks after treatment.[53] Because there is more than one effective method to detect an on-going pregnancy, we conclude that the way in which post-treatment follow-up is performed may be determined by the healthcare provider and the patient.

[50] 2016 Clinical Review, supra n. 13, at 51-57.
[51] See ACOG Practice Bulletin Number 225, supra note 22.
[52] 2016 Cross Discipline Team Leader Review, supra n. 19, at 17.
[53] ACOG Practice Bulletin Number 225, supra note 22.

iii. Misoprostol

In the Petition, you make a number of assertions regarding the use of misoprostol. We address each in turn.

First, you assert that a patient may take misoprostol before the prescribed minimum 24-hour period after taking Mifeprex, thereby rendering the regimen ineffective, and that home administration of misoprostol does not permit health providers to control when their patients take misoprostol (Petition at 7). You similarly assert that the use of buccal misoprostol sooner than 24 hours after administering mifepristone leads to significantly increased failure rates (Petition at 7).

As an initial matter, our review of the S-020 efficacy supplement in 2016 included data that evaluated the home use of misoprostol in over 30,000 women. The data showed that Mifeprex was safe and effective in a regimen with misoprostol when misoprostol was self-administered at home.[54] Therefore, any incorrect administration resulting in a failed abortion was infrequent and did not significantly affect the safety and efficacy of medical abortion. Furthermore, because the process of expelling the pregnancy may begin as soon as 2 hours after taking misoprostol, there is a benefit in allowing patients to choose when and where to start this process, to maximize the possibility of their being at a safe place at a convenient time to experience cramping and bleeding.[55]

In support of your assertion of significantly increased failure rates, you cite a pilot study by Lohr et al.[56] Lohr et al. assessed the complete abortion rate using simultaneous oral mifepristone and buccal misoprostol in three gestational age groupings (less than or equal to 49 days, 50-56 days, 57-63 days) and compared the rates with those published in previous pilot investigations[57] using simultaneous oral mifepristone and vaginal misoprostol in the same three gestational age groupings. The complete abortion rates reported by Lohr at 24 hours for oral mifepristone and buccal misoprostol were 72.5 percent, 69.2 percent, and 72.5 percent, respectively; the complete abortion rates at two weeks, however, were 97.5 percent, 100 percent, and 94.9 percent, respectively (and are consistent with the completion rates as described in the approved labeling).[58] The published complete abortion rates at 24 hours for simultaneous oral mifepristone and vaginal misoprostol administration were 90 percent, 88 percent, and 83 percent, respectively, for the gestational age groupings and the complete abortion rates at 2 weeks were 98 percent, 93 percent, 90 percent, respectively. Based on the data presented in Lohr,

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[54] See 2016 Clinical Review, supra n. 13, at 41 and 48.
[55] Id. at 38.
[56] Petition at 7 (referencing Lohr PA, Reeves MF, Hayes JL, et al., 2007, Oral Mifepristone and Buccal Misoprostol Administered Simultaneously for Abortion: A Pilot Study, Contraception, 76:215-220).
[57] Schreiber CA, Creinin MD, Harwood B, Murthy AS. A pilot study of mifepristone and misoprostol administered at the same time for abortion in women with gestation from 50 to 63 days. Contraception 2005;71:447–50; Murthy AS, Creinin MD, Harwood B, Schreiber C. A pilot study of mifepristone and misoprostol administered at the same time for abortion up to 49 days gestation. Contraception 2005;71:333–6.
[58] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

the use of buccal misoprostol at the same time as oral mifepristone does not adversely affect efficacy, although expulsion may be delayed. As recommended in Section 2.3 of the approved labeling, follow-up at 7-14 days after administration of mifepristone is more appropriate to evaluate efficacy.[59] It is misleading to only reference the abortion completion rates observed at the 24-hour timepoint from Lohr. Therefore, we do not agree that data from Lohr indicate higher failure rate with misoprostol taken before the prescribed minimum 24-hour period after taking mifepristone.

Although we disagree that Lohr demonstrates a higher failure rate with misoprostol taken before 24-hours after taking mifepristone, we note that our 2016 review of the S-020 efficacy supplement referenced a 2013 systematic review by Raymond, which concluded that if the interval between mifepristone and misoprostol interval is less than or equal to 24 hours, the procedure is less effective compared to an interval of 24-48 hours.[60] As explained above, the data reviewed in 2016 showed that Mifeprex, in a regimen with misoprostol administered at home, was safe and effective. Therefore, incorrect administration, if it occurred, was infrequent and did not significantly affect the safety and efficacy of medical abortion. However, in light of the data reviewed, section 2.1 of the labeling approved in 2016 (as well as the currently approved labeling and Medication Guide) states that there should be a "minimum 24-hour interval between" mifepristone and misoprostol (emphasis included in the labeling).[61] The approved dosing regimen also states that misoprostol is taken within 24 to 48 hours after taking mifepristone and acknowledges that the effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours after mifepristone administration.

In addition to your concerns that a woman may take misoprostol too soon after administering mifepristone, you also state that waiting until 24 hours after administering mifepristone does not guarantee success (Petition at 7-8). In support of this concern, you cite a 2015 review by Chen and Creinin. You state that this review found "women taking misoprostol earlier than 48 hours after Mifeprex are more likely to fail the regimen" (Petition at 8). Chen and Creinin included studies in which the intervals between mifepristone and buccal misoprostol were 24 hours or 24-48 hours and stated that "based on the available literature, the overall efficacy of regimens with a 24-hour interval between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2 percent compared with 96.8 percent)."[62] The rate differences were statistically significant, but both regimens were more effective than the 92 percent efficacy rate of the original regimen approved in 2000 (administering misoprostol 48 hours after taking mifepristone).

Finally, you also express concern that if misoprostol is self-administered, a woman may swallow it rather than keep the pill between her cheek and gum, and oral administration of

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[59] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.
[60] 2016 Clinical Review, supra n. 13, at 31 (citing 8 Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013;87(1):26-37.)
[61] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.
[62] See Chen MJ and Creinin MD. Mifepristone with buccal misoprostol for medical abortion. Obstet Gynecol. 2015;126(1):12-21; see also 2016 Clinical Review, supra n. 13, at 21.

misoprostol (i.e., swallowing the pill) following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy (Petition at 7). Winikoff et al. specifically studied the use of oral compared to buccal misoprostol 24-36 hours after mifepristone 200 mg with overall success rates of 91.3 percent and 96.2 percent, respectively.[63] Both regimens resulted in a greater than 91 percent successful medical abortion. Although the study showed decreased efficacy with oral versus buccal administration in 57-63 days gestational age, there were no statistical differences in other gestational age groupings. Even assuming there is a small proportion of women who are 57-63 days gestational age and use oral administration of misoprostol (rather than buccal as labeled), a small decrease in the reported efficacy in that population would not justify requiring a clinic visit for all women undergoing medical abortion.

Overall, studies support the efficacy of the mifepristone, in a regimen with misoprostol when taken by the patient at home, Therefore, we do not agree that an in-person visit is necessary to manage administration of misoprostol.

iii. Rh-Negative Patients

In the Petition, you state that a follow-up examination is particularly critical for Rh-negative patients and that without that follow-up examination, women will not receive Rhogam after the abortion, increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies (Petition at 9). You suggest that a clinic visit after the administration of Mifeprex is important for Rh-negative women to receive Rhogam and that removing the required follow-up visit puts Rh-negative women at risk for isoimmunization. We do not agree.

Rh testing is standard of care in the United States and RhD immunoglobulin (such as Rhogam) should be administered if indicated. Further, administration of RhD immunoglobulin should be given within 72 hours of a sensitizing event (e.g., medical abortion).[64] However, the facility where the RhD immunoglobulin injection occurs (clinic, hospital or laboratory) is not critical. A shift from medical clinics to hospitals for administration of injections has occurred over the years due to shortages of RhD immunoglobulin and poor reimbursement for RhD immunoglobulin injection from third-party payers.[65] This has resulted in pregnant women frequently obtaining routine 28-week RhD immunoglobulin injections at hospitals/laboratories with a prescription provided by their healthcare providers. This same process of obtaining RhD immunoglobulin via prescription is available to patients after medical termination of pregnancy and does not require a follow-up clinic visit.

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[63] Winikoff B, Dzuba, IG, Creinin MD, et al, 2008, Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion, Obstet Gynecol 112(6):1303-1310.

[64] ACOG Practice Bulletin No. 181. Prevention of Rh D Alloimmunization. August 2017.

[65] See https://www.mdedge.com/obgyn/article/61083/practice-management/rhogam-injections-payment-levels-vary-among-insurers.

In summary, the totality of data on the efficacy and safety of medical abortion at less than 70 days gestation, derived from numerous studies, has characterized the complications and rates of complications for completing medical abortion at home, and the findings show medical abortion at home is both safe and effective without three office visits. We therefore deny your request that the use of mifepristone in a regimen with misoprostol require three office visits by the patient.

c. Contraindications

In the Petition, you assert that critical language contraindicating Mifeprex for patients without access to appropriate emergency medical care was excluded from the 2016 Mifeprex labeling. You cite to a study[66] and ACOG statements as evidence that medical abortions have greater risks and more need for emergency "operation" than a surgical abortion, particularly for patients in rural areas with limited access to emergency medical care (Petition at 11).

Although inadequate access to medical facilities for appropriate care was removed from the list of contraindications in section 4 of the approved labeling when we approved the S-020 efficacy supplement, the 2016 Mifeprex labeling and the currently approved mifepristone labeling, as well as the Mifepristone REMS Program, continue to include appropriate instructions for providers regarding patient access to appropriate medical care.[67] For example, the Boxed Warning includes language directing healthcare providers to ensure that the patient knows whom to call and what to do, including potentially going to an emergency room, if the patient experiences serious events associated with the use of mifepristone. The labeling also directs healthcare providers, as part of the dosing regimen, to give the patient the name and phone number of a healthcare provider who will be handling emergencies.[68] In addition, one of the required qualifications listed in the Prescriber Agreement Form is the "[a]bility to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary."[69] Therefore, although certain language about access to medical facilities was removed from the approved labeling in 2016, we disagree that critical language about access to appropriate emergency medical care is lacking from the approved labeling.

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[66] See Petition Reference Document No. 17 (Harrison Affidavit: Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015), ¶115 (referencing M. Niinimaki et al., Immediate Complications after Medical compared with Surgical Termination of Pregnancy, Obstet. Gynecol. 114:795 (Oct. 2009)).

[67] See Mifeprex labeling, approved 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf. See also current labeling at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

[68] Id.

[69] Mifepristone REMS Program, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390. Emphasis added.

You also cite information in Box 1, Features of Medical and Surgical Abortion (page 3) in the ACOG Practice Bulletin No. 143.[70] As mentioned above, the ACOG Practice Bulletin No. 143 has been withdrawn and the language you cite is not included in the current Practice Bulletin No. 225.

d. Adverse Event Reporting

In the Petition, you assert that even under the regimen approved in 2000, it was difficult to collect accurate and complete adverse event information for Mifeprex, and that collecting such information is virtually impossible under the regimen approved in 2016 because prescribers only are required to report deaths associated with Mifeprex (Petition at 12). You also assert that FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events (Petition at 12). You state that certified prescribers should at a minimum be required to report the following to FDA's MedWatch reporting system and to the sponsor: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications, including detailed information on these events (Petition at 13).

We acknowledge that there is always a possibility with any drug that some adverse events are not being reported, because reporting to the Agency's MedWatch program by health care professionals and patients is voluntary. We do not agree, however, that the 2016 changes to the prescriber reporting requirements limit our ability to adequately monitor the safety of mifepristone for medical termination of pregnancy. Prior to the 2016 approval of the S-20 efficacy supplement, we assessed approximately 15 years of adverse event reports both from the Applicant and through the MedWatch program and determined that certain ongoing additional reporting requirements under the Mifeprex REMS, such as hospitalization and blood transfusions, were not warranted. This assessment was based on the well-characterized safety profile of Mifeprex, with known risks occurring rarely, along with the essentially unchanged safety profile of Mifeprex during this 15-year period of surveillance. Accordingly, the Prescriber Agreement Form was amended as part of our 2016 approval of the S-20 efficacy supplement to require, with respect to adverse event reporting, only that prescribers report any cases of death to the Applicant.

We also note that the reporting changes to the Prescriber Agreement Form as part of our 2016 approval do not change the adverse event reporting requirements for the Applicants. Like all other holders of approved NDAs and ANDAs, the Applicants are required to report all adverse events, including serious adverse events, to FDA in accordance with the requirements set forth in FDA's regulations (see 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81). FDA also routinely reviews the safety information provided by the Applicants in the Annual Reports. As with all drugs, FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

[70] Petition at 11. Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.

You state that FDA should provide guidance to emergency healthcare providers and physicians so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage (Petition at 13). We disagree that specific guidance is needed at this time. In the past, when appropriate, FDA has worked with the NDA Applicant to issue communications to healthcare providers and emergency department providers concerning certain serious adverse events.[71] Furthermore, the approved Medication Guide advises patients to take the Medication Guide with them if they need to go to the emergency room or seek care from a healthcare provider other than the one who dispensed the medication to them, so the emergency room or healthcare provider understands the patient is having a medical abortion. We have not identified a change in the safety profile of mifepristone that would warrant additional communications to healthcare providers and emergency department providers concerning complications following medical abortion. If we become aware of safety information that merits further communications with emergency department providers or healthcare providers, or that warrants revisions to the approved labeling, we will act as appropriate.

You also assert that many Mifeprex prescribers "violate FDA protocol," instructing their patients to lie to emergency medical personnel, and that this prevents emergency healthcare providers from appropriately caring for their patients and further decreases the likelihood that adverse events will be reported (Petition at 12). Your only support for this claim is a reference to instructions from the organization Aid Access[72] to patients that they can tell emergency room staff that they had a miscarriage and do not need to tell medical staff that they had a medical abortion. The Petition does not provide any data or additional information establishing "many Mifeprex prescribers violate FDA protocol, instructing their patients to lie," or that these providers thereby prevented appropriate care and decreased the number of adverse events reported.

B. REMS

1. Request to Retain Mifeprex REMS

In your Petition, you request that FDA retain the Mifeprex REMS (Petition at 14). We agree that a REMS is necessary to ensure that the benefits of mifepristone in a regimen with misoprostol outweigh the risks. FDA's determination as to whether a REMS is necessary

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[71] See Historical Information on Mifepristone (Marketed as Mifeprex), available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm. For example, the NDA applicant and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 and a Dear Emergency Room Director letter in September 2004. The fact that these letters were issued does not imply that the approved mifepristone regimen is unsafe; it is not uncommon for drug sponsors to issue "Dear Health Care Provider" letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, "[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely."

[72] We note that Aid Access facilitated the sale of unapproved mifepristone and misoprostol to U.S. consumers and that FDA sent Aid Access a warning letter asking it to promptly cease causing the sale of unapproved and misbranded drugs to U.S. consumers. US FDA Warning Letter to Aidaccess.org, dated March 8, 2019. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019.

to ensure that the benefits of a drug outweigh its risks is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case.[73] In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.[74]

As described in the background section of this response (see section I.A.), FDA determined that interventions in addition to the FDA-approved labeling were necessary to ensure that the benefits of Mifeprex outweighed its risks when the drug was initially approved in 2000, and periodic re-evaluations of the REMS since that time have reached the same conclusion. As further described in the background section of this response (see section I.E.), FDA recently undertook a review of the Mifepristone REMS Program. As explained below, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risks.

After review of multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FAERS reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation,[75] as well as information submitted by the Applicants, we have concluded that the REMS can be modified to reduce the burden on the health care delivery system without compromising patient safety. As explained below, we agree that the healthcare provider certification (ETASU A) and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions (ETASU D) continue to be necessary components of the REMS to ensure the benefits outweigh the risks. However, we have concluded that the Mifepristone REMS Program must be modified to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

Below, we discuss each of these elements of the Mifepristone REMS Program.

a. ETASU A – Prescriber Certification/Qualifications

ETASU A under the Mifepristone REMS Program requires healthcare providers who prescribe mifepristone to be certified. In order to become certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the Prescriber Agreement Form. In signing the Prescriber Agreement Form, prescribers agree they meet the qualifications listed below:

[73] See FDA Guidance for Industry, *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (Apr. 2019).
[74] Id.
[75] See supra n. 10.

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the Patient Agreement Form with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

Our review of the published literature did not identify any studies comparing healthcare providers who met these qualifications with healthcare providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention either personally or through others, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our conclusion continues to be that a healthcare provider who prescribes mifepristone in a regimen with misoprostol should meet the above qualifications. Absent these provider qualifications, we are concerned that serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, may not be detected or appropriately managed.

Accordingly, we have determined that ETASU A must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks. Maintaining the requirement for prescriber certification ensures that providers meet the necessary qualifications and adhere to the guidelines for use listed above. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one-time for each applicant.

Although we agree with your request to retain the REMS for mifepristone (now the Mifepristone REMS Program) insofar as it pertains to ETASU A, as discussed in section II.A.2.a of this response, we do not agree with your request that the healthcare provider needs to be a licensed physician to meet this requirement.

b. ETASU D – Requirement For The Drug To Be Dispensed With Evidence Or Other Documentation Of Safe-Use Conditions

ETASU D under the Mifepristone REMS Program requires mifepristone to be dispensed with evidence or other documentation of safe-use conditions. To receive mifepristone for medical termination of intrauterine pregnancy through 70 days gestation, the patient must sign a Patient Agreement Form indicating that the patient has received, read, and been provided a copy of the Patient Agreement Form and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The Patient Agreement Form ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication. In a number of approved REMS, Patient Agreement Forms or Patient Enrollment Forms ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[76]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the Patient Agreement Form with the patient, fully explaining the risks of the treatment regimen and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the Patient Agreement Form, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the Patient Agreement Form serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed Patient Agreement Form in the patient's medical record.

In addition, we conducted an updated review of published literature since 2016 to assess the utility of maintaining the Patient Agreement Form as part of the Mifepristone REMS Program, and these studies do not provide evidence that would support removing ETASU D. For these reasons, we have determined that ETASU D must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks.

[76] REMS@FDA, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.

c. ETASU C – In-Person Dispensing

ETASU C under the Mifepristone REMS Program currently requires mifepristone to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. This creates what we refer to in this response as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office, or hospital when the drug is dispensed. The mifepristone REMS document currently states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than a clinic, medical office, or hospital. As explained below, based on a recent review of the REMS, we believe that the Mifepristone REMS Program must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks. This conclusion is based on our review of information from the Mifepristone REMS Program one-year (1st) REMS[77] assessment data and postmarketing safety information, and supported by our review of the published literature.

i. Assessment Data

As part of our review of the REMS, we evaluated information included in the 1st REMS assessment report for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, and non-compliance data. This 1st REMS assessment report covers a reporting period between April 11, 2019 through February 29, 2020. During this reporting period, a small number of non-compliance events were reported.

As described in section I.C. of this response, during the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not enforced. To better understand whether there was any impact on safety or non-compliance during the periods when the in-person dispensing requirement was not enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or non-compliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. The NDA and the ANDA Applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no

[77] This REMS assessment report was the first submitted following the approval of the single, shared system REMS for mifepristone.

indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events.

ii. FAERS/Postmarketing Safety Data

FDA routinely monitors postmarketing safety data for approved drugs through adverse events reported to our FAERS database,[78] through our review of published medical literature, and when appropriate, by requesting applicants submit summarized postmarketing data. For our recent review of the REMS, we searched our FAERS database, reviewed the published medical literature for postmarketing adverse event reports for mifepristone for medical termination of pregnancy, and requested that the Applicants submit a summary and analysis of certain adverse events. Our review of this postmarketing data indicates there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced.

In order to evaluate the periods when in-person dispensing was and was not enforced, we conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy. The data for this time period were then further divided into the date ranges when in-person dispensing was enforced per the REMS (January 27, 2020 - July 12, 2020 and January 13, 2021 - April 12, 2021) versus when in-person dispensing was not enforced: July 13, 2020 - January 12, 2021 (in-person dispensing enforcement was temporarily enjoined) and April 13, 2021 - September 30, 2021 (enforcement discretion for in-person dispensing because of the COVID-19 PHE).

Based on the above search, a total of eight cases were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when in-person dispensing was being enforced (i.e., January 27, 2020-July 12, 2020 and January 13, 2021-April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when in-person dispensing was not enforced (i.e., July 13, 2020-January 12, 2021 and April 13, 2021-September 30, 2021); however, the narratives provided in the FAERS reports for three of the five cases explicitly stated that mifepristone was dispensed in-person. These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Of note, ongoing pregnancy and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case reported the occurrence of oral pain/soreness (case 8) in July

[78] FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

2021, but did not provide sufficient information to determine the exact date of the adverse event.

As discussed in section II.A.2.d., the Applicants report adverse events, including serious adverse events, to FDA in accordance with applicable regulations.[79] To enable additional review of adverse events, Applicants were requested to provide a summary and analysis for adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided the requested summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021. The Applicant for the generic provided the requested summary of postmarketing safety information from April 11, 2019 (date of initial approval) through September 30, 2021. The information provided by the Applicants included the same cases identified in FAERS, as discussed above.

We analyzed the FAERS data referenced above to determine if there was a difference in adverse events when in-person dispensing was and was not enforced. Based on FDA's review of this data, we concluded that there does not appear to be a difference in adverse events when in-person dispensing was and was not enforced and that mifepristone may be safely used without in-person dispensing. FDA's review of the summary and analysis data submitted by the Applicants (which, as noted above, included the same cases identified from FAERS) did not change this conclusion.

iii. Published Literature

As noted above, we also conducted an extensive review of the published literature since March 29, 2016 (the date the S-020 efficacy supplement for Mifeprex was approved) through September 30, 2021.[80] Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or equivalent healthcare provider in countries other than the United States). Some studies have examined replacing in-person dispensing in certain healthcare settings with dispensing at retail pharmacies[81]

[79] See 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81.

[80] In support of your request that we retain the REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber, you reference two studies that you assert do not comply with the REMS (Petition at 19-22). Outcomes from both of the studies you reference have been reported in the published literature and are addressed in the discussion that follows. We note that as a general matter, a clinical investigation of an approved drug that is subject to a REMS can take place in healthcare settings outside those provided for in the REMS. When an approved drug that is subject to a REMS is studied in a clinical trial, the REMS does not apply to the use of the drug in that clinical trial. However, FDA reviews the protocol to ensure that it will be conducted in a manner that adequately addresses the risks that the REMS is intended to mitigate, such that the trial participants will not be exposed to an unreasonable and significant risk of illness or injury. See 21 CFR 312.42(b)(1)(i) and (b)(2)(i).

[81] Grossman D, Baba CF, Kaller S, et al. Medication Abortion With Pharmacist Dispensing of Mifepristone. Obstet Gynecol 2021;137:613–22; Rocca CH, Puri M, et al. Effectiveness and safety of early medication

and dispensing mifepristone from pharmacies by mail.[82] Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to patients,[83] and (2) prescribers using couriered delivery of medications.[84] Different studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization."[85]

We note that the ability to generalize the results of these studies to the United States population is hampered by differences between the studies with regard to pre-abortion care (e.g., telemedicine versus in-person). In addition, the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy. There are also factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation (for example, most studies on mail dispensing of mifepristone also include telemedicine consultation); and (2) because most serious adverse events with medical abortion are infrequent, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the United States. Despite the limitations of the studies we reviewed, we have concluded that overall the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

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abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal. PLoS ONE 13(1): e0191174. https://doi.org/10.1371/journal.pone.019117; Wiebe ER, Campbell M, et al. Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol. Contracept X. 2020; 2: 100023.

[82] Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. Contraception 2021, ISSN 0010-7824, https://doi.org/10.1016/j.contraception.2021.09.008, Available online 20 September 2021; Upadhyay UD, Koenig LR, Meckstroth KR. Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic. JAMA Network Open. 2021;4(8):e2122320, doi:10.1001/jamanetworkopen.2021.22320; Hyland P, Raymond EG, Chong E. A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months. Aust N Z J Obstet Gynaecol 2018;58: 335-340.

[83] See Anger HA, Raymond EG, et al. Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail. Contraception 2021 Jul 28;S0010-7824(21)00342-5. doi: 10.1016/j.contraception.2021.07.108. Published online. Raymond E, Chong E, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States. Contraception 2019; 100:173-177. See also Chong et al., infra n. 103 Kerestes et al., infra n. 105, and Aiken et al., infra n. 106.

[84] Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjsrh-2020-200976.

[85] Endler M, Beets L, Gemzell Danielsson K, Gomperts R. Safety and acceptability of medical abortion through telemedicine after 9 weeks of gestation: a population-based cohort study. BJOG 2019;126;609-618. Norten H, Ilozumba O, Wilkinson J, Gemzell Danielsson K, Gomperts R. 10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study. BJOG 2021; https://doi.org/10.1111/1471-0528.16765; Aiken ARA, Digol I, Trussell J, Gomperts R. Self-reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland. BMJ 2017;357:j2011 http://dx.doi.org/10.1136/bmj.j2011.

Below is a summary of our review of the literature, organized by the methods of dispensing mifepristone that were studied.

(a) Retail pharmacy dispensing

Three studies reported medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation (Grossman,[86] Rocca,[87] Wiebe[88]). Grossman conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic. Complete abortion without additional procedures occurred in 93.5 percent of participants with known outcomes. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. No participants experienced a serious adverse event, were hospitalized or required transfusion. Three participants had emergency department (ED) visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study safety and efficacy outcomes are consistent with labeled outcome frequencies. The study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to United States retail pharmacies; there is insufficient information to assess this.

Rocca[89] conducted an observational study evaluating participants who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. The authors reported that, with respect to complete abortion (greater than 97 percent) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[90] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of women who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (equal to or greater than 95 percent participants with known outcomes). The telemedicine group had one case of hemorrhage (0.5 percent) and one case of infection requiring antibiotics (0.5 percent) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3 percent compared to 1.5 percent in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

[86] Grossman et al., supra n. 81.
[87] Rocca et al., supra n. 81.
[88] Wiebe et al., supra n. 81.
[89] Rocca et al., supra n. 81.
[90] Wiebe et al., supra n. 81.

None of the three studies allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the results of the studies to the current retail pharmacy environment in the United States. The outcome findings from the one United States study (Grossman)[91], in which the pharmacies were partnered with prescribers, are unlikely to be broadly generalizable to the current retail pharmacy environment and do not reflect typical prescription medication availability with use of retail pharmacy dispensing. For the retail pharmacy dispensing study in Canada (Wiebe),[92] timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that would allow timely access to medications for medical abortion would occur in retail pharmacies throughout the United States, suggesting the findings from that study may not be broadly generalizable. The third study (Rocca)[93] evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the United States retail setting.

(b) Mail order pharmacy

Three studies evaluated mail order pharmacy dispensing (Grossman,[94] Upadhyay,[95] Hyland[96]). Grossman published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. Complete abortion without additional procedures occurred in 96.9 percent of participants with known outcomes. Two (0.9 percent) participants experienced serious adverse events; one received a blood transfusion and one was hospitalized overnight. Nine (4 percent) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies.

Upadhyay[97] reports findings from a retrospective cohort study of women undergoing medical abortion in the United States without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Abortion outcome was determined by either an assessment on day 3 or a 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95 percent for participants with known outcomes and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. As recommended in Section 2.3 of the approved labeling, follow-up at

[91] Grossman et al., supra n. 81.
[92] Wiebe et al., supra n. 81.
[93] Rocca et al., supra n. 81.
[94] Grossman et al, supra n. 82.
[95] Upadhyay et al., supra n. 82.
[96] Hyland et al., supra n. 82.
[97] Upadhyay et al., supra n. 82.

7-14 days after administration of mifepristone is more appropriate to evaluate safety and efficacy. This study used a model with numerous deviations from standard provision of medical abortion in the United States, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[98] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. Complete abortions without additional procedures occurred in 96 percent of participants with documented outcomes and is consistent with labeled efficacy. Of the participants included in the analysis, 95 percent had no face-to-face clinical encounters after medications were mailed while 3 percent were admitted to the hospital and 2 percent had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up." The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. However, the reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported frequency of hospitalizations (3 percent) is higher than the less than 1 percent in the FDA-approved mifepristone labeling, conclusions on the safety findings cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that efficacy of medical abortion is maintained with mail order pharmacy dispensing. With respect to safety, in the Grossman study[99] the interim analysis, although small, does not raise serious safety concerns. Safety findings from the Hyland[100] study are difficult to interpret. Although only one transfusion is reported and the authors state the findings demonstrate safety, a higher hospitalization rate and lack of information on the reasons for hospitalization preclude reaching any conclusions about the safety findings. Lastly, the Upadhyay[101] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the United States.

(c) Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail. Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population exclusively: Raymond (outcomes from May 2016 to December

[98] Hyland et al., supra n. 82.
[99] Grossman et al., supra n. 82.
[100] Upadhyay et al., supra n. 82.
[101] Hyland et al., supra n. 82.

2018),[102] Chong (outcomes from May 2016 to September 2020)[103] and Anger (outcomes from March 2020 to September 2020).[104] A fourth study, Kerestes,[105] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020 and a fifth study, Aiken (2021)[106] reports outcomes of medical abortion up to 70 days gestational age in the United Kingdom before and during the COVID-19 PHE in a retrospective cohort study.

In Raymond,[107] complete abortion without additional procedures occurred in 93 percent of participants with known outcomes. There were two hospitalizations (one participant received a transfusion for severe anemia despite having had a complete abortion) and 7 percent of participants had clinical encounters in ED/urgent care centers. The reported outcomes are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).[108] Of note, the authors state that half of the ED/urgent care visits did not entail any medical treatment. In Chong,[109] approximately 50 percent of the medical abortions occurred during the period of the COVID-19 PHE. Complete abortion without an additional procedure occurred in 95 percent of those with known outcomes. Transfusions were 0.4 percent and hospitalizations were 0.7 percent; 6 percent of participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 4.1 percent to complete abortion. The reported outcomes in Chong (which updated the findings described in Raymond) are similar to outcomes described in approved labeling except that (as with the Raymond study it updated) the combined ED/urgent care center encounters (6 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).

Anger,[110] which compared outcomes among participants enrolled in the Gynuity study who did ("test medical abortion cohort") versus did not ("no-test medical abortion cohort")[111]

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[102] Raymond et al., supra n. 83.
[103] Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. Contraception 2021;104:43-48.
[104] Anger et al., supra n. 83.
[105] Kerestes C, Murayama S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. Contraception 2021 Jul;104(1):49-53. doi:10.1016/j.contraception.2021.03.025. Epub 2021 Mar 28.
[106] Aiken ARA, Lohr PA, et al. Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study. BJOG 2021;128:1464–1474.
[107] Raymond, supra n. 83.
[108] The authors reported the combined frequency of emergency department/urgent care visits, whereas the approved labeling includes the frequency for emergency department (emergency room) visits. Therefore it is unknown whether the frequency of emergency department visits in the trial, as distinct from the combined frequency of emergency department/urgent care visits, is comparable to the frequency of emergency department visits reflected in approved labeling.
[109] Chong et al., supra n. 103.
[110] Anger et al., supra n. 83.
[111] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al." (Raymond EG, Grossman D, Mark A, et.al. Commentary: No-test medication abortion: A sample protocol for increasing access during a pandemic and beyond. Contraception 2020;101:361-366)

have confirmation of gestational age/intrauterine location with an examination or ultrasound, found that those without an examination or ultrasound prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.[112] There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the "test" group, complete medical abortion was confirmed in 98 percent of participants with known outcomes; one participant was "hospitalized and/or blood transfusion" and 8 percent had an unplanned clinic encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion). In the "no-test" group, complete medical abortion was confirmed in 94 percent of participants with known outcomes; two participants were "hospitalized and/or blood transfusion" and 12.5 percent had an unplanned clinical encounter.

Kerestes[113] included three different delivery models: traditional in-person visits, telemedicine consultation with in-person pick-up of medications, and telemedicine consultation with delivery of medications by mail (most of the latter were enrolled through Gynuity's TelAbortion study). Among participants with follow-up data, the rates of successful medical abortion without surgery were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine plus in-person pickup group). Although ED visits occurred the most frequently in the telemedicine plus mail group (four participants or 5.8 percent) and the least in the in-person group (two participants or 2.1 percent), the study reported no increases in other serious adverse events. Aiken (2021)[114] reported outcomes before and during the pandemic in a retrospective cohort study in the United Kingdom. The study compared the two cohorts: one before the pandemic with in-person visits and dispensing (traditional model) and one during the pandemic with either an in-person visit and in-person dispensing or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Complete abortion occurred in greater than 98 percent in both cohorts; the rate was slightly higher in the telemedicine group than in the in-person group. There were no significant differences in the rates of reported serious adverse events. The investigators' analysis determined that the efficacy and safety were comparable between both cohorts and concluded the hybrid model for medical abortion is effective and safe.

Taken together, data from the three Gynuity study reports (Raymond, Chong, and Anger), Kerestes, and Aiken (2021) support that efficacy of medical abortion was maintained when mifepristone was dispensed by mail from the clinic. Study reports of Raymond, Chong, and Kerestes all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail from the clinic, but without increases in other serious adverse events. Anger's comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. The Aiken (2021) study appears to be of sufficient

[112] We note that the two cohorts were not randomized in the Anger study; they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.
[113] Kerestes et al., supra n. 105.
[114] Aiken et al., supra n. 106.

sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, significant limitations include that the analysis was based on deidentified information and the investigators were unable to verify the outcomes extracted. Further, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

Notwithstanding the limitations discussed above, these studies overall support that dispensing by mail from the clinic is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other serious adverse events related to mifepristone use.

(d) Clinic dispensing by courier

Reynolds-Wright[115] reported findings from a prospective cohort study of participants at less than 12 weeks gestational age in Scotland undergoing medical abortion at home that provided mifepristone for pick up at the service or by couriered delivery to woman's home. The outcomes from this study in Scotland are consistent with the outcomes in the approved mifepristone labeling. However, the number of couriered deliveries was not reported. Thus this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. The study shares the same limitations as the Aiken (2021) study; the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

(e) Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail. WoW uses a model with numerous deviations from the standard provision of medical abortion in the United States. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Three studies (Endler, Norten, and Aiken (2017))[116] reported outcomes based on dispensing through this model. Endler and Norten reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail because neither provide meaningful outcomes data for consideration. Although Aiken (2017) is a large cohort study, the outcomes are self-reported and an unusually high rate of outcomes are unaccounted for; these limitations result in the data being insufficient to determine the safety of dispensing mifepristone by mail though a partner organization.

In sum, there are insufficient data from the literature we have reviewed to determine the safety and efficacy of dispensing from a retail pharmacy, by courier, or by a partner organization. With respect to dispensing mifepristone by mail, our review of the literature indicates that dispensing mifepristone by mail from the clinic or from a mail order

[115] Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjsrh-2020-200976.
[116] Endler et al., Norten et al., and Aiken et al., supra n. 85.

pharmacy does not appear to jeopardize the efficacy of mifepristone for medical abortion. While the studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, the safety and efficacy outcomes reported in these studies remain within the ranges labeled for the approved mifepristone products. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other significant adverse events related to mifepristone use.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, and our review of the literature, we conclude that mifepristone will remain safe and effective if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added. Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the Mifepristone REMS Program, the REMS must be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

In your Petition, you state that "[e]liminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls" and that "health care providers prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs" (Petition at 18-19).

We do not agree that eliminating the REMS requirement for the dispensing of Mifeprex in certain healthcare settings will be dangerous to patients, nor do we agree that doing so will affect the ability of healthcare providers to evaluate women for contraindications to mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation. There are many factors that contribute to patient safety, including evaluation of a patient, informed consent, development of a follow-up plan, and provision of a contact for emergency care. All of these can occur in many types of healthcare settings. The evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber.

You also assert that telemedicine abortion absolves abortion providers of responsibility for the well-being of their patients (Petition at 19). We do not agree. Healthcare providers who prescribe mifepristone are responsible for the well-being of their patients regardless of mode of evaluation or dispensing of medication. The Agency agrees with the American Medical Association that a healthcare provider-patient relationship is entered when the "physician serves a patient's medical needs;"[117] in the context of medical abortion, this

[117] See www.ama-assn.org/delivering-care/ethics/patient-physician-relationships.

healthcare provider-patient relationship continues until resolution of the pregnancy or transfer of care to another healthcare provider.[118]

We also note that patients who are not pregnant at the time of evaluation would not be appropriate candidates for being prescribed mifepristone for medical termination of pregnancy because they do not fulfill the approved indication of having an intrauterine pregnancy of up to 70 days gestation.

2. Other Safety Issues and Additional Studies

In support of your request that we retain the Mifeprex REMS, you cite the Council for International Organizations of Medical Sciences' (CIOMS) definition of "rare" to assert that because "about 1 out of 100 women" using Mifeprex and misoprostol require surgery, serious complications are common, not rare (Petition at 15-16).[119] Although we agree that certain elements of the Mifepristone REMS Program are necessary to assure the safe use of mifepristone, we do not agree with your assertion.

In the Petition, you state that the Medication Guide improperly downplays the risks of the use of Mifeprex in a regimen with misoprostol and you cite the Medication Guide as stating "'*rarely*, serious and potentially life-threatening bleeding, infections, and other problems can occur following . . . medical abortion.' Specifically, 'in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure." (Petition at 15). Using these two separate statements in the Medication Guide, you argue that the CIOMS's definition of rare ("1 out of 1000") means that if 1 out of 100 women using Mifeprex in a regimen with misoprostol require surgery, serious complications are common, not rare. (Petition at 16). However, your reference to the two sentences in the Medication Guide conflates two different clinical scenarios: (1) the adverse event of serious and potentially life-threatening bleeding, and (2) treatment failure.

The first sentence you reference states: "Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth." This statement refers to life-threatening adverse events that can occur during termination regardless of gestational age or during miscarriage or childbirth regardless of the mode of delivery (e.g., vaginal delivery or cesarean section). At the time of our review of the clinical studies submitted to support the S-020 efficacy supplement, the reported rate of death in the studies reviewed, based on one death, was 0.007 percent (very rare under the CIOMS definition).[120] The rate of infections requiring hospitalization or

[118] See https://www.ama-assn.org/delivering-care/ethics/ethical-practice-telemedicine.
[119] Council for International Organizations of Medical Sciences. Guidelines for Preparing Core Clinical Safety Information on Drugs Second Edition. 1999. https://cioms.ch/wp-content/uploads/2018/03/Guidelines-for-Preparing-Core-Clinical-Safety-Info-Drugs-Report-of-CIOMS-Working-Group-III-and-V.pdf. Accessed December 13, 2021 (CIOMS).
[120] Id. at 36 (defining the "very rare" standard category of frequency as less than 0.01 percent).

intravenous antibiotics was less than 0.1 percent (rare under the CIOMS definition),[121] and rates of transfusion were 0.03-0.7 percent (rare to uncommon under the CIOMS definition).[122] Therefore, "rarely" accurately refers to the frequency of the adverse events referenced in this statement.

The second sentence you reference from the Medication Guide states: "In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C)." This statement refers to the rate of surgical procedures for bleeding following treatment with mifepristone. Heavy bleeding or hemorrhage after medical abortion is a small subset of bleeding and can require a surgical procedure due to ongoing pregnancy or incomplete expulsion; these are considered failed treatment rather than adverse events and are not characterized using the CIOMS definitions. Even if heavy, bleeding after medical abortion may not be considered a serious adverse event unless clinically diagnosed as hemorrhage or requiring a transfusion. Furthermore, in the vast majority of medical abortions, surgical intervention is not necessary.

You also cite a 2009 study and a 2018 study to assert that medical abortions carry greater risks than surgical abortions (Petition at 16). The 2009 Niinimaki, et al.[123] study reported overall incidences of immediate adverse events (up to 42 days) in medical and surgical abortions performed in women undergoing induced abortion from 2000-2006 based on data from the Finnish national registries. We agree that the overall incidence of adverse events for medical abortion was fourfold higher when compared with surgical abortion (20.0 percent versus 5.6 percent). Specifically, the incidence of hemorrhage, incomplete abortion, and surgical (re)evacuation were higher for medical abortion. However, the authors specifically noted that because medical abortion is associated with longer uterine bleeding, the high rate of events, which were pulled from a national registry reflecting both inpatient and outpatient visits, is not surprising. They opined that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after termination of pregnancy; the incidence of such bleeding was relatively low, although it was more common with medical abortion. In addition, the authors acknowledged there are inherent weaknesses in registry-based studies; there is variable reliability both of diagnoses and of severity of diagnoses. Nevertheless, the authors concluded that both methods are generally safe and recommended discussing the adverse event profiles of different methods when counseling women seeking pregnancy termination.

We note that Ireland, et al.[124] reported findings from a more recent retrospective cohort study of 30,146 United States women undergoing pregnancy termination before 64 days of gestation from November 2010 to August 2013. Efficacy of pregnancy termination was 99.6 percent and 99.8 percent for medical and surgical abortion, respectively.

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[121] Id. at 36 (defining the "rare" standard category of frequency as greater than or equal to 0.01 percent and less than 0.1 percent).
[122] Id. at 36 (defining the "uncommon" standard category of frequency as greater than or equal to 0.1 percent and less than 1 percent); see also 2016 Clinical Review, supra n. 13, at 47 and 51.
[123] Niinimaki M, Pouta A, Bloigu A, et al. Immediate complications after medical compared with surgical termination of pregnancy. Obstet Gynecol. 2009;114(4):795-804.
[124] Ireland LD, Gatter, M, Chen, A. 2015. Medical Compared with Surgical Abortion for Effective Pregnancy Termination in the Frist Trimester. Obstetrics & Gynecology 126;22-28.

Unanticipated aspiration for persistent pain, bleeding or both were 1.8 percent and 0.4 percent for medical and surgical abortion respectively. These findings are compatible with the Niinimaki study findings. There was no difference in major adverse events as defined by the authors (emergency department visit, hospitalization, uterine perforation, infection, hemorrhage requiring transfusion) between the groups. The authors conclude medical and surgical abortion before 64 days of gestation are both highly effective with low complication rates.

The 2018 Carlsson study is addressed above in section II.A.2.b.ii. of this response; as discussed above, that study showed no statistically significant difference between the overall complication rates between an "at home" and "at the hospital" abortion.[125]

We acknowledge that medical abortion is known to have more days of bleeding and increased rates of incomplete abortion compared to surgical abortion. However, as noted above, in the vast majority of medical abortions, surgical intervention is not necessary. Thus, medical abortion and surgical abortion are two options; both have benefits, side effects, and potential complications. Patients and their healthcare providers should discuss which method is preferable and safer according to each woman's unique situation.

You state that the Mifeprex REMS should require a formal study for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients with limited access to emergency room services; and patients who self-administer misoprostol (Petition at 13-14). As we explain below, additional studies are not needed at this time.

In justifying your assertion that a formal study is required in patients under the age of 18, you state that Mifeprex was approved for use in the pediatric population in 2000 after the requirement for studies in the pediatric population was waived (Petition at 13-14). The approved indication for mifepristone does not limit its use by age. Although patients age 17 and under were not included in the clinical trials supporting the initial approval of Mifeprex in 2000, we stated at the time that the safety and efficacy were expected to be the same for postpubertal (i.e., post-menarchal) adolescents. Our conclusion in 2000 that pediatric studies of Mifeprex were not needed for approval was consistent with FDA's implementation of the regulations in effect at that time. Because we determined that there were sufficient data from studies of mifepristone, the original Mifeprex approval should have reflected the Agency's conclusion that the pediatric study requirements were waived for pre-menarchal females and that the pediatric study requirements were met for post-menarchal adolescents, rather than stating that the Agency was waiving the requirements for all pediatric age groups.

As currently required by the Pediatric Research Equity Act (PREA),[126] certain applications or supplemental applications must include pediatric assessments of the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric

[125] Carlsson et al., supra n. 49.
[126] Section 505B of the FD&C Act (21 U.S.C. 355c).

subpopulations, unless that requirement is waived or deferred.[127] In accordance with PREA, when FDA reviewed the S-020 efficacy supplement, a partial waiver was granted for pediatric studies in pre-menarchal females because pregnancy does not occur in premenarchal females. We also determined that the applicant had fulfilled the pediatric study requirement in post-menarchal adolescents. This determination was based on data extrapolated from adults and information in literature. Review of these findings found the safety and efficacy in this population to be similar to the safety and efficacy in the adult population.[128] Therefore, we do not agree that a formal study is required in patients under 18.

With regard to your concerns about repeat abortions and your assertion that a study is necessary in this population, we acknowledge that published data concerning adverse reproductive health outcomes in U.S. women who undergo repeat medical abortions are limited. We concluded in our 2016 review of the S-020 efficacy supplement that there is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. We also noted that return to fertility after the use of mifepristone is well documented. [129] This is reflected both in Section 17 of the approved labeling, Patient Counseling Information, which states that the provider should "inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses," and in the Medication Guide, which states "You can become pregnant again right after your pregnancy ends." Although you state that more than one out of every three abortions in the United Sates is a repeat abortion (Petition at 14),[130] we are not aware of reports suggesting greater safety concerns in repeat abortions than a first-time abortion. Therefore, we do not agree that a study is necessary in this population. You also cite a published study, using a mouse model, of repeated medical termination of pregnancy that showed repeat medical abortion impaired the reproductive function of female mice (Petition at 14).[131] Per our 2016 review, there is no evidence in available clinical data that repeated medical or surgical abortion is unsafe, or that fertility is impaired by the use of mifepristone; therefore, data from a single non-clinical study in mice are not persuasive.[132]

With respect to your request for a formal study of mifepristone for medical abortion in women without access to emergency care, we disagree that such a study is necessary. In order to become a certified prescriber, a healthcare provider must agree that they have the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or have made plans to provide such care through others, and that they have the ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. These prescriber qualifications ensure that mifepristone is prescribed to women for whom emergency care is available.

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[127] Section 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(2)).
[128] 2016 Clinical Review, supra n. 13, at 74-76.
[129] Id. at 47.
[130] In support of this assertion, you cite Jones R, Jerman J, Ingerick M. Which abortion patients have had a prior abortion? Findings from the 2014 U.S. Abortion Patient Survey. J Womens Health.
[131] Lv F, Xu X, Zhang S, et al. Repeated abortion affects subsequent pregnancy outcomes in BALB/c mice. PLoS One. 2012;7(10):e48384. doi:10.1371/journal.pone.0048384.
[132] 2016 Clinical Review, supra n. 13, at 47.

Finally, you assert that FDA should require a formal study in patients who self-administer misoprostol. As explained in section II.A.2.b.ii of this response, FDA conducted a literature review of self-administration of misoprostol at home as part of its review of the S-020 efficacy supplement and found no safety or efficacy concerns with home self-administration of misoprostol. Therefore, we disagree that a formal study is required in this population.

With regard to safety generally, in addition to the FAERS data provided above (see section II.B.1.c.ii. in this response), FDA routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy through 70 days gestation. We have not identified any new safety concerns with the use of mifepristone for this indication.

3. Other Articles

In your Petition, you reference several documents that discuss alternative models of providing abortion medications and advocate for the lifting of the REMS on mifepristone (Petition at 23-24). You assert that these recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex.[133]
We agree that the overarching message in the publications you reference appears to be advocating self-management of medical abortion. Nonetheless, as discussed in this response, we have determined that the Mifepristone REMS Program continues to be necessary for the safe use of this drug product, with some modifications.

III. CONCLUSION

For the reasons set forth above, we deny your request that FDA restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000; and we grant in part and deny in part your request to retain the Mifepristone REMS Program. As with all approved drug products, we will continue to monitor the safety of mifepristone for the approved indication and take any appropriate actions.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2021.12.16 15:05:41 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[133] You also reference clinical trials relating to the use of mifepristone for spontaneous miscarriage management and question the results of studies related to this use (Petition at 16-18). The use of mifepristone for the management of early miscarriage is not an approved indication for this drug product and is outside the scope of the Mifepristone REMS Program. Therefore, we do not address it in this response.

EXHIBIT 11

Center for Drug Evaluation and Research,
Application Number: 020687Orig1s020
Summary Review
(Mar. 29, 2016)
("FDA 2016 Summary Review")

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 29, 2016
Subject	Summary Review
NDA #/Supplement #	20687/S-020
Applicant name	Danco Laboratories, LLC
Date of submission	May 28, 2015
Date of submission receipt	May 29, 2015
PDUFA goal date	March 29, 2016
Proprietary name/established name	Mifeprex/mifepristone
Dosage form/strength	Oral tablet/200 mg
Dosage regimen	Mifeprex 200 mg tablet orally followed in 24-48 hours by 800 mcg buccal misoprostol
Proposed indication	Mifeprex is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation
Action	Approval

1. **Introduction**
2. **Background**
3. **CMC**
4. **Nonclinical Pharmacology/Toxicology**
5. **Clinical Pharmacology**
6. **Clinical Microbiology**
7. **Efficacy/Statistics**
8. **Safety**
9. **Advisory Committee Meeting**
10. **Pediatrics**
11. **Other Relevant Regulatory Issues**
12. **Labeling**
13. **Decision/Action/Risk Benefit Assessment**

1. Introduction

Danco Laboratories, LLC, referred to hereafter as the Applicant, submitted an efficacy supplement (S-020) to NDA 20687 for Mifeprex (mifepristone). The Applicant sought the following changes to its approved application:

1. (b) (4) Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally; see below:
   - Day One: Mifeprex Administration (oral)
     One 200 mg tablet of Mifeprex is taken in a single oral dose
   - After a 24-48 hour interval: Misoprostol Administration (buccal)(minimum 24-hour interval between Mifeprex and misoprostol)
     Four 200 mcg tablets (total dose: 800 mcg) of misoprostol are taken by the buccal route

2. Removal of the instruction that administration of misoprostol must be done in-clinic, to allow for administration at home or other location convenient for the woman
3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex
4. Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex
5. Increase in the maximum gestational age from 49 days to 70 days
6. Change of the labeled time for expected expulsion of pregnancy from 4-24 hours to 2-24 hours post misoprostol administration
7. Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed
8. Change of "physician" to "healthcare provider" in the label and Risk Evaluation and Mitigation Strategies (REMS) document
9. Change in the indication statement to add reference to use of misoprostol: "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of pregnancy through 70 days gestation."
10. Removal of references to "under Federal law" from the Prescriber's Agreement under the REMS

11. Labeling changes addressing the pediatric requirements under the Pediatric Research Equity Act

This efficacy supplement submission includes information from published studies, review articles and additional information from the authors of some of the publications. These published studies evaluated reproductive age women in the U.S. and outside the U.S. who had early medical termination with mifepristone, in a regimen with misoprostol, including women up through 70 days of gestation.

This memorandum serves as the Division's decisional memorandum for the efficacy supplement.

2. Background

The active ingredient of Mifeprex, mifepristone, is a progestin antagonist. Mifeprex, in a regimen with misoprostol, is approved for the medical termination of pregnancy up through 49 days' gestation. The approved dosing regimen is currently labeled as follows:

- Day 1: The patient takes three 200 mg tablets of Mifeprex in a single oral dose in the clinic, medical office, or hospital.
- Day 3: The patient returns to the clinic, medical office, or hospital and takes two 200 mcg tablets of misoprostol orally.
- Day 14: The patient returns for a follow-up visit to confirm that a complete termination has occurred.

At the time of the September, 2000 approval, FDA restricted distribution of Mifeprex under 21 CFR 314.520, requiring that Mifeprex be dispensed only by or under the supervision of a physician who meets certain qualifications. With the passage of FDAAA in 2007, Mifeprex was deemed to have in effect an approved REMS. The Applicant submitted a formal REMS, which was approved on June 8, 2011 and consisted of the following: a Medication Guide, elements to assure safe use (ETASU A [special certification of healthcare providers who prescribe Mifeprex], ETASU C [dispensing only in certain healthcare settings], and ETASU D [safe use condition of a signed Patient Agreement]), an implementation system and a timetable for assessments. The goals of the REMS were 1) To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug and 2) To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications. The REMS for Mifeprex incorporated the restrictions under which the drug was originally approved.

Since 2011, the Applicant has submitted two REMS assessment reports. The Agency review of these reports determined that the REMS goals were being met and that no modifications were required to the REMS at that time.

FDA held a pre-NDA meeting with the Applicant on January 29, 2015, to discuss proposed labeling and REMS changes to be submitted in this efficacy supplement. These changes were submitted with the efficacy supplement.

The Applicant submitted published literature and supportive information to support changes to the dose, dosing regimen, gestational age, revisions to labeling, modifications to the REMS document, and to address PREA requirements. The Agency accepts the use of peer reviewed literature as primary data for an application under the framework of a 505(b)(2) application.

3. CMC

No new CMC information was submitted with this efficacy supplement. The CMC team determined no additional review or inspections were required. The CMC team completed a review of the labeling and found the CMC sections of labeling (sections 3, 11 and 16) acceptable (See review dated March 29, 2016). The CMC review team recommends approval of the efficacy supplement; refer also to the CMC review of the separate supplement proposing a single tablet blister pack for Mifeprex, dated January 11, 2016. There are no outstanding CMC issues or postmarketing commitments or requirements.

***Comment**: On March 10, 2016, a separate CMC supplement was approved that allowed the packaging of individual 200 mg tablets of mifepristone; previously packaging consisted of three 200 mg tablets per blister pack (a total of 600 mg Mifeprex as administered under the originally approved dosing regimen).*

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted in this supplement. The Pharmacology/Toxicology team revised labeling to conform to the Pregnancy and Lactation Labeling Rule. There are no outstanding nonclinical issues. The Pharmacology/Toxicology review team recommends approval of the efficacy supplement; refer to the Pharmacology/Toxicology review dated March 4, 2016.

5. Clinical Pharmacology

The Applicant did not conduct any new clinical pharmacology studies pertaining to the proposed (b) (4) regimen, but provided information on pharmacokinetics (PK) of misoprostol following various routes of administration. The PK of the 200 mg Mifeprex tablet has not been characterized in women, but data are available in men and were submitted in the original NDA. The Clinical Pharmacology review team determined that the PK data were appropriate for inclusion in labeling. Review of the labeling pertinent to the Clinical Pharmacology sections is complete and labeling relevant to pharmacokinetics and pharmacodynamics is acceptable. There are no outstanding Clinical Pharmacology issues or postmarketing commitments or requirements. The clinical pharmacology review team recommends approval of the efficacy supplement; refer to the Clinical Pharmacology review dated March 29, 2016.

6. Clinical Microbiology

Not applicable.

7. Efficacy/Statistics

The Applicant submitted published literature as the primary evidence to support the efficacy (and safety) of the proposed dosing regimen (refer to the Clinical Review dated March 29, 2016, Section 9.5 for a list of submitted references). Most published articles submitted by the Applicant and reviewed by the clinical review team reported the primary efficacy endpoint as complete termination of pregnancy without further medical or surgical intervention; the Division considers this to be a clinically relevant endpoint.

The majority of the publications included a statement that the study was conducted under institutional review board (IRB) or Ethical Review Committee approval and the women gave informed consent. The clinical review team concluded that the published literature was adequate as the primary information source to support the changes proposed in the efficacy supplement. During the course of the review, the team also requested and received more detailed information from select publications from their authors via communication with the Applicant.

Although there were slight demographic differences among the published studies from the database, these differences were not expected to alter the efficacy or safety of Mifeprex. Therefore, for the majority of the proposed efficacy changes, the clinical team assessed efficacy information from a subset of publications that evaluated a given proposed change. An independent statistical review was not needed for this review of published literature.

The clinical review team identified several major proposed clinical changes in the efficacy supplement. As these major changes are interrelated, in some cases data from a given study were relied on to provide evidence to support multiple changes. These major changes as considered by the clinical team included:

1. A proposed dosing regimen consisting of mifepristone 200 mg orally followed by the buccal administration of 800 mcg misoprostol including:
    a. Use of a revised interval between mifepristone and misoprostol from 48 hours to 24-48 hours
    b. Allowing home administration of misoprostol
    c. Use of an additional dose of misoprostol
2. Support for extending the gestation age through 70 days
3. Flexibility in follow-up visit: follow-up is needed in the range of 7-14 days after Mifeprex administration; the specific nature and exact timing of the follow-up to be agreed upon by the healthcare provider and patient.
4. Change in who can provide Mifeprex from physician to healthcare provider who prescribes

The following section summarizes the clinical review team's evaluations that supported the above proposed changes:

1. *Support for the proposed dose and dosing regimen of 200 mg of Mifeprex orally and 800 mcg of misoprostol buccally 24-48 hours after Mifeprex administration:* The clinical review team reviewed the submission and identified studies and review articles that evaluated over 35,000 women who were treated with efficacy in the 91-98% range. For additional details on the efficacy from these studies, please refer to Section 6 of the Clinical Review.

2. *Support for extending the gestational age to 70 days:*
   The Applicant submitted a number of published articles and systematic reviews that supported the proposed dose and dosing regimen. Four studies and one systematic review evaluated the exact proposed dosing regimen through 70 days gestation. These include three prospective observational studies (Winikoff et al 2012[1], Boersma et al[2] , Sanhueza Smith et al[3]) and one randomized controlled trial (RCT) (Olavarrieta et al[4]) that had a primary objective of evaluating medical abortion provision by non-physicians. The systematic review by Chen and Creinin[5] covered 20 studies including over 30,000 women; all but one of the studies used the proposed regimen in gestations through 70 days (the remaining study used 400 mcg of buccal misoprostol). For those publications that provided overall success rates, these were in the range of 97-98%. Other relevant publications include the systematic review by Raymond[6] of 87 studies, which covered a variety of misoprostol doses and routes of administration used with 200 mg of mifepristone. Assessing the efficacy by misoprostol dose, the paper noted that doses ≥ 800 mcg had a success rate of 96.8%, with an ongoing pregnancy rate of 0.7%.

[1] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6
[2] Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011; 16: 61-6
[3] Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015; 22: 75-82
[4] Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousieguez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. Bull World Health Organ 2015; 93: 249-258
[5] Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion Obstet Gynecol: a Systematic Review. Obstet Gynecol 2015; 126(1): 12-21
[6] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

The original dosing regimen specifies taking misoprostol 2 days after Mifeprex. This efficacy supplement proposes a more flexible time frame of 24 to 48 hours between Mifeprex and misoprostol administration. Data from a review article by Wedisinghe et al[7] evaluated different time intervals using administration of misoprostol after Mifeprex. A meta-analysis of all five studies found a non-significant odds ratio for failure for shorter vs. longer dosing intervals, but a trend for lower success if a dosing interval < 8 hours is used. Chen & Creinin's systematic review[8] of 20 studies including over 33,000 women, all but one using the proposed regimen, compared the success of dosing intervals of 24 hours with intervals ranging from 24-48 hours. The success rate in six studies that used a 24-hour interval through 63 days gestation was 94.2%, compared to the rate of 96.8% in 14 studies that used a 24-48 hour interval, and this difference was statistically significant. The clinical team concluded that the efficacy of the revised dosing regimen was not compromised by revising the dosing interval to 24-48 hours. In addition, they noted that the overall rate of ongoing pregnancies did not differ significantly by dosing interval.

3. *Administration of misoprostol after Mifeprex administration at home:* Currently, the dosing regimen specifies that misoprostol is taken in the clinic setting following Mifeprex administration. No specific publication evaluated treatment outcomes with use of misoprostol at home compared to in-clinic dosing. However, one large literature review (Raymond et al[9]) evaluated a variety of mifepristone treatment regimens with different misoprostol doses, routes of administration and dosing intervals used in gestations through 63 days. Roughly half of the studies included in this review did not require women to take misoprostol in-clinic. Rates of treatment failure and of ongoing pregnancy were very similar regardless of whether misoprostol was taken in-clinic or at another location. The clinical review team concluded that the review provided sufficient data to support labeling that misoprostol does not need to be restricted to in-clinic administration.

4. *Use of a repeat misoprostol dose, if necessary:* The Applicant submitted several published studies that supported use of a repeat misoprostol dose, when complete uterine expulsion did not occur after the initial misoprostol dose following Mifeprex. In clinical practice, the usual treatment for incomplete expulsion (retained products of conception) may include either a repeat dose of misoprostol, expectant management or a surgical procedure (suction aspiration or a dilation and curettage). Studies that specifically report the success rate of a repeat dose of misoprostol are:

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[7] Wedisinghe L and Elsandabesee D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. Contraception 2010; 81(4): 269-74. doi: 10.1016/ j.contraception.2009.09.007. Epub Oct 29, 2009

[8] Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004; 103: 851-859

[9] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

- Winikoff et al[10] – studied the proposed regimen through 70 days gestation; of the few women who received a second dose for an incomplete abortion at follow-up, the success rate was 91% at 57-63 days and 67% at 64-70 days.
- Chen and Creinin [11] – a systematic review of 20 studies, all but one of which used the proposed regimen up through 70 days; success of a second dose ranged from 91-100%
- Boersma et al[12] – included pregnancies through 70 days treated with the proposed regimen; five of 330 women took a second dose due to absence of bleeding 48 hours after first dose; the success rate was 80%
- Louie et al[13] – studied the proposed regimen to 63 days; in 16 women (of 863) who took a second dose of misoprostol, the success rate was 100%
- Chong et al[14] – compared the proposed regimen to a lower dose of misoprostol; the success of a second dose of misoprostol was 92% overall, but the number of women in each dose arm getting a second dose was not specified.
- Winikoff et al[15] – 14 women in the proposed regimen took a second dose of misoprostol with a success rate of 92.9%.

Using the information from the above studies and other supportive data, the clinical team concluded that the available data support the efficacy of a repeat dose of misoprostol if complete expulsion has not occurred. The relatively high complete pregnancy termination rates indicate that this option is likely to reduce the need for a surgical intervention.

5. *Requirements regarding follow-up care:* Current labeling states that women will return to the clinic 14 days after Mifeprex administration for follow-up. This provision was based on the follow up regimen in the U.S. phase 3 trial that supported the initial approval in 2000. Although the Applicant submitted several studies that evaluated flexibility in the time of follow-up, the key publication identified by the review team that addressed this issue was a 2013 article by

[10] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6
[11] Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004; 103: 851-859
[12]Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011; 16: 61-6
[13] Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. Eur J Contracept Reprod Health Care 2014; 19(6): 457-464
[14] Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. Contraception 2012; 86: 251-256
[15] Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008; 112(6): 1303-1310

Raymond[16]. The impact of the timing of follow-up was assessed in Raymond's systematic review of studies using various treatment regimens. While some have posited that earlier follow-up may result in a higher rate of surgical intervention (for women who would have had complete expulsion had they been given a bit more time), Raymond's analyses found no difference in failure rates for women followed less than one week after mifepristone as compared to a week or more after mifepristone. As follow-up was anticipated to not alter the efficacy of the proposing dosing regimen, this change is also discussed below in Section 7.

6. *Allowing qualified healthcare providers to use Mifeprex.*

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies included a study by Warriner et al[17] that showed efficacy of 97.4% with nurses versus 96.3% by physicians.

Conclusions: I concur with the clinical review team's assessments and conclusions and these conclusions will be reflected in labeling. The data and information reviewed constitute substantial evidence of efficacy to support the proposed dosing regimen for Mifeprex for pregnancy termination through 70 days gestation. Other proposed changes to the Mifeprex labeling, including the time interval between Mifeprex and misoprostol dosing, and use of a repeat dose, were also adequately supported by evidence. Finally, I concur with the clinical review team that the information from the published literature also supported efficacious use of Mifeprex by non-physician providers.

Comment: Discussion was held as to whether the original dosing regimen approved in 2000 (i.e., Mifeprex 600 mg and misoprostol 400 mcg up to 49 days gestation) should remain in labeling. (b) (4) the clinical review team and I concur with their (b) (4) request to remove the current regimen from the labeling. Removal of the original dosing regimen simplifies labeling, and avoids any confusion regarding instructions. Therefore, the revised labeling, and REMS materials accompanying the approval of this efficacy supplement, will include only the proposed dosing regimen and instructions. It should be noted that there are no safety or efficacy concerns about the originally approved dosing regimen that led to removing it from the labeling.

[16]Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013;87(1):26-37.
[17] Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet 2011; 377: 1155-61.

8. Safety

The safety of the proposed dosing regimen for Mifeprex was supported by the evidence from submitted published literature and postmarketing experience. The focus of the safety analysis was on published studies that evaluated the proposed dosing regimen (Mifeprex 200 mg followed by 800 mcg misoprostol buccally 24-48 hours later), with comparison to the known safety profile of the currently approved dosing regimen.

Exposure: Per the Applicant's submission, the clinical review concluded that there have been approximately 2.5 million uses of Mifeprex by U.S. women since the drug's approval in 2000. The clinical review team estimated that exposure to the proposed dosing regimen for their safety analysis was based on approximately 30,000 patients (refer to Table 11 for a list of references used to evaluate safety). Such exposure volume is sufficient to characterize the safety profile of the proposed dosing regimen and other proposed changes in this efficacy supplement.

Deaths: Deaths with medical abortion rarely occur and causality can be difficult to determine. Most of the publications did not specifically report any deaths with medical abortion with Mifeprex. Among the seven U.S. studies submitted to support the safety profile of Mifeprex and misoprostol, only one (Grossman, et al[18]) explicitly addressed deaths and noted that there were no deaths among 578 subjects evaluated in the study. Only one observational study (Goldstone, et al[19]) from Australia contained a report of a death after a mifepristone and misoprostol dosing regimen. In this retrospective review of 13,345 pregnancy terminations, the authors identified one death from sepsis. The article stated that the death was in an individual who failed to follow-up with her healthcare provider despite showing signs of illness. Based on this information, deaths in association with abortion are extremely rare.

Deaths reported from the postmarketing experience of Mifeprex are summarized below in the Postmarketing Experience section.

Nonfatal serious adverse events: The clinical review team identified key nonfatal serious adverse events (SAEs) associated with the proposed dosing regimen for Mifeprex. These SAEs include: hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. Section 7 of the clinical review dated March 29, 2016, provides a detailed discussion of reported rates of hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. The latter is not an adverse reaction because an ectopic pregnancy would exist prior to the Mifeprex regimen; it represents instead a failure to diagnose an ectopic pregnancy. Overall rates identified by the clinical review team from the published literature are as follows:

- Hospitalization: 0.04-0.6% in U.S. studies of over 14,000 women; 0-0.7% in international studies of over 1,200 women

[18]Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectivenesss and acceptability of medical abortion provided thorugh telemedicine. Obstet Gynecol 2011;118:296-303.
[19]Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. Med J Austral 2012; 197: 282-6.

- Serious infection/sepsis: 0-0.2% in U.S. and international studies of over 12,000 women
- Transfusion: 0.03-0.5% in U.S. studies of over 17,000 women; 0-0.1% in international studies of over 12,000 women

A study by Upadhyay et al[20] reported a 0.31% rate of major complications (including incomplete or failed abortion, hemorrhage, infection or uterine perforation that required hospitalization, surgery or transfusion) for medical abortions (dosing regimen unspecified) through 63 days; this was about double the rate reported for first trimester aspiration abortions and statistically significantly higher. However, these rates were driven by higher rates of incomplete/failed abortion; rates of hemorrhage (0.14%) and infection (0.23%) did not differ from those associated with aspirations.

Only one submitted study reported an ectopic pregnancy. This study (Winikoff et al[21]) reported one ectopic among 847 women (0.12%).

Comment: The proposed dosing regimen has been studied extensively in the literature using U.S. and global sites. Serious adverse events including deaths, hospitalization, serious infections, bleeding requiring transfusion and ectopic pregnancy are rarely reported. The rates of these serious adverse events are well below 1% and do not suggest a safety profile different from the original approved Mifeprex dosing regimen. Although there is less serious adverse event data on women who received Mifeprex and misoprostol between 64-70 days of gestation, the data from a U.S. study of 379 women (Winikoff et al)[22] in that gestational age is reassuring that the rates of these serious adverse events are not clinically different from that of other gestational age ranges.

In summary, based on the published literature, nonfatal serious adverse events occur with Mifeprex and misoprostol use with rates generally less than 1%. Increased gestational age (64-70 weeks) was not associated with an increased incidence of nonfatal SAEs. Other submission- specific safety issues that were evaluated including uterine rupture and angioedema/anaphylaxis are discussed in the Postmarketing Experience section below.

Loss to follow-up: The studies included in this safety review revealed a wide range of loss to follow-up, from 0.6% loss to follow-up in the study with telephone follow-up (Ngoc et al[23]) to 22% in the Grossman et al[24] study using telemedicine to deliver medical

[20]Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. Obstet Gynecol 2015;125(1):175-183.
[21]Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008;112(6):1303-1310.
[22]Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012;120:1070-6.
[23] Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. Obstet Gynecol 2014;123:88-95.
[24] Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectivenesss and acceptability of medical abortion provided thorugh telemedicine. Obstet Gynecol 2011;118:296-303.

abortion services.

Comment: Based on these data reviewed by the clinical review team, there is no literature that suggests that follow-up modality alters safety. Therefore, labeling will not be directive regarding follow-up; that will be a decision left to the patient and provider.

Common adverse events: The clinical review team evaluated common adverse reaction data and compared U.S. and global study locations. The comparison revealed that there were differences in the frequency of common adverse reactions, with the reporting rates considerably higher among the U.S. studies. There is no reason to anticipate regional differences in the safety profile for the same treatment regimen, so these differences likely reflect lower ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data in labeling would not be appropriate, as it is unlikely to be informative to the U.S. population of users. The data to be reported in labeling is outlined in Table 1 below:

Table 1: Common Adverse Events (≥ 15%) in U.S. Studies of the Proposed Dosing Regimen

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

Source: Data from Middleton[25], Winikoff[26] and Winikoff[27] as outlined in Table 2 of the CDTL review dated March 29, 2016.

One concerning adverse event is severe vaginal bleeding. Severe vaginal bleeding can result in interventions such as hospitalization and transfusion and may be associated with infection. The overall rate of bleeding across publications varied between 0.5% and 4.2%. Two publications (Sanhueza Smith et al[28] and Gatter et al[29]) evaluated clinically significant bleeding by gestational age. Although the publications reported slightly different rates, there was no trend of increased bleeding requiring intervention with Mifeprex and misoprostol use with increasing gestational age.

[25] Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. Contraception 2005; 72: 328-32

[26] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6

[27] Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008; 112(6): 1303-1310

[28] Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015;22:75-82.

[29] Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.

Comment: While not all of the studies reported common adverse events, those that reported did not have unexpected rates of common adverse events. These common adverse events are included in labeling in section 6.1 (Clinical Trial Experience) in the ADVERSE REACTIONS section.

Postmarketing experience – Spontaneous reports:

The safety profile for Mifeprex includes over 15 years of postmarketing safety data available on Mifeprex due to the reporting requirements under the REMS. The Year 3 REMS Assessment report was submitted by the Applicant in June, 2015. The (b) (6) (b) (6) provided a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. Findings include:

- No Clostridial septic deaths reported in the U.S. since 2009, and none worldwide since 2010.
- The postmarketing rates of hospitalization, severe infection, blood loss requiring transfusion and ectopic pregnancy reported from publications and remain stable and relatively low.

Submission-specific safety issues:

- Anaphylaxis/angioedema: The (b) (6) ((b) (6) identified a safety signal of anaphylaxis and angioedema with mifepristone administration. This signal was based on a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. A FAERS search retrieved one case of anaphylaxis and six cases of angioedema with mifepristone administration. Six of the seven cases were seen in women using mifepristone for termination of pregnancy. Six of the seven cases noted some type of medical intervention, such as treatment with an antihistamine, a histamine H2 antagonist, a corticosteroid, or a combination of various medications. Hospitalization was noted in three of the seven total cases; all three hospitalization cases occurred in patients who experienced angioedema. There were no additional cases of anaphylaxis or angioedema identified in the literature.

  Comment: (b) (6) and the clinical review team recommended that anaphylaxis and angioedema be described in the Contraindications and Adverse Reactions sections of labeling. These labeling sections were discussed with the Applicant and labeling was revised for those sections to describe these serious adverse events.

- Uterine rupture: As discussed in the clinical review, the potential risk of uterine rupture was considered because the current labeling for misoprostol includes a Boxed Warning against the use of misoprostol for gestations more than 8 weeks due to the risk of uterine rupture. Although misoprostol is used alone for various obstetric indications, including induction of labor at term, it was important to consider whether labeling about this potential risk is warranted for Mifeprex. Both the clinical reviewer and the (b) (6) ((b) (6) reviewed the literature and (b) (6) searched FAERS for adverse event reports.

Published literature reported three case reports[30,31,32] of uterine rupture with mifepristone/misoprostol treatment in the first trimester. Of these three reports, two patients had a risk factor for uterine rupture (prior uterine surgery). The third case was in a patient who received more than two doses of misoprostol. After consideration, the clinical review team decided that labeling should include information about this event. The FAERS search did not identify any reports of uterine rupture with use of mifepristone alone. Of 80 reports, 77 cited use of misoprostol alone, and three of mifepristone and misoprostol. Only two reports of uterine rupture in the first trimester were identified, both using misoprostol alone; one entailed an unspecified dose and route of misoprostol at 5 weeks gestation, and one involved vaginal administration of 800 mcg misoprostol at 8 weeks gestation for cervical preparation prior to a surgical abortion in a woman with a prior uterine scar.

Based on the available safety reports of uterine rupture, the review team from (b) (6) and clinical review team concluded that these data demonstrated that uterine rupture with Mifeprex and misoprostol in the first ten weeks (70 days) of gestation is exceedingly uncommon, and occurs most often in the face of a risk factor (previous uterine surgery).

Comment: I agree with the clinical review team and the (b) (6) team that the risk of uterine rupture with first trimester use of mifepristone and misoprostol appears to be extremely rare, and most often associated with a prior uterine scar, a known risk factor for uterine rupture. Labeling of these reports is included in section 2.3 of the DOSAGE AND ADMINISTRATION and section 6.2 of the ADVERSE REACTIONS of labeling to provide additional information to healthcare providers, but no restriction of use is needed based upon this extremely rare adverse reaction.

The clinical review team also evaluated the safety for each of the following major changes proposed in this efficacy supplement:

1. Changing the dosing interval between Mifeprex and misoprostol from 48 hours to 24-48 hours
2. Home administration of misoprostol
3. Use of a repeat dose of misoprostol
4. Change in the follow-up timeframe and method of follow-up
5. Allowing providers other than physicians to provide Mifeprex

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[30] Khan S et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. Journal of Obstet Gynaecol 2007; 27: 869-870

[31] Bika O, Huned D, Jha S, Selby K Uterine rupture following termination of pregnancy in a scarred uterus J Obstet Gynaecol 2014; 34(2): 198-9. doi: 10.3109/01443615.2013.841132

[32] Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. BJOG 2008;15:575-77

To evaluate each of these changes, the reviewers evaluated the adverse event information regarding:

- *Changing the timing interval between Mifeprex and misoprostol and change in the gestational age to 70 days:* Support for the 24-48 hour interval and use up through 70 days was primarily based on a large systematic review by Shaw et al[33]. This review evaluated studies looking at different follow-up modalities and demonstrated that there are a variety of acceptable alternatives to in-clinic follow-up that can identify cases in which there is need for additional intervention. In addition, the systematic review did not identify any significant difference in adverse events with different time intervals. Based on these findings, labeling will not be directive regarding specific details of how follow-up should be performed; this will be a decision between the patient and her healthcare provider.

- *Home administration of misoprostol:* The Applicant supplied several published studies that supported this change including Gatter et al[34] and Ireland et al[35]. These studies reported on large numbers of women in the U.S. who took misoprostol at home. The authors showed that home administration of misoprostol, as part of the proposed regimen, is associated with exceedingly low rates of serious adverse events, and with rates of common adverse events comparable to those in the studies of clinic administration of misoprostol that supported the initial approval in 2000. Given that information is available on approximately 45,000 women from the published literature, half of which incorporated home use of misoprostol, there is no clinical reason to restrict the location in which misoprostol may be taken. Given the fact that the onset of cramping and bleeding occurs rapidly (i.e., generally within 2 hours) after misoprostol dosing, allowing dosing at home increases the chance that the woman will be in an appropriate and safe location when the process begins.

- *Use of a repeat dose of misoprostol:* Safety reporting from studies that evaluated a repeat dose of misoprostol did not specifically assess the subset of women who received a second dose, but no unexpected findings were identified. One randomized controlled trial (Coyaji et al[36]) conducted in 300 women seeking medical abortion in India looked at a single misoprostol dose as compared to two misoprostol doses. Although there was no difference in the complete pregnancy termination rate in women who received a second misoprostol dose compared to those who did not, the repeat misoprostol dose reduced the need for surgical intervention. This study was reassuring in that there was no significant difference in the adverse events observed—similar percentages of women experienced

[33] Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. Obstet Gynecol 2013;121(6):1335-1347.
[34] Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[35] Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. Obstet Gynecol 2015;126:22-8.
[36] Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? BJOG 2007;114:271-278.

cramping (87% in the single dose group, 89% in the repeat dose group), nausea (both groups 1%), vomiting (both groups 0%), and diarrhea (0% in the single dose group versus 2% in the repeat dose group). A supportive systematic review by Gallo et al[37] also provided safety information on subjects who received repeat misoprostol. In this review, the only side effects discussed in the trials were diarrhea, which was more common on those groups receiving misoprostol orally than in those receiving it exclusively vaginally (26-27% versus 9%). Rash was reported <1%. Based on these findings, labeling will be changed because the misoprostol dose does not need to be restricted to in clinic administration to assure safe pregnancy termination using the proposed dosing regimen. Given the onset of bleeding and cramping after misoprostol, allowing home administration increases the likelihood that a woman will be in an appropriate and safe location when the pregnancy termination process begins.

- *Change in the follow-up timeframe and method of follow-up:* The Applicant submitted several articles that described different methodologies in follow-up including phone calls and standardized instructions. The clinical reviewers evaluated a study in Scotland by Cameron et al[38] that evaluated self-assessment as compared to standard follow-up methodologies (clinic visit or phone call). Most of the women chose self-assessment over an in-clinic visit or phone call, and there were no significant differences in adverse outcomes between women who underwent self-assessment of health compared to those who had a clinic visit or phone call. Among women with an ongoing pregnancy after Mifeprex and misoprostol, the majority self-identified and presented within two-weeks for care. Based on this information and the other data from the Raymond systematic article[39] that did not identify a difference in failure rate for earlier (less than one week) as compared to one week or greater of follow-up, sufficient support was provided to use a broadened window of 7 to 14 days for follow-up. This revised follow-up time frame will be included in labeling.

- *Allowing providers other than physicians to provide Mifeprex*: The current Prescriber's Agreement in the REMS specifies that "…Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications…" In addition, current labeling states that Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. However, labeling states that other healthcare providers, acting under the supervision of a qualified physician, may also provide Mifeprex to patients. Several published studies submitted by the Applicant indicate that health care providers such as nurse practitioners, nurse midwives, and physician assistants are

[37] Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. Contraception 2006;74:36-41.
[38] Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? Contraception 2015;91:6-11.
[39] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

currently providing abortion services. One of these studies (Kopp Kallner et al[40]) was a randomized controlled trial of 1,068 women in Sweden who were randomized to receive medical abortion care from two nurse midwives experienced in medical terminations and trained in early pregnancy ultrasound versus a group of 34 physicians with varying training and experience. Success rates were ≥ 96% regardless of gestational age. The nurse midwife group had few complications, though this was not statistically significant (4.1% for nurse midwives, versus 6.1% for doctors, p=0.14). No serious complications were reported and no blood transfusions were administered in the study. Based on this and other supportive studies, the information supports the efficacy and safety of allowing healthcare providers other than physicians can effectively and safely provide abortion services, provided that they meet the requirements for certification described in the REMS. The clinical team also felt that the term "healthcare provider who prescribes" would be the appropriate terminology as prescribing ability is a critical factor in dispensing Mifeprex.

The clinical review team concluded that the evidence demonstrated acceptable safety for each of the above proposed changes, and I concur with their conclusion. The proposed dosing regimen has a similar safety profile as the original regimen approved in 2000. Adverse outcomes of interest, such as deaths, serious infection, transfusions, ectopic pregnancies and uterine rupture, remain rare, and are not necessarily attributable to Mifeprex use. Overall, the rate of deaths and nonfatal serious adverse events are acceptably low, and data for the proposed regimen do not suggest a safety profile that deviates from that of the originally approved regimen No association between adverse outcomes and increasing gestational age was identified. Finally, the available information supports the safety of the other proposed changes, including increasing the flexibility of the time interval between Mifeprex and misoprostol, at home use of misoprostol, use of a repeat dose of misoprostol, change in the follow-up timeframe and allowing health care providers other than physicians to prescribe and dispense Mifeprex were acceptable.

9. Advisory Committee Meeting

Mifeprex is not a new molecular entity requiring discussion before an advisory committee. In addition, an advisory committee was not necessary as the application did not raise complex scientific or other issues that would warrant holding an AC before approval.

10. Pediatrics

This efficacy supplement triggered requirements under the Pediatric Research Equity Act (PREA). The Agency granted a partial PREA waiver for pre-menarcheal females ages birth to 12 years because it would be impossible to conduct studies in this pediatric population, as pregnancy does not exist in premenarcheal females.

[40] Kopp Kallner H, Fiala C, Stephansson O, Gemzell-Danielsson K. Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days. Human Reprod 2010;25(5):1153-1157.

The Applicant fulfilled the remaining PREA requirement in postmenarcheal females by submitting published studies of Mifeprex for pregnancy termination in postmenarcheal females less than 17 years old. Efficacy and safety information in these adolescents was based on a U.S. study in 322 postmenarcheal adolescents (Gatter et al[41]). Of the 322 adolescents, 106 of these adolescents were under 16; see Table 2 below:

Table 2: Age and Number of Adolescents Undergoing Medical Abortion (Gatter et al[42])

Age of Subject	Number of Subjects evaluated
11	1
12	1
13	2
14	20
15	82
16	216

Source: Refer to Table 17 of the Medical Officer's review dated March 29, 2016

The Gatter et al[43] study reported that postmenarchal females less than 18 years old had a 98.7% pregnancy termination rate as compared to females aged 18-24, who had a rate of 98.1%. This article reported that loss to follow-up was slightly higher in those less than 18 years old, however, age did not adversely impact efficacy outcomes.

One issue was whether adolescents would comply with at home use of misoprostol. The Gatter[44] et al study incorporated at home use of misoprostol into the Mifeprex dose regimen given to all females, including postmenarchal females less than 18 years old. The overall efficacy in adolescents was similar to that of all older women. This information supports at home administration of misoprostol in postmenarchal females under 17.

Two other published studies provided additional efficacy on Mifeprex use by adolescents for pregnancy termination:

- Phelps et al[45] evaluated data from 28 adolescents aged 14 to 17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. In this study, 100% of subjects had a complete pregnancy termination, with five not requiring misoprostol.

[41]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[42] Ibid.
[43]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[44]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[45]Phelps RH, et al. Mifepristone abortion in minors. Contraception 2001;64:339-343.

- Niinimaki et al[46] used data from a Finnish Registry from 2000-2006. An analysis of efficacy between adolescents under age 18 compared to the women ≥ age 18 indicated that the adolescent group had a lower rate of incomplete abortions as compared to adults. And efficacy outcomes in adolescents were similar to those of adult women.

The safety of Mifeprex in postmenarcheal adolescents was primarily supported by adverse event information from the Gatter et al[47] study. (b) (6), (b) (4) Supportive data from a Finnish registry (Niinimaki et al) from 3024 adolescent females under 18 years of age reported that, compared to adult women, the risks of hemorrhage (adjusted odds ratio 0.87 [95% confidence interval: 0.77 to 0.99]), incomplete abortion (0.69, [95% confidence interval: 0.59 to 0.82]), and surgical evacuation (0.78, [95% confidence interval: 0.67 to 0.90]) were lower in the adolescent cohort. In the Finnish registry study, a majority of adolescents and adults received both Mifeprex and misoprostol. Safety findings from the Gatter et al and Niinimaki et al studies are reassuring and indicate that the safety profile of Mifeprex is similar between postmenarcheal adolescents and adult women.

Additional details from this article and other published data on Mifeprex use in adolescents (females under 17) are described in the clinical review (Refer to the Medical Officer's review dated March 29, 2016).

(b) (6) concurred that the efficacy and safety data in postmenarcheal adolescents less than 17 years old was sufficient to support the use of Mifeprex in this pediatric population and to fulfill the PREA pediatric study requirement. The revised Mifeprex labeling will state that that efficacy and safety are similar to adult women in the Pediatric Use section (8.4).

11. Other Relevant Regulatory Issues

(b) (6)

reviewed the Medication Guide in conjunction with the (b) (6) ((b) (6) Both (b) (6) and (b) (6) found the Medication Guide to be acceptable with recommended changes (See review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in

[46]Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.
[47]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[48]Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.

the Medication Guide and incorporated appropriate changes into the final agreed upon Medication Guide.

(b) (6) (b) (6)

reviewed the Prescribing Information (PI) in addition to the joint review with (b) (6) of the Medication Guide in conjunction with (b) (6) After review, (b) (6) provided recommended changes (See (b) (6) review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in the PI and incorporated appropriate changes into the final label.

(b) (6) (b) (6)

(b) (6) (b) (6) in the (b) (6)) reviewed the proposed modifications to the REMS. The (b) (6) review reflected agreement with the Applicant's proposed REMS changes which include:

- Removal of the term "under Federal law" from the Prescriber's Agreement.
- Replacement of the word "physician" with a broader term to describe appropriate healthcare professionals who may order, prescribe and administer Mifeprex. (b) (6) believes that the Applicant's proposed terminology of " (b) (4) is too broad and that a more appropriate description is "healthcare provider who prescribes," which limits acceptable healthcare providers to those who are licensed in their state to prescribe medications.
- Removal of the Medication Guide from the REMS. The Medication Guide remains an important education tool for patients. It will still be dispensed to each patient in accordance with 21 CFR part 208. As described in the Medication Guide Guidance, a Medication Guide is not necessary to ensure that the benefits outweigh the risks of Mifeprex
- Modification of Element to Assure Safe Use (ETASU) A, the Prescriber's Agreement. (b) (6) recommends changing the name of the document to the Prescriber's Agreement Form to be consistent with other REMS programs. References to "physician" should be changed to "healthcare provider who prescribes."
- (b) (6) recommends removing the Patient Agreement from the REMS for a number of reasons:
  1. The established safety profile over 15 years of experience with Mifeprex is well-characterized, stable, and known serious risks occur rarely
  2. The Medication Guide contains the same risk information addressed in the Patient Agreement, and will still be provided to patients under 21 CFR part 208
  3. The Prescriber's Agreement Form will continue to require providers to explain the treatment, its effects and risks associated with Mifeprex and to answer any questions that a patient may have
  4. Established clinical practice provides for counseling, informing the patient about follow-up, when to contact the provider/clinic, answering questions and obtaining signed informed consent before treatment. FDA has removed REMS

requirements in other programs based on the integration of the REMS safe use condition into clinical practice.

Other revisions to the REMS document will be made for consistency with changes described above and to reflect current FDA thinking and practice regarding format, language and flow in REMS documents. These changes include modification of the Mifeprex REMS goal, changes in requirements to certify prescribers (removal of the requirement to obtain a Patient Agreement) and other minor edits.

In summary, the overall (b) (6) recommendation for the REMS modification for this efficacy supplement was approval (Refer to (b) (6) review dated March 29, 2016).

12. Labeling

Carton and container labeling was reviewed by the (b) (6) ((b) (6) the (b) (6) ((b) (6) and the (b) (6) ((b) (6) (b) (6) Their comments were conveyed to the Applicant as appropriate.

The label was submitted in the format prescribed by the PLR. Although the supplement was submitted prior to when it would otherwise have been required to comply with the PLLR requirements, the review team believed it would be of value to harmonize with this labeling standard to the extent possible.

Specific issues discussed during labeling negotiations included the selection of studies for inclusion in Section 6.1 (Clinical Trial Experience in the ADVERSE REACTIONS section) and 14 (CLINICAL STUDIES section). Only studies that evaluated the specific proposed regimen were included in these sections. For the Adverse Reactions section, examination of the common adverse reaction data by U.S. compared to non-U.S. study location revealed that there were large differences in the frequency of common adverse reactions, with the reporting rate considerably higher among the U.S. studies. This may reflect differences in ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data would not be appropriate, as it is unlikely to be informative to the U.S. population of users. In the case of serious adverse reactions, the reported frequency was quite similar regardless of study location; for this reason, serious adverse reaction information from global studies is reported. Agreement on labeling was reached on March 29, 2016.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

Postmarketing Requirements/Postmarketing Commitments: None.

Risk Evaluation and Mitigation Strategies (REMS): The Applicant proposed a REMS modification for the Mifeprex REMS program with the submission of this efficacy supplement. The review teams from the (b) (6) evaluated the current Mifeprex REMS program and the proposed REMS modifications to determine whether each Mifeprex REMS element remains necessary to ensure that the benefits of Mifeprex outweigh the risks. Factors that impacted the decision included findings from two REMS assessments (the more recent REMS assessment review was completed in October 2015), an unchanged safety profile, and published literature that documented adequate safeguards in clinical practice with the use of Mifeprex in a regimen with misoprostol.

The teams determined that the following REMS modifications were warranted:

1. Revisions to the Prescriber Agreement Form to reflect the new dosing regimen and to reflect current REMS formatting and language standards
2. Removal of the Medication Guide as a REMS element, as distribution of the Medication Guide is required under 21 CFR 208
3. Removal of the Patient Agreement as a Documentation of Safe Use Condition (ETASU D)
4. Updating of the REMS goals to reflect the above 3 changes.
5. Removal of the phrase "Under Federal law" from the Prescriber's Agreement
6. Replacing the term "licensed physician" with "healthcare provider who prescribes"

The above modifications to the Mifeprex REMS program were discussed with the (b) (6) (b) (6) on January 15, 2016, as per (b) (6) .

The (b) (6) concurred with conforming changes to the Prescriber's Agreement to reflect the new dosing regimen, and with removal of the Medication Guide from the REMS. The Medication Guide would remain a part of labeling to inform patients about the risks associated with Mifeprex use. The (b) (6) also concurred with revisions to the REMS goals to reflect these changes.

The (b) (6) concurred with the removal of the term "under Federal law". A rationale for the original inclusion of the phrase "Under Federal law" cannot be discerned from available historical documents, nor is it consistent with REMS materials for other products. All the conditions of approval, including the REMS materials, are under Federal law; therefore, the phrase is unnecessary and it was decided that the phrase be removed from the Prescriber's Agreement.

The (b) (6) concurred with use of the term "healthcare providers who prescribe." To support a change in the REMS that would allow qualified healthcare providers other than physicians to prescribe Mifeprex through the Mifeprex REMS program, the Applicant provided information from over 3,200 women in randomized controlled trials and 596 women in prospective cohort studies comparing medical abortion care by physicians versus other providers (nurses or nurse midwives). These studies were conducted in a variety of settings (international, urban, rural, and low-resource). No differences in serious adverse events, ongoing pregnancy or incomplete abortion were identified between the groups. Given that providers other than physicians are providing family planning and abortion care under supervision and that the approved labeling and REMS program stipulate that prescribers must be able to refer patients for additional care, including surgical management, allowing these prescribers to participate in the Mifeprex REMS program is acceptable.

The (b) (6) also concurred with the teams' recommendation to remove the Patient Agreement (ETASU D) from the REMS although some (b) (6) members commented that additional support for the review team's rationale for this modification was needed. The review team's rationale for this change was:

APPEARS THIS WAY ON ORIGINAL

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and Informed Consent, and, more specifically with Mifeprex, includes counseling on all options for termination of pregnancy, access to pain management and emergency services if needed.
- Medical abortion with Mifeprex is provided by a well-established group of organizations and their associated providers who are knowledgeable in this area of women's health. Their documents and guidelines cover all the safety information that also appears in the Patient Agreement.
- ETASUs A and C remain in place: The Prescriber's Agreement under ETASU A requires that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprex can only be dispensed under the direct supervision of a certified prescriber.
- Labeling mitigates risk: The Medication Guide, which will remain a part of labeling, contains the same risk information covered under the Patient Agreement.

The Mifeprex REMS program will have a modified ETASU REMS that will continue to ensure that Mifeprex can only be prescribed by certified prescribers and be dispensed to patients in certain healthcare settings, specifically, clinics, medical offices and hospitals. The Medication Guide will continue to be distributed to patients required under 21 CFR part 208. As required for all ETASU REMS, ongoing assessments of the Mifeprex REMS program will continue to ensure that the modified Mifeprex REMS program is meeting its goals.

13. Decision/Action/Risk Benefit Assessment

Decision:

All regulatory and scientific requirements have been adequately addressed in this efficacy supplement. Review teams involved in this supplement have recommended approval of the supplement from their disciplines' perspective. The submitted efficacy and safety information supported approval of the proposed dosing regimen through 70 days gestation, and other changes discussed in this summary memo. This supplement will receive an Approval action.

Benefit Risk Assessment:

This efficacy supplement provided substantial evidence of efficacy for the proposed dosing regimen through 70 days gestation. The efficacy findings were similar to those that led to the approval of the original dosing regimen in 2000. In addition, the submitted published literature supported other changes sought in this efficacy supplement that will

be reflected in labeling: 1) a more flexible time interval of 24 to 48 hours between Mifeprex and misoprostol administration, 2) the option of at home administration of misoprostol, 3) the option of repeat misoprostol dosing, if clinically indicated, 4) flexibility in the follow–up time frame of 7 to 14 days, and 5) permitting qualified healthcare providers other than physicians to prescribe Mifeprex.

The safety findings of the proposed dosing regimen were acceptable and were similar to those seen with the original dosing regimen approved in 2000.

After review of the REMS modifications proposed by the Sponsor, I concur with the clinical team and (b) (6) recommendations that:

1. The Medication Guide can be removed from the Mifeprex REMS program. The Medication Guide requirements under 21 CFR part 208 require the Medication Guide to be distributed to patients. Mifeprex will only be dispensed by a healthcare professional who will be knowledgeable and able to provide the patient instructions on appropriate use of the drug, including what potential side effects may occur or follow-up that may be required as appropriate, and who will answer any questions the patient may have. In that setting, the Medication Guide will already be a required available tool for counseling. Therefore, given the existing requirements under 21 CFR part 208, I concur that there is no reason for the Medication Guide to specifically be a part of the REMS.

2. The Prescriber Agreement Form (ETASU A) as revised reflects current FDA format and content to conform to current REMS programs and reflect the labeling changes that will be approved in this supplement. I concur that the changes are acceptable.

3. Revision of the Mifeprex REMS goals (ETASU C) will adequately mitigate the risk of serious complications by requiring certification of healthcare providers who prescribe and ensuring the Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber.

4. Removal of the Patient Agreement Form (ETASU D): I concur with the clinical review team that the Patient Agreement Form, which requires a patient's signature, does not add to safe use conditions for the patient for this REMS and is a burden for patients. It is standard of care for patients undergoing pregnancy termination to undergo extensive counseling and informed consent. The Patient Agreement Form contains duplicative information already provided by each healthcare provider or clinic. I believe that it is much more critical for the healthcare provider who orders or prescribes Mifeprex to provide and discuss informed consent derived from their own practice so that care can be individualized for the patient.

I support that the Mifeprex REMS with ETASUs A and C remain in place to support conditions critical to the use of the drug. Therefore, the implementation system and timetable for assessments should continue.

I also agree with the clinical review team that the reporting requirements should only be required for deaths. It is important that the Agency be informed of any deaths with Mifeprex to monitor new safety signals or trends. However, after 15 years of reporting serious adverse events, the safety profile for Mifeprex is essentially unchanged. Therefore, I agree that reporting of labeled serious adverse events other than deaths can be collected in the periodic safety update reports and annual reports to the Agency.

In summary, I believe that the benefit-risk profile for Mifeprex continues to be favorable and with the agreed-to labeling changes and REMS modifications, the Mifeprex REMS program will continue to assure safe use. Therefore, I support approval of this efficacy supplement and REMS modifications.

Addendum:

On March 28, 2016, Dr. Janet Woodcock, the Director, Center for Drug Evaluation and Research, asked (b) (6) and the (b) (6) to continue to include a Patient Agreement Form in the REMS for Mifeprex (see March 28, 2016 Memorandum from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, through the (b) (6) (6) Therefore, the Patient Agreement Form will be retained and other changes will be made in the REMS to reflect that it is being retained.

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/s/

(b) (6)

03/29/2016

EXHIBIT 12

Maarit Niinimaki et al.,
Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study,
BMJ (April 20, 2011)

BMJ

RESEARCH

Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study

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ABSTRACT

Objective To determine the risks of short term adverse events in adolescent and older women undergoing medical abortion.

Design Population based retrospective cohort study.

Setting Finnish abortion register 2000-6.

Participants All women (n=27 030) undergoing medical abortion during 2000-6, with only the first induced abortion analysed for each woman.

Main outcome measures Incidence of adverse events (haemorrhage, infection, incomplete abortion, surgical evacuation, psychiatric morbidity, injury, thromboembolic disease, and death) among adolescent (<18 years) and older (≥18 years) women through record linkage of Finnish registries and genital *Chlamydia trachomatis* infections detected concomitantly with abortion and linked with data from the abortion register for 2004-6.

Results During 2000-6, 3024 adolescents and 24 006 adults underwent at least one medical abortion. The rate of chlamydia infections was higher in the adolescent cohort (5.7% *v* 3.7%, P<0.001). The incidence of adverse events among adolescents was similar or lower than that among the adults. The risks of haemorrhage (adjusted odds ratio 0.87, 95% confidence interval 0.77 to 0.99), incomplete abortion (0.69, 0.59 to 0.82), and surgical evacuation (0.78, 0.67 to 0.90) were lower in the adolescent cohort. In subgroup analysis of primigravid women, the risks of incomplete abortion (0.68, 0.56 to 0.81) and surgical evacuation (0.75, 0.64 to 0.88) were lower in the adolescent cohort. In logistic regression, duration of gestation was the most important risk factor for infection, incomplete abortion, and surgical evacuation.

Conclusions The incidence of adverse events after medical abortion was similar or lower among adolescents than among older women. Thus, medical abortion seems to be at least as safe in adolescents as it is in adults.

INTRODUCTION

Pregnancies among teenagers are mostly unplanned and offer a special challenge to family planning services. Most of all such pregnancies (up to 82% in the United States) are unintended.[1] The decision to continue or terminate a pregnancy is strongly associated with age. Besides age, being a student or being single are important factors in young women's decisions on abortion.[2] In the United States, 6% of all abortions are carried out in under 18s.[1] In the United Kingdom, 9.5% of abortions in 2009 were in adolescents.[3] Thus abortions among teenagers are common and are an important public health problem.

The medical termination of pregnancy using the antiprogestin mifepristone and a prostaglandin analogue has been widely established in several countries during the past decade. In 2009, 40% of abortions were medical in the United Kingdom.[3] In Sweden and Finland the corresponding figures were 72% and 76%.[4,5]

Increasing use of medical termination of pregnancy points to a need for appropriate studies to confirm its safety in various target groups. Using nationwide register based data we showed that both medical and surgical abortions are generally safe, with few serious complications when gestation is less than 63 days.[6] The most common adverse events were haemorrhage and incomplete abortion. However, in that study we did not assess the safety of medical abortion among adolescents.

Data on the safety of medical abortion among adolescents are limited. In a small prospective study, medical abortion was found to be highly effective and well tolerated in adolescents aged 14 to 17 when gestation was less than 56 days. Initially, half of the participants experienced stress and fear, but these emotions improved significantly within the month after abortion.[7]

In the present nationwide study we compared the safety of medical abortion between adolescents and adults. To eliminate the possible influence of previous pregnancies on the outcome of termination of pregnancy, we carried out a subgroup analysis among primigravid women. In addition we assessed the impact of a positive *Chlamydia trachomatis* test result at the time of

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Case 1:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 295 of 525 PageID 17325

abortion on the incidence of infections after abortion—a situation of great clinical relevance to adolescents.

METHODS

From the national abortion register compiled by the National Institute for Health and Welfare we identified all women who had undergone induced abortion in Finland during 2000-6. The study population consisted of women who had had a medical abortion (mifepristone alone or in combination with misoprostol or other prostaglandins) at 20 weeks or less of gestation. We divided the women into two cohorts based on age at the time of abortion: adolescents (<18 years) and adults (≥18 years). To keep the observations independent, we included only the first abortion for women who had more than one during the study period. To assess the potential learning curve in the introduction of medical abortion, we analysed the results in part separately for the first years (2000-3) of its use compared with established use (2004-6). We linked the data with the care register for health institutions (later called the hospital register) and the national infectious diseases register, both compiled by the National Institute for Health and Welfare, and the cause of death register of Statistics Finland. We followed the women for 42 days after the induced abortion and linked all events recorded in the hospital register and cause of death register with the abortion register.

The Finnish national register on induced abortions and sterilisations has been maintained since 1977. In accordance with the current legislation, doctors performing induced abortions are obliged to report cases to the register within one month, using a specific data collection form. In Finland, data on induced abortions are collected from all hospitals and clinics that carry out induced abortions. The register contains data on women having termination of pregnancy. These data include information on pregnancy history, occupation, type of residence, municipality, and marital status. Data on current pregnancy include information on duration of gestation at the time of abortion, indication for abortion, and method of termination.[5]

We have previously described Finnish legislation on induced abortion.[8] Briefly, current legislation permits termination of pregnancy of up to 20 weeks' gestation (24 weeks in cases of a medical condition of the fetus) for social, medical, or ethical reasons. A national guideline on the care of women seeking abortion was published in 2001 and updated in 2007.[9] Based on this guideline all women should be screened for *C trachomatis* and treated if it is present and screened for bacterial vaginosis at the first visit before the termination of pregnancy. Prophylactic antibiotics are not routinely used.

Classification of adverse events

- Haemorrhage—all reported haemorrhage
- Infection—pelvic inflammatory disease, endometritis, cervicitis, wound infections, pyrexia of unknown origin, urinary tract infections, and septicaemia
- Any reported incomplete abortion
- Surgical evacuation
- Psychiatric morbidity—depression, intoxication, psychoses (ICD-10 codes F10-F48)
- Injury or other reason for surgical operation—all injuries, cervical laceration, uterine perforation, all surgical interventions during follow-up
- Thromboembolic disease—pulmonary embolism, deep vein thrombosis
- Death—death from any cause, pregnancy related death according to the World Health Organization definition

Data collection

All hospitals in Finland are required by law to provide the hospital register with information on inpatient treatment (all hospitals) and outpatient visits (public hospitals). This register contains information on diagnosis (international statistical classification of diseases and related health problems, ICD-10[10]) and treatment, (Nordic classification of surgical procedures[11]), as well as the dates of the treatment episodes. To analyse adverse events related to induced abortion we linked information on the study participants in the hospital register for all hospital inpatient episodes and outpatient visits within 42 days after termination of pregnancy with data in the abortion register. We selected diagnoses and codes for surgical procedures in the cohorts for those considered to be of clinical importance.

We divided the complications into eight categories (see box): haemorrhage, infection, incomplete abortion, surgical evacuation, psychiatric morbidity, injury or other reason for surgical operation, thromboembolic disease, and death. The classification was based on that reported in the joint study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists[12] and modified for this and our previous study.[6]

The cause of death register contains data from death certificates and covers all deaths of Finnish citizens and permanent residents in Finland, classified according to ICD-10 codes. All the early deaths (within 42 days of termination of pregnancy) were classified as direct, indirect, or accidental.[13]

The National Department of Infectious Disease Epidemiology and Control at the National Institute for Health and Welfare collects information on cases of detected *C trachomatis* infections. Since 1997 it has been mandatory for laboratories to report all positive cases to the national infectious diseases register based on the Communicable Diseases Act and Decree of 1987.[14] Since 2004, laboratory notifications have included personal identification numbers, enabling linkage of the data with that in other registries. Since 2004 genital *C trachomatis* has been detected by DNA or RNA testing.[14]

Statistical analysis

To assess differences between the groups we used the Mann-Whitney test for age and the χ^2 test for categorical variables. The χ^2 test was also used to calculate the difference in the incidence of adverse events, except for rare ones (psychiatric morbidity, injury, thromboembolic disease, and death) when we used Fisher's

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Table 1 | Characteristics of the two study cohorts. Values are numbers (percentages) unless stated otherwise

Characteristics	Adolescent cohort (<18 years) (n=3024)	Adult cohort (≥18 years) (n=24 006)	P value
Mean (median) age (years), range	16.1 (16.0), 13-17	27.6 (26.0), 18-50	<0.001
Previous pregnancies:			
None	2913 (96.3)	10 474 (43.6)	<0.001
Yes	111 (3.7)	13 532 (56.4)	
Previous deliveries:			
None	2972 (98.3)	12 059 (50.2)	<0.001
Yes	52 (1.7)	11 947 (49.8)	
Previous induced abortions:			
None	3004 (99.3)	19 432 (80.9)	<0.001
Yes	20 (0.7)	4574 (19.1)	
Marital status:			
Married	12 (0.4)	5634 (23.5)	<0.001
Cohabiting	126 (4.2)	4546 (18.9)	
Single	2882 (95.3)	13 785 (57.4)	
Data missing	4 (0.1)	41 (0.2)	
Type of residence:			
Urban	1979 (65.4)	17 977 (74.9)	<0.001
Densely populated	486 (16.1)	2986 (12.4)	
Rural	559 (18.5)	3043 (12.7)	
Duration of gestation (weeks):			
<9	2424 (80.2)	20 143 (83.9)	<0.001
9-12	139 (4.6)	660 (2.7)	
13-16	283 (9.4)	1741 (7.3)	
17-20	171 (5.7)	1151 (4.8)	
Data missing	7 (0.2)	311 (1.3)	
Chlamydia trachomatis positive test result*	99/1749 (5.7)	496/13 547 (3.7)	<0.001

*Data available for 2004-6.

exact test. We used the confidence interval analysis program to calculate the rates of adverse events.[15] For small proportions we used the exact binomial method. The estimated risks of adverse events were determined by logistic regression analyses, and are presented as odds ratios with 95% confidence intervals. Variables that showed statistically significant associations with complications in univariate analysis (type of residence, marital status, duration of gestation, year of abortion, and adolescent or adult cohort) were further entered in multivariate analysis. SPSS 16.0 for Windows was used for the statistical analyses.

RESULTS

During 2000-6, 27 030 women underwent medical abortion between five and 20 weeks of gestation. Of these women, 3024 were younger than 18 (adolescent cohort) and the remaining 24 006 were older (adult cohort). Including only the first induced abortion for each woman during 2000-3, medical abortion was carried out in 1275 (29.3%) adolescents and in 10 459 (31.7%) adults. In 2004-6 the corresponding numbers were 1749 (61.9%) and 13 547 (63.3%).

The two cohorts differed significantly for various characteristics (table 1). The adolescents had fewer previous deliveries and induced abortions and were more often single and living in a non-urban setting. In both groups, most of the medical abortions (over 80%) were performed before nine weeks of gestation, but the mean duration of gestation was more advanced among adolescents. The incidence of *C trachomatis* infections, diagnosed four weeks before to six weeks after abortion, was higher in the adolescent cohort, as calculated for 2004-6.

Table 2 describes the incidence of adverse events among the two cohorts, as well as among the primigravid women. The adult cohort had a significantly higher incidence of haemorrhage (3690 (15.4%) *v* 386 (12.8%), P<0.001), incomplete abortion (2450 (10.2%) *v* 212 (7.0%), P<0.001), and surgical evacuation of retained products of conception (3121 (13.0% *v* 333 (11.0%), P=0.002). Odds ratios were calculated for main adverse events (haemorrhage, infection, incomplete abortion, and surgical evacuation), after adjustment for parity, previous abortions, marital status, type of residence, duration of gestation, and year of abortion. In the adolescent cohort the adjusted odds ratios were significantly lower for haemorrhage, incomplete abortion, and surgical evacuation than in the adult cohort. In addition, the adult cohort had more participants with adverse events (5535 (23.1%) *v* 575 (19.0%), P<0.001).

In the subgroup analysis carried out among the primigravid women, the proportion of women with haemorrhage (1505 (14.4%) *v* 374 (12.8%), P=0.035), incomplete abortions (887 (8.5%) *v* 201 (6.9%), P=0.006) and a higher overall number of adverse events (2224 (21.1%) *v* 552 (18.9%), P=0.031) was significantly higher in the adult cohort. After adjustment for marital status, type of residence, duration of gestation, and year of abortion, the risks for incomplete abortion and surgical evacuation were lower in the primigravid adolescents than in the primigravid adults (table 2).

The incidence of a psychiatric diagnosis was higher among the adolescents in both the cohort and the primigravid cohort, even though the overall numbers were low. Two deaths were reported during the follow-up period. Both of these occurred in adults and were unrelated to the pregnancy (intracranial trauma and melanoma).

The figure shows the results of logistic regression among the primigravid women for risk of main adverse events (haemorrhage, infection, incomplete abortion, and surgical evacuation). An increased risk of haemorrhage was associated with living in a densely populated area. The risk of bleeding after medical abortion was higher during 2004-6 than during 2000-3. Gestations of 9-12 or 13-16 weeks were associated with a lower risk of haemorrhage than gestations of less than nine weeks. The risk of haemorrhage was also significantly lower in the adolescent cohort.

Advanced duration of gestation (9-12, 13-16, and 17-20 weeks) was associated with an increased risk of infections after abortion (figure). Additionally, being married or cohabiting compared with being single was associated with an increased risk of infection.

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Case 1:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 297 of 525 PageID 17327

Table 2 | Incidence of adverse events in study cohorts for all women (3024 adolescents and 24 006 adults) and for primigravid women (2913 adolescents and 10 474 adults)

Adverse events	Adolescent cohort (<18 years)	% (95% CI)	Adult cohort (≥18 years)	% (95% CI)	P value	Adjusted odds ratio (95%CI)*
All women						
Haemorrhage	386	12.8 (11.6 to 14.0)	3690	15.4 (15.0 to 16.0)	<0.001†	0.87 (0.77 to 0.99)†
Infection	60	2.0 (1.5 to 2.6)	489	2.0 (1.9 to 2.2)	0.742	0.97 (0.73 to 1.30)
Incomplete abortion	212	7.0 (6.1 to 8.0)	2450	10.2 (9.8 to 10.6)	<0.001†	0.69 (0.59 to 0.82)†
Surgical evacuation	333	11.0 (9.9 to 12.1)	3121	13.0 (12.6 to 13.4)	0.002†	0.78 (0.67 to 0.90)†
Psychiatric morbidity	3	0.10 (0.02 to 0.29)	2	NA	0.012†	—
Injury	4	0.13 (0.04 to 0.34)	35	0.15 (0.10 to 0.19)	1.000	—
Thromboembolic disease	2	0.07 (0.01 to 0.24)	26	0.11 (0.07 to 0.15)	0.764	—
Death	0	NA	2	NA	0.392	—
No of adverse events per woman:						
0	2449	81.0 (79.6 to 82.4)	18471	76.9 (76.4 to 77.5)	<0.001†	—
1	488	16.1 (14.8 to 17.4)	4456	18.6 (18.1 to 19.1)		—
2	82	2.7 (2.2 to 3.4)	994	4.1 (3.9 to 4.4)		—
3	5	0.17 (0.05 to 0.39)	83	0.35 (0.27 to 0.42)		—
4	0	NA	2	NA		—
Primigravid women						
Haemorrhage	374	12.8 (11.6 to 14.1)	1505	14.4 (13.7 to 15.0)	0.035†	0.88 (0.78 to 1.00)
Infection	57	2.0 (1.5 to 2.5)	227	2.2 (1.9 to 2.5)	0.486	1.01 (0.75 to 1.37)
Incomplete abortion	201	6.9 (6.0 to 7.9)	887	8.5 (7.9 to 9.0)	0.006†	0.68 (0.56 to 0.81)†
Surgical evacuation	311	10.7 (9.6 to 11.8)	1136	10.8 (10.3 to 11.4)	0.794	0.75 (0.64 to 0.88)†
Psychiatric morbidity	3	0.10 (0.02 to 0.30)	1	NA	0.034†	—
Injury	4	0.14 (0.04 to 0.35)	10	0.10 (0.04 to 0.16)	0.521	—
Thromboembolic disease	2	0.07 (0.01 to 0.25)	10	0.10 (0.04 to 0.16)	1.00	—
Death	0	NA	1	NA	0.391	—
No of adverse events per woman:						
0	2361	81.1 (79.6 to 82.5)	8250	78.8 (78.0 to 79.5)	0.031†	—
1	468	16.1 (14.7 to 17.4)	1838	17.5 (16.8 to 18.3)		—
2	79	2.7 (2.2 to 3.4)	356	3.4 (3.1 to 3.8)		—
3	5	0.17 (0.06 to 0.40)	30	0.29 (0.18 to 0.39)		—
4	0	NA	0	NA		—

NA=not applicable owing to small number of women.
*Adult cohort as reference for all women adjusted for parity, previous abortions, marital status, type of residence, duration of gestation, and year of abortion; adult cohort as reference for primigravid women adjusted for marital status, type of residence, duration of gestation, and year of abortion.
†Statistically significant.

Also, the risk was higher in the later period (2004-6) than in 2000-3. The risk of infection was similar between the two cohorts.

Advanced duration of gestation was strongly related to the risk of incomplete abortion and surgical evacuation. The risk of incomplete abortion was lower in adolescents (odds ratio 0.69, 95% confidence interval 0.58 to 0.82) than in adults. The risk of surgical evacuation was increased in women living in rural areas and in those who were married or cohabiting. When abortion was carried out in the later period (2004-6) the risk of surgical evacuation was diminished (figure).

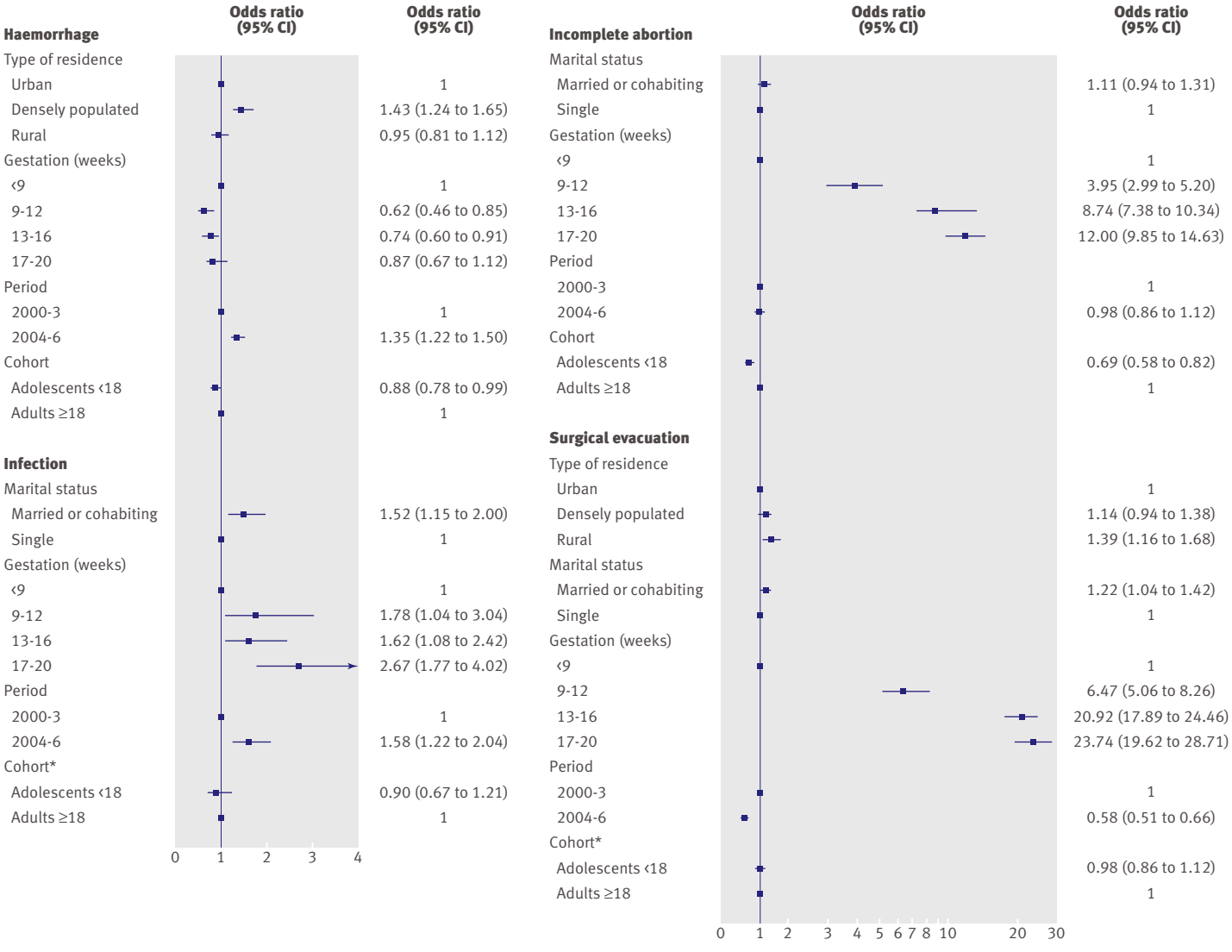
The risk of infections after abortion as a result of concurrent chlamydia infection was assessed among women who underwent abortion during 2004-6. In logistic regression analysis of the whole cohort, the risk of infection after abortion was not associated with concurrent chlamydia infection (1.02, 0.58 to 1.78). Moreover, no significant difference in the rate of infections after abortion emerged between adolescents and those with a positive test result for *C trachomatis* (data not shown).

DISCUSSION

In the present study the rate of adverse events and complications after medical abortion in adolescents was similar to or lower than that in adults. Various characteristics of the two cohorts differed significantly (table 1), but the risk of adverse events was calculated after adjustment for these factors. This study covered almost all abortions carried out in Finland in all regions and hospitals during a seven year period and thus shows reliable national trends. Earlier studies assessing the completeness of the Finnish abortion register found that 99% of abortions were reported to the register and at least 95% of information matched the medical records.[16 17]

One limitation of the study is that the registry based data lack detailed information as the diagnoses were made on clinical grounds, and the severity of adverse

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Logistic regression analysis of risk factors for main adverse events (haemorrhage, infection, incomplete abortion, and surgical evacuation) among primigravid women in entire cohort. Results of multivariate analysis are shown unless stated otherwise. Variables showing significance in univariate analysis are included. *Derived from univariate analysis

events may vary substantially. Another drawback is that no conclusions can be made on the effects of abortion beyond the 42 days of follow-up. A further limitation is that data on *C trachomatis* could only be linked with registry data from 2004, when identification numbers were first archived.

More women sought help for bleeding after abortion when gestation was less than nine weeks. This finding parallels that reported in our previous study.[6] This might be explained partly by the fact that medical abortions at nine weeks or more of gestation are carried out by hospitals, and not on an outpatient basis.[9] Moreover, an increasing number of these early abortions are carried out at home using self administered misoprostol.

The risk of surgical evacuation of retained products after medical abortion decreased during 2004-6 compared with 2000-3, whereas the number of incomplete abortions remained the same. These findings probably reflect a learning curve in providing medical abortion. However, the lower number of surgical evacuations occurred at the expense of an increased rate of consultations as a result of uterine bleeding. We took into account the possible bias caused by the differences between the study periods (2000-3 and 2004-6) by adjusting the odds ratios of adverse events by study period.

The rate of infections after abortion was higher (2.0%) than that reported in an earlier review in which medical abortion was assessed (0.9%).[18] The higher figure may in part be a result of the register based nature of the present study—that is, the diagnostic criteria lacked uniformity. In recent reviews, however, the incidence of infections after medical abortion in the second trimester has been estimated to be about 3%.[19,20] Thus in the present study, concerning pregnancies of up to 20 weeks' duration, the incidence of infections was comparable with that reported in the recent

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Case 0:22-cv-00223-Z Document 264-3 Filed 09/19/25 Page 299 of 525 PageID 17329

WHAT IS ALREADY KNOWN ON THIS TOPIC

Teenage pregnancies are mostly unplanned and often result in induced abortion

Medical abortion is increasingly used, albeit its safety has not been properly assessed among adolescents

WHAT THIS STUDY ADDS

The risk of adverse events (haemorrhage, incomplete abortion, infection) after medical abortion is similar or even lower in adolescent (<18 years) compared with adult women

reviews. The risk of infection was increased when the abortion was carried out in the later period (2004-6). The explanation for this is unclear. The incidence of *C trachomatis* infections in the Finnish population did not change at the same time.[14]

C trachomatis is a notable cause of pelvic inflammatory disease. Screening for and treatment of *C trachomatis* can prevent the development of the disease after abortion.[21] To prevent infection after termination of pregnancy both prophylactic antibiotic therapy for all and screen and treat strategies are in use. In a recent study in the United States, routine provision of doxicycin at the time of medical abortion was associated with a significant reduction in the rate of serious infections.[22]

We found no correlation between *C trachomatis* diagnosed at the time of abortion and subsequent infections. In Finland, systematic screening for *C trachomatis* after termination of pregnancy is enforced by national guidelines.[9] In 2004-6 the national incidence of *C trachomatis* among girls and young women aged 10-19 was 1.7% in Finland,[14] whereas a higher rate of 5.7% was detected in the present adolescent cohort. The results of this study do not rule out the possible association with infections after abortions in the cases of untreated *C trachomatis* infections, or with delayed antibiotic treatment. The present study suggests that by timely screening it is possible to treat the infection before the clinical manifestation.

In the present study psychiatric morbidity was significantly more common among adolescents than among adults, although the number of cases was small. Register based studies are not ideal for studying psychiatric disorders, as only some women seek professional help for mental disorders and only some women with mental disorders are treated in specialised healthcare. In a recent register based Danish study, the risk of a psychiatric disorder in women with no such previously detected disorders was not increased after induced abortion in the first trimester.[23] The risk of psychiatric contact was not, however, significantly affected by age. In a US survey, adolescents were not at increased risk for depression or lower self esteem after abortion than the controls during follow-up.[24] The present studies only assessed psychiatric diagnoses during the short follow-up but not possible psychiatric morbidity before abortion. Thus the association of mental disorders and termination of pregnancy among adolescents remains unresolved.

Experience of pain or satisfaction with care could not be studied in the present setting, as these outcomes are not registered in the Finnish abortion register. In a randomised study, women with higher gestational age and first pregnancy seemed to be less satisfied with medical abortion as a result of more pain during the termination.[25] The effective treatment of pain must be taken into account when adolescents, predominantly nulliparous women, undergo induced abortion.

Conclusion

The present population based national study provides evidence that medical abortion is not associated with additional risks of adverse events among adolescents in the short term compared with adult women. The data were derived from one country with a homogeneous population but can be generalised to populations with high quality healthcare and easy access to specialist treatment.

The preliminary results of this study were presented at the International Federation of Obstetrics and Gynecology (FIGO) meeting in Cape Town, South Africa October 2009, and in the International Federation of Professional Abortion and Contraception Associates (FIAPAC) meeting in Seville Spain, October 2010 (MN). We thank Aini Bloigu (National institute for Health and Welfare, Oulu, Finland) for her professional help with the statistics.

Contributors: All authors participated in the design of the study. MN carried out the data analysis, wrote the first draft of the manuscript, and is a guarantor of the study. All authors contributed to the subsequent writing of the paper and gave substantial input into the study. OH obtained funding for the study. MG is in charge of the Finnish reproductive registries (including the abortion register).

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: OH has lectured at an educational event organised by Nordic Drugs and has been principal investigator in clinical studies sponsored by the Concept Foundation; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the ethics committee of the Northern Ostrobothnia Hospital District in October 2005 (No 46/2005). The Ministry of Social Affairs and Health, and Statistics Finland gave permission for the use of confidential personal level data from the registries. The data protection ombudsman was notified about the data linkage before the analyses, as required by national data protection legislation.

Data sharing: No additional data available.

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EXHIBIT 13

Jamie Bryan Hall & Ryan T. Anderson,
The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Patients Experiences a Serious Adverse Event,
Ethics & Pub. Pol'y Ctr. (Apr. 28, 2025)

LIFE AND FAMILY INITIATIVE

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The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Patients Experiences a Serious Adverse Event

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April 28, 2025

Summary

- This largest-known study of the abortion pill is based on analysis of data from an all-payer insurance claims database that includes 865,727 prescribed mifepristone abortions from 2017 to 2023.
- 10.93 percent of women experience sepsis, infection, hemorrhaging, or another serious adverse event within 45 days following a mifepristone abortion.
- The real-world rate of serious adverse events following mifepristone abortions is at least 22 times as high as the summary figure of "less than 0.5 percent" in clinical trials reported on the drug label.
- The FDA should immediately reinstate its earlier, stronger patient safety protocols to ensure physician responsibility for women who take mifepristone under their care, as well as mandate full reporting of its side effects.
- The FDA should further investigate the harm mifepristone causes to women and, based on objective safety criteria, reconsider its approval altogether.

Danco Laboratories markets Mifeprex as "the safe and effective abortion pill," but our research shows that mifepristone abortion, as currently practiced in the U.S., is not safe and effective.[1] The manufacturer and the FDA rely on the results of 10 clinical trials with a total of 30,966 participants, less than 0.5 percent of whom reportedly experienced serious adverse reactions. In contrast, we analyzed real-world insurance claims data for 865,727 prescribed mifepristone abortions, broadly representative of women who obtain mifepristone abortions in the U.S. today, and we find a serious adverse event rate of 10.93 percent—at least 22 times as high as the summary figure reported on the drug label. In light of this research, we urge the FDA to reinstate earlier, stronger patient safety protocols and reconsider its approval of mifepristone altogether. Women deserve better than the abortion pill.

Our Key Findings

10.93 percent of women experience sepsis, infection, hemorrhaging, or another serious or life-threatening adverse event within 45 days following a mifepristone abortion, far greater than the summary figure of "less than 0.5 percent" in clinical trials reported on the drug label. *Figure 1, next page.*

[1] Danco Laboratories, "The Safe and Effective Abortion Pill | Mifeprix (mifepristone)," https://www.earlyoptionpill.com (accessed April 14, 2025)

Figure 1

Serious Adverse Events by Category

	Number with adverse events	Serious adverse event rate
Sepsis	824	0.10%
Infection	11,707	1.34%
Transfusion	1,257	0.15%
Hemorrhage	28,658	3.31%
Hospitalization (related to the abortion)	5,699	0.66%
ER visit (related to the abortion)	40,960	4.73%
Ectopic pregnancy	3,062	0.35%
Other life-threatening adverse events (cardiac, pulmonary, thrombosis, anaphylaxis, surgery)	1,956	0.22%
Repeated (surgical) abortion	24,563	2.84%
Other abortion-specific complications	49,169	5.68%
Overall	94,605	10.93%

Note: The overall serious adverse event rate of 10.93% is adjusted for the fact that some women suffer from adverse events in multiple categories.

Simply stated, mifepristone, as used in real-world conditions, is not "safe and effective."

Our real-world post-market observational study of mifepristone is, to our knowledge, the most comprehensive study of chemical abortion safety ever conducted in the U.S.:

- We identify and include 865,727 prescribed mifepristone abortions, 28 times as many as were included in all FDA-cited clinical trials combined.
- Our dataset is more recent, no earlier than 2017, while the FDA approval of mifepristone relies entirely on data from more than a decade ago.
- The women in our dataset are broadly representative of the women who obtain mifepristone abortions in the U.S.; they are not a prescreened group of generally healthy women recruited into various clinical trials conducted at different times around the world.
- The women in our dataset receive (or fail to receive) pre- and post-abortion healthcare of the real-world quality that prevails in the U.S. today, not the carefully controlled regimen of care that ordinarily prevails in a clinical trial.

Policy Implications

The FDA should reinstate the original patient safety protocols that were required when mifepristone was first approved. Doing so will likely reduce the harms to women and permit better monitoring to determine whether this drug should remain on the market:

- Prescribing mifepristone and misoprostol for the termination of pregnancy should require at least three in-person office visits by the patient—as originally required by the FDA.
- Mifepristone should be prescribed only by physicians—as originally required by the FDA—who have read and understood the prescribing information.
- Mifepristone should be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies—all of which was originally required by the FDA.
- Physicians must be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Healthcare providers should be required once again to report to the FDA (and manufacturers of mifepristone) all serious adverse events resulting from the use of mifepristone.
- Mifepristone should only be prescribed to a woman who is confirmed by a physician to be in the first seven weeks of pregnancy—as originally required by the FDA.

Background on FDA Approval and Regulation of Mifepristone

Mifepristone was developed by the French pharmaceutical company Roussel Uclaf S.A. and brought to the United States at the urging of President Clinton and after Congressional pressure. The FDA approved it under a little-used approval process for "certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments."[2] Thus, to grant approval in this manner, the FDA had to consider an unwanted pregnancy a "serious or life-threatening illness" and find that mifepristone was more effective than surgical abortion in treating it. The FDA's decision cites minimal data: clinical trials with only 859 participants in the U.S. and 1,800 in France.[3]

The original FDA-approved drug label for Mifeprex (the brand name of mifepristone) from September 2000 indicated use of the drug for "the medical termination of intrauterine pregnancy through 49 days' pregnancy."[4] It required several modest safeguards for women's health:

> Treatment with Mifeprex and misoprostol for the termination of pregnancy requires three office visits by the patient. Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.[5]

During the Obama and Biden administrations, the FDA chipped away at these initial safeguards, risking women's health in order to increase access to abortion. Under the current Risk Evaluation and Mitigation Strategy (REMS) in effect since 2023:

1. a mifepristone abortion now requires as a little as one telehealth visit with any approved healthcare provider (not necessarily a physician),
2. a woman may self-administer drugs obtained from a mail-order pharmacy, and
3. the prescriber need not report any adverse events unless he or she knows that a patient has died. *Figure 2.*

Figure 2

Weakening FDA Safeguards for Mifepristone

	2000 Clinton Initial Approval	2016 Obama REMS Changes	2023 Biden REMS Changes
Required number of in-person visits	3	1	0
Maximum gestational age (LMP)	7 weeks	10 weeks	10 weeks
Drugs prescribed only by physician	✓	✗	✗
Drugs dispensed only in office	✓	✓	✗
Drugs taken only in office	✓	✗	✗
Required in-office follow-up	✓	✗	✗
Required reporting of adverse events	✓	✗	✗

2 Alliance for Hippocratic Medicine v. FDA, Complaint, https://adflegal.org/wp-content/uploads/2022/11/Alliance-for-Hippocratic-Medicine-v-FDA-2022-11-18-Complaint.pdf
3 Mifeprex (mifepristone) drug label, September 2000, page 3, https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf
4 Mifeprex (mifepristone) drug label, September 2000, page 6, https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf
5 Mifeprex (mifepristone) drug label, September 2000, page 14, https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf

The current FDA-approved drug label refers to the results of 10 clinical trials with a total of 30,966 participants, less than 0.5 percent of whom reportedly experienced serious adverse reactions.[6] But these figures are based entirely on data from trials taking place more than a decade ago.

The Increasing Market Share of Chemical Abortion

Increased access to chemical abortion has coincided with a rapid increase in its prevalence. Chemical abortions—the vast majority of which are performed using a combination of mifepristone and misoprostol—now account for roughly two-thirds of all abortions in the United States. *Figure 3.*

In fact, Danco Laboratories boasts that more than 5 million U.S. women have used its abortion pill since it was approved in 2000.[7] Thus, it has become increasingly important to understand the risks and harms to women from chemical abortion in general and from mifepristone in particular.

How We Identified Mifepristone Abortions

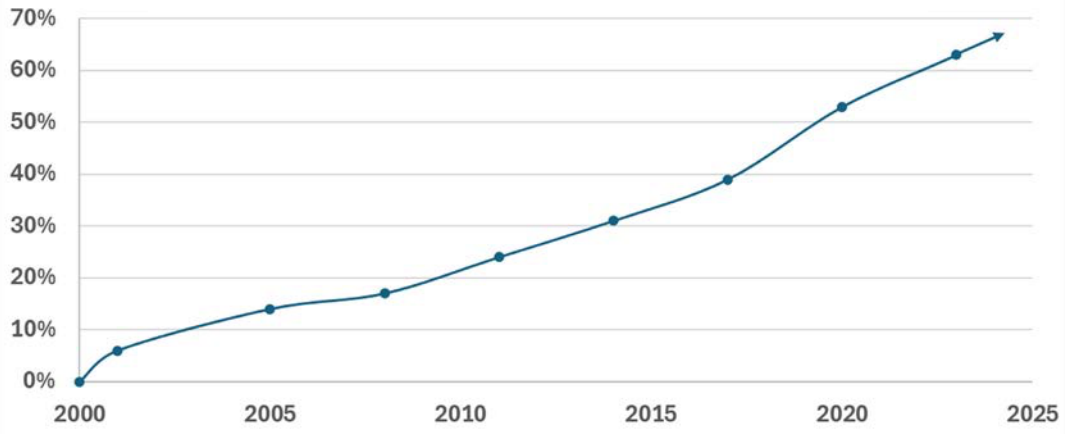
In our data, a mifepristone abortion was identified in one of three ways:

1. procedure code S0199: medically induced abortion by oral ingestion of medication including all associated services and supplies,
2. a prescription for mifepristone (with or without misoprostol within the next 3 days), or
3. a diagnosis code for elective termination or unwanted pregnancy, along with other billing coding consistent with manufacturer instructions for reimbursement for a mifepristone abortion for a given state and insurer combination.[8]

Following this method, we identified a total of 865,727 mifepristone abortions prescribed for a total of 692,873 women from 2017 to 2023. This includes 566,446 women, each of whom had one such abortion, and 126,427 women with multiple such abortions.

Figure 3

Chemical abortion has increased rapidly since approval in 2000 and now accounts for approximately two-thirds of all abortions.



Source: Guttmacher Abortion Provider Census and Monthly Abortion Provision Study,via https://www.guttmacher.org/2024/03/medication-abortion-accounted-63-all-us-abortions-2023-increase-53-2020

6 Page 7 of the drug label states, "Serious adverse reactions were reported in <0.5% of women. Information from the U.S. and non-U.S. studies is presented in Table 2." Table 2 on page 8 indicates that some categories of serious adverse reactions were observed at higher rates in some trials, but this is never discussed in the text, leaving only the previous statement with which to interpret the table. See Mifeprex (mifepristone) drug label, January 2023, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf

7 Danco Laboratories, "The Safe and Effective Abortion Pill | Mifeprex (mifepristone)," https://www.earlyoptionpill.com (accessed April 14, 2025)

8 Danco Laboratories, "Mifeprex State Payer Policies," https://www.earlyoptionpill.com/how-do-i-get-mifeprex/state-payer-policies (accessed April 14, 2025)

How We Identified Serious Adverse Events

We followed the official FDA definition of "serious adverse event."[9] To do so, we identified relevant ICD-10 diagnosis codes and CPT/HCPCS procedure codes for adverse events from multiple sources:

- CDC Severe Maternal Morbidity (SMM) indicators,[10]
- CMS Diagnosis-Related Group (DRG) 770 and 769 codes,[11]
- FDA Adverse Events Reporting System (FAERS) reports (interpreted and translated into diagnosis and procedure codes by the doctors on our team),[12] and
- a small number of (mostly gynecological) codes suggested by our doctors.

These codes were then graded by a team of physicians using the the NIH Common Terminology Criteria for Adverse Events (CTCAE version 5), which categorizes adverse events by severity on a 5-point scale.[13] We included CTCAE Grade 3 (severe) and Grade 4 (life-threatening). We did not include Grade 1 (mild) or Grade 2 (moderate). (Grade 5 is death, which would count as a serious adverse event under the FDA definition but could not necessarily be observed in the insurance claims data. We hope to show the rate of death in a subsequent report.)

For reporting, we have grouped the relevant diagnosis and procedure codes as follows:

1. The mifepristone label divides serious adverse events into six categories identified in the clinical trials: sepsis, infection, transfusion, hemorrhage, hospitalization, and emergency room visit. Only those hospitalizations and emergency room visits with abortion-related diagnosis and procedure codes are included in our analysis.
2. FAERS received reports of various events that our doctors judge to be life-threatening and have grouped into broad categories: ectopic pregnancy, surgery, cardiac, pulmonary, thrombosis, and anaphylaxis.
3. Repeated (surgical) abortion procedures are considered serious adverse events.
4. Other abortion complications include codes specifically related to an abortion or miscarriage, as well as life-threatening mental health diagnoses, etc.

We consider only serious adverse events that occurred within 45 days following the abortion. This is conservative, as some adverse events may present later (and studies relied on by the FDA used a timeframe as long as 72 days). Additionally, the likelihood of a subsequent pregnancy within this timeframe is negligible, which ensures that adverse events are related to the abortion rather than to a subsequent pregnancy.

Our Data

Our team has purchased access to a commercially available all-payer health insurance claims database including de-identified data for all U.S. patients during the years 2017 to 2023. It includes information on hospital and office visits, diagnoses, procedures, and prescriptions processed through private health insurance, Medicaid, Medicare, TRICARE, and the Department of Veterans Affairs (VA). The data excludes transactions for which the insurer is also the provider (as is the case with some HMOs and much VA care), as well as cash pay transactions (which are disproportionately common for abortion). This dataset provides longitudinal tracking of medical diagnoses, procedures, and prescriptions for each patient and is widely used in academic and regulatory research.

9 FDA, "What is a Serious Adverse Event?," https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event
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12 FDA, "FDA Adverse Events Reporting System (FAERS) Public Dashboard," https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f-7f1c25ee/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis
13 NIH, "Common Terminology Criteria for Adverse Events (CTCAE)," https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Our Research Project Team

Our research project was conducted and validated by a team of data scientists, analysts, and engineers, with assistance from our clinical team of board-certified obstetricians and gynecologists. Members have a history of academic research and peer-reviewed publication.

Conclusion

Our research shows unequivocally that mifepristone abortion, as currently practiced in the U.S., is considerably more dangerous to women than is represented on the FDA-approved drug label. The FDA should immediately reinstate its earlier, stronger patient safety protocols to ensure physician responsibility for women who take mifepristone under their care, as well as mandate full reporting of its side effects. The FDA should further investigate the harm this drug causes to women and, based on objective safety criteria, reconsider its approval altogether. Women deserve better than the abortion pill.

This paper is the first in a series investigating women's health and abortion using real-world data.

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EXHIBIT 14

James Studnicki et al.,
Comparative Acuity of Emergency Department Visits Following Pregnancy Outcomes Among Medicaid Eligible Women, 2004–2015,
Int'l J. Epidemiology & Pub. Health Rsch.,
Apr. 2024

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Research Article

Comparative Acuity of Emergency Department Visits Following Pregnancy Outcomes Among Medicaid Eligible Women, 2004-2015

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Abstract:

Objectives: We sought to compare the acuity of emergency department (ED) visits following various pregnancy outcomes.

Methods: Cohorts of ED visits by continuously eligible Medicaid women between 2004-2015 were determined by the type of pregnancy outcome and a control group as follows: within 30 days of a chemical (mifepristone) abortion, surgical abortion, or live birth; and at any time for women who were never pregnant. The primary outcome was the percent of ED visits coded as either severe or critical (CPT codes 99284-99285). The study population was extracted from the 17 states where Medicaid pays for abortion services.

Results: All cohorts exhibited a pattern of both increasing incidence and acuity of ED visits. For the entire observation period, an ED visit following a chemical abortion was significantly more likely to have a severe or critical acuity rating than a visit following surgical abortion, live birth, or an ED visit at any time by a woman who was never pregnant. With never-pregnant women as a reference cohort, odds ratios (ORs) are as follows: chemical abortion 2.01 [1.93-2.28]; surgical abortion 1.53 [1.43-1.63]; live birth 1.01 [1.00-1.01]. With chemical abortion as the reference cohort, odds ratios (ORs) are: never-pregnant 0.48 [0.44-0.54]; live birth 0.52 [0.49-0.55]; surgical abortion 0.73 [0.68-0.77].

Conclusion: Consistent with national trends for ED visits, both the number and acuity of ED visits following pregnancy outcomes are increasing. ED visit acuity following chemical abortion is persistently and significantly higher than for surgical abortion or live birth.

Keywords: pregnancy outcomes; induced abortion; emergency department visits; patient acuity

Introduction

Background: There is consensus that the overall incidence of adverse events and emergency department (ED) complication rates are higher following chemical abortion than surgical abortion (1,2). However, the acuity of ED visits following each type of abortion has been contested.

Importance: Some investigators have suggested that ED visits following abortion, especially chemical abortion, are frequently for observation care only rather than treatment purposes (3). This view, if demonstrated, would support the notion that the risks of chemical abortion are exaggerated by the high incidence of ED utilization. To date, no objective independently derived

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acuity methodology has been applied to ED visits following pregnancy outcomes.

Goals of This Investigation: We sought to compare the acuity of ED visits within a defined population of women who had undergone abortion or birth.

Methods

Study Design: Analytic observational prospective cohort
Setting and Selection of Participants: Centers for Medicare and Medicaid Services (CMS) Medicaid Analytic eXtract files for the 17 states which funded abortion services were used to identify emergency department (ED) visits within 30 days following a chemical (mifepristone) abortion, surgical abortion, or live birth between 2004-2015. ED visits following a defined pregnancy outcome were determined for women who were 16 years of age in 1999 and who were enrolled in Medicaid in at least a single month in every calendar year 1999-2015. Observation years of 2004-2015 were selected based upon the availability of ED visits related to chemical abortion which was approved by the Food and Drug Administration (FDA) in 2000. The first chemical abortions (n=15) and related ED visits (n=1) appeared in the data in 2001 and were not of sufficient volume for analysis until 2004. In the first observation year, 2004, there were 1,319 chemical abortions and 198 related ED visits. A 5% sample from a control cohort of Medicaid enrollees with no history of pregnancy was also analyzed.

Exposures: The primary exposure of interest was the type of pregnancy outcome. Live births were identified using ICD-9 codes V27.0, V27.2, and V27.5x and ICD-10 codes Z37.0, Z37.2, and Z37.5x. Induced abortions were identified using ICD-9 codes 635.xx and ICD-10 codes O04.xx; CPT4 codes 59840, 59841, 59850, 59852, 59855, 59856, and 59857; and HCPCS codes S0199, S2260, S2265, S2267, X7724, X7726, S0190 and S0191.
Outcomes: The primary outcome of interest was the percent of ED visits coded as either severe or critical. The acuity determination uses five Current Procedure Terminology (CPT) codes to stratify ED visits: nonurgent (99281), urgent (99282), moderate (99283), severe (99284) and critical (99285). ED visits were identified using Place of Service code 23. This coding considers the severity of the presenting problem and the complexity of the medical decision making required for treatment. This method is part of the Ambulatory Payment System (APC) of coding by which the federal government prospectively pays hospitals for covered services by considering resource utilization, clinical intensity and cost (4,5).

Data Analysis: We calculated the percentage change in counts of ED visits between 2004-2015. For each cohort, we derived a linear equation to express the trend in the proportion of severe and critical (99284 and 99285) visits to total visits. Coefficients of determination (R^2, Microsoft Excel, version 16) and Cochran-Armitage Chi-squared (X^2, MedCalc) trend tests were calculated for each cohort. Logistic regression adjusted odds ratios and 95% confidence limits (SAS/STAT, version 10) were calculated with chemical abortion and never-pregnant as reference cohorts.

Ethics Approval: The study has been exempted from Institutional Review Board (IRB) review pursuant to the U.S. Department of Health and Human Services Policy for the Protection of Human Research Subjects at C.F.R. 46.101(b). See IRB ID: 7269, www.sterlingirb.com.

Results

Between 2004 and 2015, the total number of ED visits across all four cohorts increased from 51,307 to 68,798, or 17,491, which is more than a third (34.1%) larger than the 2004 number. Specific percentage increases in each of the cohorts in total visits were: no pregnancy (42.8%); surgical abortion (280.4%); chemical abortion (2649.7%); and live birth (9.2%). ED visits coded severe or critical (99284-5) increased as follows: no pregnancy (101.0%); surgical abortion (450.6%); chemical abortion (4041.1%); and live birth (20.9%) (Table 1).

CPT codes	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2004-15	Δ 2004-15
No Pregnancy														
99281-83(%)	162(61.3)	167(66.8)	162(62.3)	167(53.8)	203(57.0)	182(56.1)	184(51.8)	240(50.2)	242(50.5)	191(48.1)	205(44.8)	172(45.6)	2277(52.8)	6.2%
99284(%)	78(29.5)	59(23.6)	71(27.3)	95(30.6)	107(30.0)	92(28.3)	130(36.6)	172(35.9)	169(35.2)	131(33.0)	149(32.6)	126(33.4)	1379(32.7)	61.5%
99285(%)	24(09.1)	24(09.6)	27(10.3)	48(15.4)	46(12.9)	51(15.6)	41(11.5)	66(13.8)	68(14.1)	75(18.8)	103(22.5)	79(20.9)	652(14.5)	229.2%
Total	264	250	260	310	356	325	355	478	479	397	457	377	4,308	42.8%
99284+5(%)	102(38.6)	83(32.3)	98(34.7)	143(36.7)	153(39.8)	143(42.3)	171(46.3)	238(48.1)	237(50.2)	206(52.1)	252(54.5)	205(54.0)	2031(47.2)	101.0%
Surgical Abortion														
99281-83(%)	1502(54.3)	2144(51.7)	2565(51.3)	2876(47.9)	3281(47.6)	3362(42.8)	3538(40.4)	3828(38.3)	3926(34.9)	3611(31.1)	3228(32.5)	3562(33.9)	37423(39.5)	137.2%
99284(%)	1005(36.3)	1381(33.3)	1692(33.8)	2119(35.3)	2299(33.3)	3051(38.9)	3444(39.3)	3667(36.7)	4201(37.4)	4287(36.9)	3600(36.2)	3891(37.0)	34637(36.6)	287.2%
99285(%)	259(09.4)	621(15.0)	747(14.9)	1013(16.9)	1316(19.1)	1434(18.3)	1776(20.3)	2488(24.9)	3120(27.7)	3719(32.0)	3104(31.3)	3069(29.2)	22666(23.9)	1084.9%
Total	2766	4146	5004	6008	6896	7847	8758	9983	11247	11617	9932	10522	94,726	280.4%
99284+5(%)	1264(45.7)	2002(48.3)	2439(48.7)	3132(52.1)	3615(52.4)	4485(57.2)	5220(59.6)	6155(61.7)	7321(65.1)	8006(68.9)	6704(67.5)	6960(66.1)	57303(60.5)	450.6%
Chemical Abortion														
99281-83(%)	98(49.7)	164(51.7)	114(32.5)	174(38.6)	307(38.4)	440(39.3)	605(35.8)	899(34.1)	917(30.6)	618(27.5)	557(22.8)	1317(24.3)	6210(30.1)	1243.9%
99284(%)	70(35.5)	103(32.5)	184(52.4)	200(44.3)	299(37.4)	446(39.8)	722(42.8)	995(37.8)	1113(37.1)	912(40.5)	1100(45.1)	2269(41.9)	8413(40.7)	3141.4%
99285(%)	29(14.7)	50(15.8)	53(15.1)	77(17.1)	194(24.3)	235(21.0)	361(21.4)	740(28.1)	967(32.3)	720(32.0)	784(32.1)	1831(33.8)	6041(29.2)	6213.8%
Total	197	317	351	451	800	1121	1688	2634	2997	2250	2441	5417	20,664	2649.7%
99284+5(%)	99(50.3)	153(48.3)	237(67.5)	277(61.4)	493(61.6)	681(60.7)	1083(64.2)	1735(65.9)	2080(69.4)	1632(72.5)	1884(77.2)	4100(75.7)	14454(69.9)	4041.4%
Live Birth														
99281-83(%)	23505(48.9)	26127(47.6)	25880(45.6)	26903(44.2)	29780(43.6)	31411(42.1)	31991(41.9)	34398(42.6)	35383(41.3)	33661(41.0)	29240(44.1)	22774(43.4)	351053(43.5)	-3.1%
99284(%)	16244(33.8)	18763(34.2)	20132(35.4)	21524(35.4)	24606(36.0)	27024(36.2)	28262(37.0)	29052(36.0)	30789(35.9)	29553(36.0)	22447(33.9)	17972(34.2)	286368(35.5)	10.6%
99285(%)	8331(17.3)	9966(18.2)	10792(19.0)	12388(20.4)	13969(20.4)	16246(21.8)	16036(21.0)	17258(21.4)	19595(22.8)	18913(23.0)	14573(22.0)	11736(22.4)	169803(21.0)	40.9%
Total	48080	54856	56804	60815	68355	74681	76289	80708	85767	82127	66260	52482	807224	9.2%
99284+5(%)	24575(51.1)	28729(52.4)	30924(54.4)	33912(55.8)	38575(56.4)	43270(57.9)	44298(58.1)	46310(57.4)	50384(58.7)	48466(59.0)	37020(55.9)	29708(56.6)	456171(56.5)	20.9%
Grand Total	51307	59569	62419	67584	76407	83974	87090	93803	100490	96391	79090	68798	926922	34.1%
Grand Total 99284+5 (%)	26040(50.7)	30967(51.9)	33698(53.9)	37464(55.4)	42836(56.0)	48579(57.8)	50772(58.2)	54438(58.0)	60022(59.7)	58310(60.4)	45860(57.9)	40973(59.5)	529959(57.1)	57.3%

Table 1: ED visit acuity by pregnancy outcome

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The percentage of total visits coded severe or critical (99284-85) increased for all cohorts from 2004-2015: no pregnancy (38.6%-54.0%); surgical abortion (45.7%-66.1%); chemical abortion (50.3%-75.7%); and live birth (51.1%-56.6%). The trends in the proportion of severe and critical visits are all significant (X^2, $p<.0001$) for each cohort: never-pregnant (58.80); surgical abortion (1848.18); chemical abortion (347.88); and live birth (818.02) (Figure 1).

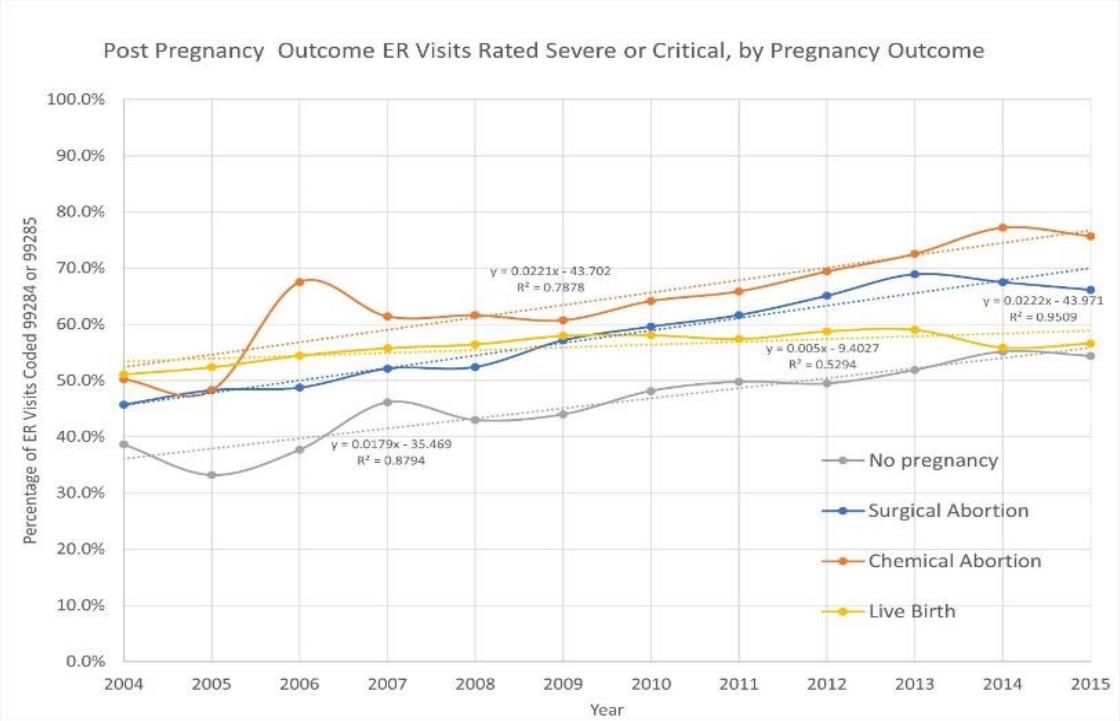


Figure 1: Post pregnancy outcome ED visits rated severe or critical, by pregnancy outcome

The logistic multiple regression adjusted odds ratios for the entire observation period (2004-2015) with never-pregnant as the reference cohort are: chemical abortion, OR 2.01 [1.93-2.28]; surgical abortion, OR 1.53 [1.43-1.63]; and live birth, OR 1.01 [1.00-1.01]. The adjusted odds ratios with chemical abortion as the reference cohort are: never-pregnant, OR 0.48 [0.44-0.54]; live birth, OR 0.52 [0.49-0.55]; surgical abortion, OR 0.73 [0.68-0.77].

Limitations

Findings from a Medicaid population may not be generalizable to populations of a different socioeconomic and demographic composition. The use of administrative claims data has recognized limitations including inconsistent and mistaken coding which may vary from state to state, the exclusion of codes considered unnecessary for billing purposes, and the possible upcoding to maximize revenue (6,7,8). Acuity increases may reflect a pattern of ED use by sicker patients (9). The use of a comprehensive measure of total acuity does not allow for comparison of specific complication rates between cohorts.

Discussion

This pattern of increasing ED utilization and acuity aligns with previous research (10). Both the volume and acuity of ED visits by Medicaid eligible women following a pregnancy outcome increased between 2004 and 2015. ED visits following chemical abortion had the greatest comparative increase in incidence, likely reflecting the rapidly growing percentage that they represented of all abortions during the observation period (11). Similarly, the growth in the percentage of high acuity ED visits was the largest for the chemical abortion cohort followed by the surgical abortion cohort. Increases in both incidence and acuity were smallest following live birth.

While multiple factors may influence these results, persistently and significantly higher ED visit acuity following chemical abortion is clearly evident. ED visit acuity for either method of abortion is significantly higher than for visits following a live birth. The increasing preference for this method of induced abortion, along with this evidence of the growing acuity of related ED visits, suggests that a greater level of surveillance will enhance patient safety for these patients.

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Conflicts of Interest: None declared

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EXHIBIT 15

Will a doctor be able to tell if you've taken abortion pills?
Women Help Women (Sept. 23, 2019)

Will a doctor be able to tell if you've taken abortion pills?

Monday, September 23, 2019 blog (/en/blog) Share

Can a doctor tell if someone has used abortion pills?



(/en/page/1094/woman-with-laptop-and-mug)

There are many reasons one might choose to take abortion pills, as opposed to seeking abortion care in a clinical setting. Because 90% of US counties (https://data.guttmacher.org/states/table?state=US&topics=58&dataset=data) lack an abortion clinic, she may be unable to afford the cost of travel, which also may involve taking one or more days off of work (depending on the abortion regulations in her state), finding childcare, lodging, and more. She may prefer to control where and when she takes the pills, and where she experiences cramping, bleeding (https://womenhelp.org/en/page/1045/how-much-and-for-how-long-should-you-bleed-after-taking-misoprostol), and other symptoms. She may not want her abusive partner (https://womenhelp.org/en/page/976/what-reproductive-coercion-has-to-do-with-abortion-access), her parents (https://womenhelp.org/en/page/904/parental-notification-laws-are-toxic-for-young-people-seeking-abortion-care), or anyone in her life to find out about her pregnancy or her abortion. If this is the case, she will likely be anxious that, even once her abortion is complete (https://womenhelp.org/en/page/991/how-do-i-know-if-my-medical-abortion-was-successful), that someone in the future, namely a doctor, will learn that she's had an abortion.

Can a doctor tell if someone has used abortion pills? The answer is no, if they have been taken orally. (If the pills are inserted into the vagina, a doctor may be able to tell if there are traces remaining.) If one took the mifepristone/misoprostol combination, or misoprostol on its own, and she does seek medical care because of complications (https://consult.womenhelp.org/en/page/416/signs-of-complication), she does not need to tell a health care provider that she took abortion pills. The symptoms of a miscarriage and a medical abortion are the same, and there are no tests that can prove one has had a medical abortion(s). (https://nwhn.org/abortion-pills-vs-miscarriage-demystifying-experience/)

So a doctor can't tell if one has had a medical abortion, and in situations where one fears for her personal safety, or doesn't trust her health care provider with this information, that's a good thing. But if neither of these is the case, it's important to consider why someone would not want her doctor to know her entire medical history, including abortions. Is she holding back this information out of shame? Does she secretly fear that abortion has endangered her fertility? Abortion doesn't impact future fertility, and doctors who traffic in actual medicine know this, and should make sure their patients know it as well.

Abortion stigma (https://womenhelp.org/en/page/946/abortion-stigma-101-and-how-it-interferes-with-access-to-self-managed-abortion), or ideas and beliefs about abortion that are medically inaccurate and negative, can result in those who take abortion pills not seeking medical care if they need it, taking the pills incorrectly, or getting the pills from sources that aren't safe, since they don't want anyone to know that they're seeking abortion. Health care providers should not in any way contribute to the perpetuation of abortion stigma; in fact, it's their job to ensure that people get accurate information and medical care regardless of their personal beliefs.

To learn more about about abortion pills, how they work, what to expect, and more, check out Women Help Women's FAQs (https://consult.womenhelp.org/en/page/377/questions-and-answers).

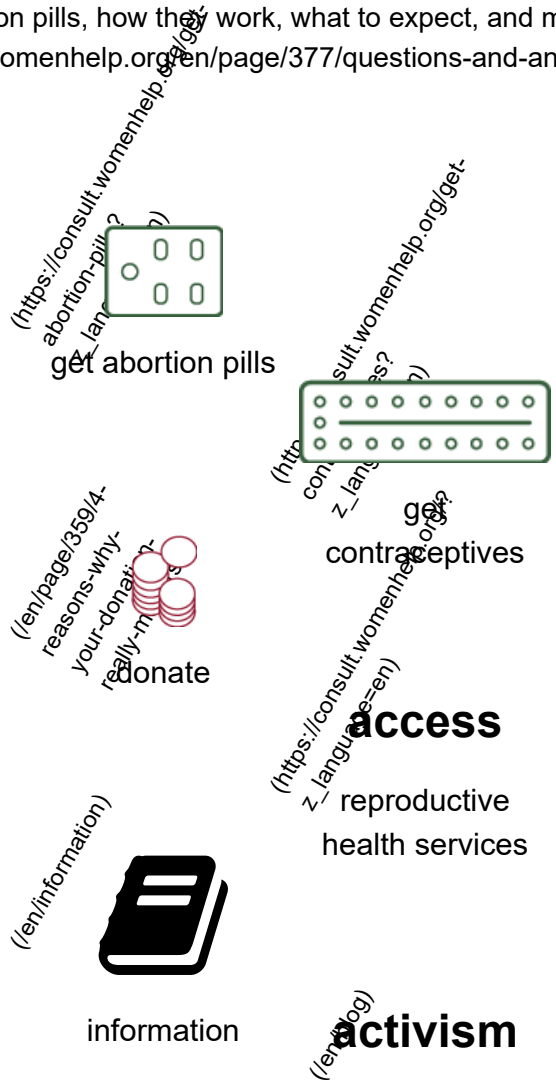


EXHIBIT 16

How do you know if you have complications and what should you do?
Aid Access

← Back to FAQs Complications

How do you know if you have abortion complications?

If performed in the first 13 weeks, a medical abortion carries a very small risk of complications. This risk is the same as when a woman has a miscarriage.

What are the possible abortion pill complications and what should you do?

These are the possible complications, their symptoms and treatment:

Heavy bleeding (occurs in less than 1% of medical abortions)

- **Symptom**: Bleeding that lasts for more than 2 hours and soaks more than 2 maxi sanitary pads per hour. Feeling dizzy or light-headed can be a sign of too much blood loss. This is dangerous to your health and must be treated by a doctor.
- **Treatment**: a vacuum aspiration (curettage.) When available, a woman should start taking 2 Misoprostol under the tongue immediately at home before going to the hospital. Very rarely (less than 0.2%) a blood transfusion is needed.

Incomplete abortion

- **Symptoms**: heavy or persistent bleeding and/or persistent severe pain.
- **Treatment**: 2 tablets of Misoprostol or/ and a vacuum aspiration (curettage)

Infection

- **Symptom**: If you have a fever (more than 100.4 degrees Fahrenheit) for more than 24 hours, or you have a fever of more than 102.2 degrees Fahrenheit, there might be an infection that needs treatment.
- **Treatment**: antibiotics and/or vacuum aspiration.

If you think you might have a complication you should go to a doctor immediately. You do not have to tell the medical staff that you tried to induce an abortion; you can tell them that you had a spontaneous miscarriage. Doctors have the obligation to help in all cases and know how to handle a miscarriage.

Miscarriage vs abortion symptoms

The symptoms of a miscarriage and an abortion with pills are exactly the same and the doctor will not be able to see or test for any evidence of an abortion, as long as the pills have completely dissolved. If you used the Misoprostol under the tongue as our protocol recommends, the pills should have dissolved within 30 minutes. If you took the pills vaginally, you must check with your finger to make sure that they are dissolved. Traces of the pills may be found in the vagina up to four days after inserting them.

Ongoing pregnancy

Less than 1% of women experience ongoing pregnancy.[1] This can be determined by a pregnancy test after 3 weeks or an ultrasound within 10 days. If the medical abortion treatment failed, there is a slight increase in the risk of birth defects such as deformities of the hands or feet and problems with the nerves of the fetus. To treat an ongoing pregnancy, you must repeat a medical or surgical abortion.

[1] "Low-dose Mifepristone Regimens are Effective and Safe for Early Abortion." The Guttmacher Institute. https://www.guttmacher.org/journals/ipsrh/2013/07/low-dose-mifepristone-regimens-are-effective-and-safe-early-abortion

EXHIBIT 17

Am. Coll. of Obstetricians and Gynecologists Practice Bulletin No. 181: Prevention of Rh D Alloimmunization,
130 Obstetrics & Gynecology 481 (Aug. 2017)

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 181, AUGUST 2017 *(Replaces Practice Bulletin Number 4, May 1999)*

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics in collaboration with Robert M. Silver, MD.

Prevention of Rh D Alloimmunization

Advances in the prevention and treatment of Rh D alloimmunization have been one of the great success stories of modern obstetrics. There is wide variation in prevalence rates of Rh D-negative individuals between regions, for example from 5% in India to 15% in North America (1). However, high birth rates in low prevalence areas means Rh hemolytic disease of the newborn is still an important cause of morbidity and mortality in countries without prophylaxis programs (1). In such countries, 14% of affected fetuses are stillborn and one half of live born infants suffer neonatal death or brain injury (1). The routine use of Rh D immune globulin is responsible for the reduced rate of red cell alloimmunization in more economically developed countries. First introduced in the 1970s, the postpartum administration of Rh D immune globulin reduced the rate of alloimmunization in at-risk pregnancies from approximately 13–16% to approximately 0.5–1.8% (2, 3). The risk was further reduced to 0.14–0.2% with the addition of routine antepartum administration (2, 3). Despite considerable proof of efficacy, there are still a large number of cases of Rh D alloimmunization because of failure to follow established protocols. In addition, there are new data to help guide management, especially with regard to weak D phenotype women. The purpose of this document is to provide evidence-based guidance for the management of patients at risk of Rh D alloimmunization.

Background

Nomenclature

Nomenclature for red blood cell surface proteins is complex and can be confusing. The red cell membrane contains many anchored surface proteins. Many of these proteins are polymorphic and carry different blood groups. A blood group system consists of one or more antigens controlled at a single gene locus, or by two or more closely linked homologous genes with little or no observable recombination between them. Most blood group antigens are glycoproteins, and their specificity is mostly determined either by the oligosaccharide or amino acid sequence. The 30 human blood group system genes have been identified and sequenced, and all the polymorphisms are known (4).

A variety of terminologies has been used to denote human blood groups since their discovery in 1900. In 1980, the International Society of Blood Transfusion established a Working Committee to devise and maintain a genetically-based numerical terminology for red cell surface antigens. The numerical terminology was devised for computer storage of information on blood groups antigens and to provide a framework for genetic classification. The numerical terminology is not suitable for everyday communication, which has led to a variety of alternative names being used for some blood group antigens. In an attempt to introduce some uniformity, a recommended list of alternative names for antigens is available through the International Society of Blood Transfusion (4). In most cases the name or symbol is identical to that originally published, but in a few cases the more commonly used name is provided, as with ABO and Rh. Specific subtypes or polymorphisms use a second designation (eg, Rh D, Rh C, Rh E). This document uses the designation Rh D to signify the erythrocyte antigen. Women who carry the Rh D antigen are identified as Rh D positive. Those who do not carry the Rh D

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antigen are identified as Rh D negative. Details regarding the nomenclature for partial D or weak D antigens are described as follows (see "How should a weak D blood type be interpreted and what management should be undertaken?"). The frequency of the Rh D-negative phenotype is most common in individuals of European and North American descent (15–17%), is comparatively decreased in the regions of Africa and India (3–8%), and is rarest in Asia (0.1–0.3%) (1, 5). The immune globulin used specifically to bind the Rh D antigen is referred to as Rh D immune globulin or anti-D immune globulin. Alloimmunization refers to an immunologic reaction against foreign antigens that are distinct from antigens on an individual's cells. In this case, it refers to the maternal formation of antibodies against fetal Rh D. Fetal–maternal hemorrhage is the term used to identify varying amounts of fetal cells in the maternal circulation from small interruptions at the fetal–maternal placental interface (6).

Causes of Rh D Alloimmunization

Rh D alloimmunization occurs when a Rh D-negative woman is exposed to red cells expressing the Rh D antigen. Although the fetal and maternal circulations are separate, there is often some antenatal mixing of fetal and maternal blood, even in asymptomatic women. Events such as miscarriage, ectopic pregnancy, antenatal bleeding, and delivery, as well as procedures such as chorionic villus sampling, amniocentesis, pregnancy-related uterine curettage, and surgical treatment of ectopic pregnancy can lead to maternal exposure to fetal red blood cells and, consequently, Rh D alloimmunization (Box 1). Between 3% and 11% of women with threatened abortion in the first trimester, and approximately 45% giving birth in the third trimester, have a fetal–maternal hemorrhage (7, 8). The volume of fetal–maternal hemorrhage leading to Rh D alloimmunization can be as small as 0.1 mL or as large as 30 mL (7, 8).

Box 1. Potential Sensitizing Events in Rh D-Negative Women in Pregnancy

- Chorionic villus sampling, amniocentesis, cordocentesis
- Threatened miscarriage or miscarriage
- Ectopic pregnancy
- Evacuation of molar pregnancy
- Therapeutic termination of pregnancy
- Antepartum hemorrhage
- Abdominal trauma
- Intrauterine fetal death
- External cephalic version
- Delivery

Fetal–maternal hemorrhage also may take place in the first and second trimesters in association with spontaneous pregnancy loss or uterine instrumentation (eg, dilation and curettage or evacuation). The risk of Rh D alloimmunization is estimated to be 1.5–2% in susceptible women after spontaneous miscarriage and 4–5% after dilation and curettage (3, 7). There are insufficient data from studies that evaluated the efficacy of administration of anti-D immune globulin after spontaneous miscarriage and, although alloimmunization appears rare, it is possible and recommendations continue to include administration of anti-D immune globulin after such losses (3, 9, 10). Ectopic pregnancy also may lead to Rh D alloimmunization, although data regarding the probability are lacking. Until further evidence is available, expert advice continues to recommend administration of anti-D immune globulin within 72 hours of suspected breach of the choriodecidual space (9).

Historically, chorionic villus sampling has been estimated to carry a 14% risk of fetal–maternal hemorrhage of 0.6 mL or more (11). Later studies corroborate these earlier findings and continue to support the administration of anti-D immune globulin to Rh D-negative women who have chorionic villus sampling (12, 13). Traditionally, amniocentesis led to a 2–6% rate of fetal–maternal hemorrhage, even if the placenta was not traversed (14, 15). Recent studies suggest the rate of fetal–maternal hemorrhage may be lower than previously thought but not negligible (16, 17) and alloimmunization is possible. Similarly, other invasive procedures such as cordocentesis also can cause fetal–maternal hemorrhage (16) and warrant anti-D immune globulin prophylaxis. Although not invasive, external cephalic version (regardless of success) is associated with a 2–6% risk of fetal–maternal hemorrhage and anti-D immune globulin is indicated for unsensitized Rh D-negative patients (18, 19).

Anti-D Immune Globulin to Prevent Alloimmunization

Anti-D immune globulin is extracted by cold alcohol fractionation from plasma donated by individuals with high-titer anti-D immune globulin G antibodies. Original work in the 1960s noted maternal sensitization to fetal Rh-positive blood could be prevented by administering anti-D immune globulin. A prophylactic dose of 300 micrograms of anti-D immune globulin can prevent Rh D alloimmunization after exposure to up to 30 mL of Rh D-positive fetal whole blood or 15 mL of fetal red

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blood cells (20). Subsequently anti-D immune globulin became more widely available and a single dose given to susceptible Rh D-negative women within 72 hours of delivery reduced the rate of Rh D alloimmunization by 80–90% (7, 21, 22). However, it became clear that asymptomatic fetal–maternal hemorrhage during the third trimester triggered alloimmunization in 2% of at-risk women before delivery. This rate was shown to be reduced to less than 0.2% with routine antenatal administration of anti-D immune globulin at 28 weeks of gestation (7).

In the United States, a recommendation for the administration of anti-D immune globulin was introduced in the 1970s. The current practice of administering a single antenatal dose of 300 micrograms of anti-D immunoglobulin at 28 weeks of gestation followed by a second dose after birth when newborn Rh D typing has identified the infant as Rh positive, based on recommendations from a conference at McMaster University in 1977, is associated with less than a 0.2% rate of Rh alloimmunization (7, 23). In the United Kingdom, recommendations have differed somewhat from those in the United States in that antenatal Rh D immune globulin using different doses may be given as two injections at 28 weeks of gestation and at 34 weeks of gestation, or as a single administration at 28 weeks of gestation (24, 25). There is no trial comparing the two-dose regimens with a single dose, and no evidence of a difference in efficacy between these regimens (24). However, an observational study from the United Kingdom noted better adherence with the single-dose compared with the two-dose protocol (26). There is also potential cost reduction with a single dose (27). Thus, there are no compelling data indicating a change from the single-dose procedure currently used in the United States to the two-dose regimen.

Although administration of anti-D immune globulin at 28 weeks of gestation is highly effective, pharmacokinetic studies suggest that levels of anti-D vary between patients and some may not have adequate anti-D levels at delivery (28). In the past, some authorities advised giving a second dose of Rh D immune globulin in women who have not given birth 12 weeks after receiving their antenatal dose (29). However, the vast majority of women who give birth more than 12 weeks after receiving antenatal Rh D immune globulin do not become alloimmunized. Because of this low risk of alloimmunization and the fact that 40% of infants of Rh D-negative women will be Rh D negative, most guidelines do not recommend that a second dose of anti-D immune globulin be given until after delivery when newborn Rh D typing becomes available. Additional anti-D immune globulin is needed to prevent alloimmunization for exposures larger than 30 mL of Rh D-positive fetal whole blood. Rarely, in 2–3 per 1,000 deliveries, a fetal–maternal hemorrhage may be greater than 30 mL (6, 7). For this reason, Rh D-negative women who give birth to Rh D-positive infants should undergo additional testing to assess the volume of fetal–maternal hemorrhage and guide the amount of Rh D immune globulin required to prevent alloimmunization (5, 25, 30, 31). It is advised that all women undergo such screening after delivery because a policy of only screening deliveries with high-risk conditions for excess fetal–maternal hemorrhage, such as abruptio placentae or manual removal of the placenta, will fail to identify a large number of cases requiring more than the standard postpartum dose of Rh D immune globulin (32).

Screening for fetal–maternal hemorrhage in routine situations typically begins with the rosette fetal red blood cell assay. The erythrocyte rosette screen is a sensitive, qualitative test that can detect greater than 2 mL of fetal whole blood in the maternal circulation (32). The rosette test is performed by incubation of a maternal blood sample with Rh immunoglobulin that will bind fetal Rh D-positive red blood cells, followed by the addition of enzyme-treated reagent indicator red blood cells. Rh D-positive fetal red blood cells present in maternal circulation result in forming aggregates (rosettes) that can be visualized by light microscopy. A positive rosette test should be followed with a method to determine the percentage of fetal red blood cells in maternal circulation, such as the Kleihauer–Betke test or flow cytometry. The Kleihauer–Betke acid elution test relies on the principle that fetal red blood cells contain mostly fetal hemoglobin F, which is resistant to acid elution, whereas adult hemoglobin is acid sensitive. Although the Kleihauer–Betke test is inexpensive and requires no special equipment, it lacks standardization and precision, and may not be accurate in conditions in which the mother has a coexistent medical condition that is associated with red blood cells containing an increased percentage of hemoglobin F, such as sickle-cell disease and the thalassemias. Flow cytometry is a specialized technique that is an alternative method available in some hospitals for quantification of fetal–maternal hemorrhage, although its use is limited by equipment and staffing costs. Flow cytometry uses monoclonal antibodies to hemoglobin F or the Rh D antigen with quantification of fluorescence, and is highly sensitive and accurate in identifying fetal red blood cells in maternal blood (32). In clinical situations in which fetal–maternal hemorrhage has occurred in a volume that is not covered by the standard 300 microgram dose of Rh immune globulin (greater than 30 mL of fetal whole blood or 15 mL of fetal red cells) additional vials of Rh immune globulin can be administered at one

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time (up to eight full vials). These additional doses can be administered intramuscularly at separate sites every 12 hours until the desired dosage has been reached (33, 34). An intravenous Rh immune globulin is available that also may be used in these cases and provides more comfort for the patient (34).

Because Rh D immune globulin is obtained from human plasma, there is a theoretical risk of transmission of viral infection. In the 1990s, it was discovered that immune globulin contaminated with hepatitis C virus had been administered to women from 1977 to 1979 in Ireland and Germany (35). Most of these exposed women showed only slight to moderate hepatic inflammation 17–35 years later (35, 36). A later analysis of samples manufactured between 1991 and 1994 again demonstrated a low potential for transmission of the hepatitis C virus, with 0.59% of potential exposures showing evidence of seroconversion (37). Regardless, because the product is a purified immune globulin, the risk of viral infection from anti-D immune globulin is exceedingly low. Since 1985, all plasma used for the production of anti-D immune globulin has been tested for viral infections, and several fractionation and purification steps, including micropore filtration, are used to remove and inactivate viruses. Other contaminations and inadvertent exposures have not been reported, and anti-D immune globulin has been manufactured without mercury-containing thimerosal since 2001 (38).

Failure to Prevent Rh D Alloimmunization

Rh alloimmunization during pregnancy in Rh D-negative women may still occur. This might be because of a failure of administering antenatal prophylaxis in the third trimester of pregnancy, insufficient dosage or timely administration (within 72 hours) of anti-D immune globulin given after a known sensitizing event during pregnancy (or after birth), or an unrecognized fetal–maternal hemorrhage at some point in the pregnancy (39). In spite of recommendations for immunoprophylaxis, approximately 0.1–0.4% of women at risk become sensitized during pregnancy (22). A recent retrospective study from New Zealand identified reasons for continued cases of sensitization, including omission of immune globulin after a recognized sensitizing event in 41% of cases and administration outside of recommended guidelines in 13% of cases (40). An additional reason for Rh D alloimmunization is the small rate (0.1–0.2%) of spontaneous immunization despite adherence to the recommended prophylaxis protocol (22). These cases most often occur in pregnancies during which there have been no prior overt sensitizing events. In other words, prophylaxis is not 100% effective (41).

Potential Shortage of Anti-D Immune Globulin

Anti-D immune globulin is collected by apheresis from volunteer donors who have high titers of circulating anti-Rh D antibodies. The donated plasma is pooled and fractionated by commercial manufacturers, and anti-D immune globulin is prepared in varying doses. In the 1990s, concerns were raised regarding future supplies of anti-D immune globulin for worldwide demands because the number of potential donors may dwindle (42). At that time, experts in the United Kingdom estimated that supplies of anti-D immune globulin would be inadequate for immunoprophylaxis of all susceptible Rh D-negative women if standard recommendations were followed (43). In Australia in 1995, a shortage prompted importation of anti-D immune globulin. Subsequently, some physicians proposed strictly limiting the dose given for first-trimester indications and discontinuing administration of anti-D immune globulin after external cephalic version (unless fetal–maternal hemorrhage is documented), ectopic pregnancy, or threatened miscarriage (44). Others disagreed, considering it unethical to withhold anti-D immune globulin in any situation. Estimates regarding future needs compared with potential supply in the United States have not been published. No reports of supply shortages of anti-D immune globulin have been published since initial concerns were expressed 20 years ago. Despite these earlier concerns, national guidelines from the United States, United Kingdom, and Canada still recommend routine administration of anti-D immune globulin to all Rh D-negative nonsensitized women in the third trimester, within 72 hours of delivery in women giving birth to a Rh-positive infant, or when a sensitizing event occurs (eg, ectopic pregnancy, external cephalic version, or invasive obstetric procedures such as chorionic villus sampling or amniocentesis) (5, 25, 31).

Other sources of anti-D immune globulin have been explored. There is the potential to generate recombinant Rh D immune globulin, which would alleviate any future shortages of donors. No commercially available, efficacious recombinant products are currently available. Nonetheless, a monoclonal antibody (Roledumab) and a recombinant antibody mixture (Rozrolimupab) are being designed for prevention of hemolytic disease of the newborn and are in phase II clinical trials (45, 46).

Cost Effectiveness of Rh D Prophylaxis Programs

The cost effectiveness of different screening strategies to guide the administration of Rh D immune globulin to Rh D-negative pregnant women in circumstances where fetal–maternal hemorrhage may occur have been mixed.

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Strategies of selective administration of Rh D immune globulin depending on partner's blood type have been shown to be cost equivalent to systematic prophylaxis (47, 48). If the Rh type of the partner is not known, and given that immunological typing of the father would probably not be carried out by most clinicians, routine antenatal prophylaxis remains the preferred option (48). Although initial economic analysis of antenatal anti-D immune globulin prophylaxis suggested that it was only cost effective in primigravid women (27, 47), more recent data indicate that prophylactic administration to all women at risk is cost beneficial (48).

Noninvasive determination of fetal Rh status is now possible through the analysis of cell-free DNA in maternal plasma. Up to 40% of Rh D-negative pregnant women will carry an Rh D-negative fetus. In this clinical situation, antenatal anti-D immune globulin administration is unnecessary. Concerns have been raised about the unwarranted exposure of these pregnant women to a plasma-based product (49). Some parts of the world now are using circulating cell-free DNA testing to ascertain the fetal Rh D status and to establish candidates for antenatal anti-D immune globulin prophylaxis (50). Recent retrospective and prospective observational studies have reported that fetal Rh D status determination in the first trimester has a sensitivity greater than 99% and a specificity of greater than 95% (51–53). However, concerns have been noted because of the rate of inconclusive results (range 2–6%), which are influenced by race (52, 53).

Despite the improved accuracy of noninvasive fetal RHD genotyping, cost comparisons with current routine prophylaxis of anti-D immunoglobulin at 28 weeks of gestation have not shown a consistent benefit. Four cost analyses from North America and Europe have shown no economic benefit at current test-cost levels (48, 54–56), whereas a single report from Canada suggested it would be cost effective, although the estimated cost of performing the cell-free DNA was based on a low-cost, high-throughput method (57). As the cost of this technology diminishes, this may become an attractive and cost-effective strategy. However, at current costs, noninvasive assessment of fetal Rh D status is not recommended for routine use at present.

Clinical Considerations and Recommendations

▶ *Is anti-D immune globulin indicated in a sensitized pregnancy?*

All pregnant women should be tested at the time of the first prenatal visit for ABO blood group and Rh D type and screened for the presence of erythrocyte antibodies. If anti-D antibody is identified, further history should be obtained and investigation undertaken to determine whether this is immune mediated or passive (as a result of previous injection of anti-D immune globulin). If it is clear that the origin of the anti-D antibodies detected is a previous routine antenatal anti-D immune globulin prophylaxis or anti-D immune globulin given for a potentially sensitizing event, then the woman should continue to be offered anti-D prophylaxis (25). If Rh D antibodies are present because of sensitization, anti-D immune globulin is not beneficial, and management should proceed in accordance with protocols for Rh D-alloimmunized pregnancies (58).

▶ *How should one deal with the issue of paternity?*

Reliable rates of nonpaternity are difficult to ascertain but a recent review indicates that the mean rate among population studies is approximately 3% (59). Strategies of selective administration of Rh D immune globulin depending on the partner's blood type have been shown to be cost equivalent to systematic prophylaxis (47, 48). If paternity is certain and the father is known to be Rh D negative, antenatal prophylaxis is unnecessary. If the Rh type of the partner is not known, and given that immunological typing of the father would probably not be carried out by most clinicians, routine antenatal prophylaxis remains the preferred option (48). An alternative strategy is to assess fetal RHD genotype with noninvasive testing and only administer Rh D immune globulin if the fetus is Rh D positive. Despite the improved accuracies noted with noninvasive fetal RHD genotyping, cost comparisons with current routine prophylaxis of anti-D immunoglobulin at 28 weeks of gestation have not shown a consistent benefit and, thus, this test is not routinely recommended (48, 54–56).

▶ *How should a weak D blood type be interpreted, and what management should be undertaken?*

In the past, a woman whose blood was typed as weak D (formerly known as Du) was thought to have blood cells positive for a variant of the Rh D antigen (60). The prevalence of serologic weak D phenotypes varies by race and ethnicity. Serologic weak D phenotypes are the most common D variants detected in Europe and the United States. An estimated 0.2–1.0% of Caucasians inherit *RHD* genes that code for serologic weak D phenotypes and, in the United States, 80% are associated with weak D type 1, 2, or 3 (60). Some of these individuals express reduced numbers of normal Rh D antigens whereas others express partial or abnormal Rh D antigens. It

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is possible for the latter group to develop antibodies against the part of the Rh D antigen that they are missing, and several cases of clinically severe Rh D alloimmunization have been reported in weak D phenotype women (60). Accordingly, the American Association of Blood Banks (AABB) recommends that testing for weak D is unnecessary in individuals who will be transfusion recipients of red blood cells (5). This approach categorizes individuals with weak D as Rh D negative for transfusion, and if pregnant, they are considered a candidate for anti-D immune globulin, hence avoiding potential Rh D alloimmunization.

However, the AABB requires that blood donors be assessed for weak D and if detected, the donors are interpreted to be Rh D positive. This policy prevents the transfusion of Rh D-negative individuals with weak D-positive blood, avoiding cases of Rh D alloimmunization. These seemingly contradictory policies likely have helped to avoid potential cases of Rh D alloimmunization. However, it can be extremely confusing for patients and clinicians. For example, the same individual may be variably characterized as Rh D positive or Rh D negative depending upon whether they are a potential donor or recipient and if weak D is or is not assessed (60). This could easily lead to errors and potential cases of Rh D alloimmunization.

An attractive solution to this problem is to perform molecular genetic RHD typing in weak D phenotype individuals as suggested by the Work Group on RHD Genotyping (60). This would allow for consistency in Rh D typing for individuals during their lifetime. In addition, the administration of Rh D immune globulin could be avoided in the Rh D individual with serologic weak D type 1, 2, or 3, because these are not associated with risk of Rh D alloimmunization, which could potentially reduce the need for tens of thousands of units of Rh D immune globulin each year (60). Currently, there is a lack of comprehensive cost-benefit analysis for this clinical approach. Clinicians are advised to administer Rh D immune globulin to patients with weak D blood type in appropriate clinical situations, by the same rationale as that for Rh D typing blood donors, until further scientific and economic studies are available.

▶ *Is threatened pregnancy loss an indication for anti-D immune globulin prophylaxis?*

Whether to administer anti-D immune globulin to a patient with threatened pregnancy loss and a live embryo or fetus at or before 12 weeks of gestation is controversial, and no evidence-based recommendation can be made. The Rh D antigen has been reported on fetal erythrocytes as early as 38 days from fertilization or 7 3/7 weeks of estimated gestational age (61), and fetal–maternal hemorrhage, although rare, has been documented in 3–11% of women with threatened pregnancy loss from 7 weeks to 13 weeks of gestation (7, 8).

Recommendations regarding anti-D immune globulin with threatened miscarriage have been inconsistent. Several national guidelines recommend against giving anti-D immune globulin to women with threatened pregnancy loss, particularly if bleeding stops before 12 weeks of gestation (25, 30, 62). Other guidelines recommend that anti-D immune globulin should be given (as described below) to all Rh D-negative women with a threatened miscarriage or when vaginal bleeding is heavy, repeated, or associated with abdominal pain, particularly if these events occur as gestational age approaches 12 weeks (25, 31). Because of insufficient evidence that a threatened pregnancy loss before 12 weeks of gestation requires anti-D immune globulin, no recommendation can be made at this time.

▶ *Should anti-D immune globulin be given in cases of molar pregnancy?*

Although alloimmunization has been reported with hydatidiform mole (63), the risk is unknown. In theory, Rh D alloimmunization should not occur in cases of classic complete molar pregnancy because organogenesis does not occur, and Rh D antigens are probably not present on trophoblast cells, although this theory has been disputed (64–66). In partial and transitional molar pregnancies, however, the embryonic development may cease after erythrocyte production has begun, making maternal exposure to the Rh D antigen possible (67). Given that the diagnosis of partial versus complete molar pregnancy depends on pathologic and cytogenetic evaluations, it is reasonable to administer anti-D immune globulin to Rh D-negative women who are suspected of molar pregnancy and who undergo uterine evacuation (25, 31).

▶ *How much anti-D immune globulin should be given for first- or second-trimester events (eg, spontaneous abortion, therapeutic abortion, ectopic pregnancy) and invasive obstetric procedures (eg, chorionic villus sampling, amniocentesis)?*

Although the optimal dose of anti-D immune globulin for potentially sensitizing events in the first and second trimesters is unknown, because of the smaller fetal red cell mass at these gestations, the recommended dosage is typically less than that used for routine antenatal prophylaxis in the third trimester. At 12 weeks of gestation, the

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total fetal–placental blood volume is 3 mL or 1.5 mL of fetal red cells (44). Regardless, this volume is adequate to sensitize some patients, and the risk of Rh D alloimmunization is estimated to be 1.5–2% in susceptible women after spontaneous miscarriage and 4–5% after dilation and curettage (3).

There are no adequate data to support an evidence-based recommendation, and expert opinion varies on whether anti-D immune globulin should be given with a spontaneous abortion. Because of the small volume of fetal blood and the low incidence of alloimmunization, some groups do not recommend prophylactic anti-D immunoglobulin in cases of spontaneous complete miscarriage before 12 weeks of gestation when the uterus is not instrumented (25, 62). Other experts recommend that either 50 micrograms or 120 micrograms of anti-D immune globulin be given after a complete miscarriage during the first 12 weeks of gestation (30, 31). Although the risk of alloimmunization is low, the consequences can be significant, and administration of Rh D immune globulin should be considered in cases of spontaneous first-trimester miscarriage, especially those that are later in the first trimester. If given, a dose of at least 50 micrograms should be administered. Because of the higher risk of alloimmunization, Rh D-negative women who have instrumentation for their miscarriage should receive Rh D immune globulin prophylaxis. Patients who have a miscarriage after 12 weeks of gestation should receive 300 micrograms of Rh D immune globulin.

Rh D immune globulin should be given to Rh D-negative women who have pregnancy termination, either medical or surgical. Most consensus guidelines have recommended 50 micrograms or 120 micrograms of anti-D immune globulin up to 12 weeks of gestation (25, 30, 31, 62), and a dose of 300 micrograms after 12 weeks of gestation (31).

Alloimmunization has been reported to occur in 24% of women with a ruptured tubal pregnancy (68). Again, guidelines differ with regard to the recommended dose of anti-D immune globulin up to 12 weeks of gestation, ranging from 50 micrograms to 120 micrograms (25, 30, 31, 62). After 12 weeks of gestation, 300 micrograms Rh D immune globulin is recommended (31). One expert group differentiates whether anti-D immune globulin should be administered depending upon the treatment method used for the unruptured ectopic pregnancy. Without clear evidence to support the distinction, they do not recommend anti-D immune globulin for women who solely receive medical management, but a dose of 50 micrograms is recommended in women who have a surgical procedure to manage an ectopic pregnancy (62). This notwithstanding, until additional data are available, administration of Rh D immune globulin for all cases of ectopic pregnancy in Rh D-negative women is recommended.

Administration of Rh D immune globulin is recommended with all invasive diagnostic procedures, such as chorionic villus sampling or amniocentesis, in Rh D-negative women when the fetuses could be Rh D positive. Doses from 50 micrograms to 120 micrograms have been recommended before 12 weeks of gestational age (25, 30, 31). For chorionic villus sampling and amniocentesis performed after 12 weeks of gestation, 125 micrograms or 300 micrograms is recommended (30, 31).

▶ *Is second- or third-trimester antenatal hemorrhage an indication for anti-D immune globulin prophylaxis?*

In patients with antenatal hemorrhage after 20 weeks of gestation, the risk of Rh D alloimmunization is uncertain. However, consensus guidelines recommend that susceptible women with bleeding receive anti-D prophylaxis (25, 30, 31). Anti-D immune globulin is recommended for Rh D-negative women who experience antenatal hemorrhage after 20 weeks of gestation. Management of the patient with persistent or intermittent antenatal bleeding is complex. The most conservative approach may be to assess the volume of fetal–maternal hemorrhage with a quantitative test (such as the Kleihauer–Betke test). The appropriate amount of Rh D immune globulin then can be administered to cover the estimated volume of fetal–maternal hemorrhage. In cases of chronic or episodic bleeding this approach may need to be repeated. An intuitive but unproven strategy is to monitor the Rh D-negative patient with continuing antenatal hemorrhage with serial indirect Coombs testing for anti-D approximately every 3 weeks. If the result is positive, indicating the persistence of anti-D immune globulin, then theoretically no additional treatment with anti-D immune globulin is necessary. If the Coombs test result is negative, excessive fetal–maternal hemorrhage may have occurred, and a Kleihauer–Betke test should be performed in order to determine the amount of additional anti-D immune globulin necessary. However, the most conservative approach is to administer additional Rh D immune globulin as needed based on the quantity of fetal–maternal hemorrhage with some authorities recommending an estimation of fetal–maternal hemorrhage be carried out at 2-week intervals (25). Finally, it has been proposed in this clinical situation to use cell-free DNA testing to ascertain the fetal Rh D status and, thus, avoid repeated administration of doses of anti-D immune globulin with an Rh D-negative fetus (25).

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Is it necessary to repeat antibody screening in patients at 28 weeks of gestation before the administration of anti-D immune globulin?

Current U.S. Preventive Services Task Force guidelines recommend repeated Rh D antibody testing for all unsensitized Rh D-negative women at 24–28 weeks of gestation, unless the biological father is known to be Rh D negative (grade B recommendation) (69). Consensus guidelines from around the world recommend that a routine antenatal antibody screen should be obtained at 28 weeks of gestation before administration of anti-D immune globulin (25, 30, 31). The primary rationale for repeating the antibody screen is to identify women who have become alloimmunized before 28 weeks of gestation in order to manage their pregnancies properly. The cost effectiveness of routinely repeating the antibody screen has been questioned because of the low incidence of Rh D alloimmunization occurring before 28 weeks of gestation (70). Regardless, routine antibody screening before anti-D immune globulin administration is advised.

How long does the effect of anti-D immune globulin last?

The median half-life of anti-D immune globulin is 23 days in the third trimester (28). If delivery occurs within 3 weeks of the standard antenatal anti-D immune globulin administration, the postnatal dose may be withheld in the absence of excessive fetal–maternal hemorrhage (29). The same is true when anti-D immune globulin is given for antenatal procedures, such as external cephalic version or amniocentesis, or for third-trimester bleeding. An excessive number of fetal erythrocytes not covered by anti-D immune globulin administration can be assumed to have entered maternal blood if the results of a Kleihauer–Betke test are positive, and an appropriate dose of Rh-immune globulin should be administered.

When should routine antenatal anti-D prophylaxis be given during pregnancy to prevent alloimmunization?

Studies comparing the routine antenatal administration of anti-D immune globulin to historic controls have shown significant reductions in the incidence of maternal sensitization to the Rh D antigen. Women originally were offered targeted anti-D immunoglobulin with the aim of preventing sensitization after the birth of a Rh-positive infant and after other potentially sensitizing events such as miscarriage, termination of pregnancy, or invasive obstetric procedures. With this approach, the incidence of hemolytic disease of the newborn was substantially reduced (7). In a meta-analysis of six trials with more than 10,000 women that compared postpartum anti-D immune globulin prophylaxis within 72 hours of birth with no treatment or placebo, anti-D immune globulin greatly lowered the incidence of Rh D alloimmunization 6 months after birth (risk ratio [RR], 0.04; 95% CI, 0.02–0.06), and in a subsequent pregnancy (RR, 0.12; 95% CI, 0.07–0.23) (71). However, because of concerns of alloimmunization occurring before delivery, experts advocated for prophylactic antenatal anti-D immune globulin to be given in the third trimester (7). Several clinical trials have been conducted; however, the studies have been criticized for being of poor quality and varying substantially in study design with many of the studies using historical rather than concurrent controls (72). In a meta-analysis of two randomized controlled trials of 3,902 Rh D-negative women that compared anti-D immune globulin at 28 weeks and 34 weeks of gestation with no antenatal treatment (but all women who delivered a Rh-positive infant received postpartum anti-D immune globulin), there was no clear difference in the incidence of Rh D alloimmunization during pregnancy, after the birth of a Rh-positive infant, or within 12 months after the birth of a Rh-positive infant. No outcome information was available on the incidence of Rh D alloimmunization in a subsequent pregnancy (22). However, methods for performing bias-adjusted meta-analysis, which enables adjustment for differences in quality and design and, thus, allows all available evidence to be synthesized, are available. A meta-regression using these techniques was performed to estimate the association between the observed effectiveness of different anti-D dose regimens (73). In a bias-adjusted meta-analysis of 10 studies, the pooled odds ratio for a reduction of sensitization was estimated as 0.31 (95% CI, 0.17–0.56). The authors interpreted this result as providing strong evidence for the effectiveness of routine antenatal anti-D immune globulin prophylaxis in preventing sensitization of pregnant Rh D-negative women. Prophylactic anti-D immune globulin should be offered to unsensitized Rh D-negative women at 28 weeks of gestation. Following birth, if the infant is confirmed to be Rh D positive, all Rh D-negative women who are not known to be sensitized should receive anti-D immune globulin within 72 hours of delivery.

Is anti-D immune globulin prophylaxis indicated after abdominal trauma in susceptible pregnant women?

Although the exact risk of Rh D alloimmunization is unknown, abdominal trauma is sometimes associated

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with fetal–maternal hemorrhage, which may lead to alloimmunization (74). The efficacy of anti-D immune globulin in this clinical situation has not been tested in properly designed trials. However, authorities agree that anti-D immune globulin should be administered to Rh D-negative women who have experienced abdominal trauma (25, 30, 74). In Rh D-negative pregnant patients who have experienced abdominal trauma, quantification of fetal–maternal hemorrhage should be done to determine the need for additional doses of anti-D immune globulin (74).

▶ *Should anti-D immune globulin be given in cases of intrauterine fetal death occurring in the second or third trimester?*

Fetal death occurs in fetal–maternal hemorrhage in up to 13% of cases in which no obvious other cause (eg, hypertensive disease, fetal anomalies) is found (75–77). Rh D alloimmunization has been reported in cases of fetal death from massive fetal–maternal hemorrhage (78), although the contribution of this cause to the overall problem of Rh D alloimmunization is unknown. The efficacy of anti-D immune globulin in this clinical situation has not been tested in properly designed trials. However, because the benefits are thought to outweigh the risk, anti-D immune globulin should be administered to Rh D-negative women who experience fetal death in the second or third trimester. All such cases should be screened for excessive fetal–maternal hemorrhage at the time of diagnosis of fetal death to determine if additional anti-D immune globulin is required (25).

▶ *Should administration of anti-D immune globulin be repeated in patients with a pregnancy greater than 40 weeks of gestation?*

Anti-D immune globulin appears to persist for approximately 12 weeks in most patients, based on pharmacokinetic studies using modern assay methods (28). In the past, some authorities advised giving a second dose of Rh D immune globulin to women who have not given birth 12 weeks after receiving their antenatal dose (29). However, the vast majority of women who give birth more than 12 weeks after receiving antenatal Rh D immune globulin do not become alloimmunized. There is insufficient evidence at this time to make a recommendation for or against administering another dose of anti-D immune globulin to a Rh D-negative woman who remains undelivered at 40 weeks of gestation. Current consensus guidelines either have no recommendation (25, 30) or state that a repeat antepartum dose of anti-D immune globulin is generally not required at 40 weeks of gestation, provided the routine antenatal prophylaxis was given no earlier than 28 weeks of gestation (31).

▶ *Should all Rh D-negative women be screened for excessive fetal–maternal hemorrhage after delivery of a Rh D-positive infant?*

The risk of excessive fetal–maternal hemorrhage exceeding 30 mL of Rh D-positive fetal whole blood (the amount covered by the standard 300-microgram dose of anti-D immune globulin) at the time of delivery is approximately 2 to 3 per 1,000 (6, 7). Screening only pregnancies designated as high risk of excessive fetal–maternal hemorrhage, including cases of abruptio placentae, placenta previa, intrauterine manipulation, or fetal death detects only 50% of patients who require additional anti-D immune globulin (79). For this reason, it is recommended that all Rh D-negative women giving birth to Rh D-positive infants undergo additional testing initially with a qualitative screening test (such as the rosette assay) and, if indicated, quantitative testing (such as the Kleihauer–Betke test) to determine the number of doses of Rh D immune globulin required (5, 25, 30, 31).

▶ *Should anti-D immune globulin be withheld from a woman undergoing postpartum sterilization?*

Although a primary reason to prevent alloimmunization is to reduce risk in future pregnancies, there are other indications as well. Pregnancies occur despite sterilization procedures, and most are intrauterine. In addition, alloimmunization complicates crossmatching of blood products in the future (80). Thus, Rh D-negative women who are undergoing postpartum tubal sterilization are candidates for treatment with anti-D immune globulin. The downside of this approach is the low cost effectiveness of the strategy because of the low probabilities of sensitization with the just-completed pregnancy, of sterilization failure, and of a need to receive Rh D incompatible blood in the future (81). If an Rh D-negative woman who has had a sterilization procedure does become pregnant later, even with a miscarriage or ectopic pregnancy, she should be offered anti-D immune globulin in a similar manner as women without sterilization.

▶ *What should be done if an Rh D-negative patient is discharged without receiving anti-D immune globulin after a potentially sensitizing event?*

The ideal time to administer anti-D immune globulin is within 72 hours of a potentially sensitizing event.

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However, volunteers have received a range of partial to complete protection when anti-D immune globulin was given as late as 13 days after exposure (82). The longer prophylaxis is delayed the less it will be protective, but it has been suggested that a patient may still receive some benefit from anti-D immune globulin as late as 28 days postpartum (29, 31).

Summary of Recommendations and Conclusions

The following recommendations are based on good and consistent scientific evidence (Level A):

- Prophylactic anti-D immune globulin should be offered to unsensitized Rh D-negative women at 28 weeks of gestation. Following birth, if the infant is confirmed to be Rh D positive, all Rh D-negative women who are not known to be sensitized should receive anti-D immune globulin within 72 hours of delivery.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Administration of Rh D immune globulin is recommended with all invasive diagnostic procedures such as chorionic villus sampling or amniocentesis in Rh D-negative women when the fetuses could be Rh D positive.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- External cephalic version (regardless of success) is associated with a 2–6% risk of fetal–maternal hemorrhage, and anti-D immune globulin is indicated for unsensitized Rh D-negative patient.
- It is reasonable to administer anti-D immune globulin to Rh D-negative women who are suspected of molar pregnancy and who undergo uterine evacuation.
- Although the risk of alloimmunization is low, the consequences can be significant, and administration of Rh D immune globulin should be considered in cases of spontaneous first-trimester miscarriage, especially those that are later in the first trimester.
- Because of the higher risk of alloimmunization, Rh D-negative women who have instrumentation for their miscarriage should receive Rh D immune globulin prophylaxis.
- Rh D immune globulin should be given to Rh D-negative women who have pregnancy termination, either medical or surgical.
- Administration of Rh D immune globulin for all cases of ectopic pregnancy in Rh D-negative women is recommended.
- Anti-D immune globulin is recommended for Rh D-negative women who experience antenatal hemorrhage after 20 weeks of gestation.
- Anti-D immune globulin should be administered to Rh D-negative women who have experienced abdominal trauma.
- Anti-D immune globulin should be administered to Rh D-negative women who experience fetal death in the second or third trimester.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1980 and February 2017. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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EXHIBIT 18

Katherine A. Rafferty & Tessa Longbons,
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#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives

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ABSTRACT

One out of four women in the United States will have an abortion by age 45. While abortion rates are steadily declining in the United States, the rate of medication abortions continues to increase, with 39% of all abortions being medication abortions. Our study is one of the first to analyze women's narratives after having had a medication abortion. Using relational dialectics theory, we conducted a case study of the nonpartisan website, *Abortion Changes You*. Our contrapuntal analysis rendered four sites of dialectical tension found across women's blog posts: *only choice* vs. *other alternatives, unprepared* vs. *knowledgeable, relief* vs. *regret*, and *silence* vs. *openness*. Each site of struggle characterized a different noteworthy moment within a woman's medication abortion experience: the decision, the medication abortion process, identity after abortion, and managing the stigmatizing silence before and after the abortion. We discuss theoretical and practical implications about how the larger politicized discourses prevalent within the abortion debate impact the liminality of women who are contemplating a medication abortion and affect their own narrative construction about the medication abortion experience.

One out of four women will undergo an abortion procedure in the United States by age 45 (R. K. Jones & Jerman, 2017), and 862, 320 reported abortions occur each year (Jones et al., 2019). Despite its frequency, abortion remains a highly contested and stigmatized biopolitical public health issue in the United States (Altshuler et al., 2017). The historic *Roe v. Wade* case has resulted in two nationalized political movements – Right to Life and Right to Choice – that have juxtaposed stances on the legality of abortion. However, the stigma and shame associated with abortion precede and transcend this historic case. Stormer (2010) concluded that a collective memory of secrets and shame has characterized the topic of abortion since Planned Parenthood's 1955 conference, "Abortion in the United States".

While abortion rates are steadily declining in the U.S. (Jones et al., 2019), the rate of medication abortions continues to increase. In 2000, the U.S. Food and Drug Administration (FDA) approved mifepristone to be used in combination with misoprostol as a form of medication abortion. Since then, the annual number of medication abortions has risen steadily: less than 6% of all abortions in 2001 to 39% of all abortions in 2017 (Jones et al., 2019, 2008). Between 2014–2017, the number of medication abortions provided at facilities other than hospitals increased by 25% (Jones et al., 2019). Presently, over one-third of all reported abortions in the U.S. are medication abortions (Jones et al., 2019). In 2016, the FDA protocol expanded provider eligibility for dispensing mifepristone to women. Thus, abortion provision is transitioning from formalized medical procedures conducted in health care settings to a protocol where most of the abortion occurs individually at home with limited clinician assistance (Biggs et al., 2019). Given the privatization of abortion provision, research is needed to examine the distinct experiences of women who have undergone this type of abortion. After all, researchers have found that women often elect to have a medication abortion over a surgical abortion because of more privacy, convenience, and the perception of having more control (Newton et al., 2016). However, medication abortion has been found to have a higher complication rate that results in more emergency department visits post-medication abortion compared to post-surgical abortion (Upadhyay et al., 2015).

Medication abortion practices in the U.S. adhere to the following evidence-based guidelines: using mifepristone in combination with a prostaglandin to carry success rates up to 99% for early pregnancy termination with rare occurrence of serious adverse events. However, the focus of this research is on successful terminations, increases in abortion access, and reductions of in-person clinic visits (H. E. Jones et al., 2017). There remains a dearth of research, particularly in the U.S., that examines women's personal experiences with having this type of abortion procedure (e.g., acknowledging their emotions, understanding their self-efficacy with completing the abortion at home, being aware of whether they are adequately informed about the process). To our knowledge, the only study is from Sweden; researchers used semi-structured telephone interviews with 119 women who had a medication abortion (Hedqvist et al., 2016). They found that almost half (43%) experienced more bleeding than expected, and one-

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fourth (26%) bled for more than four weeks. In addition, one-third (34%) stated that they received insufficient information about what to expect. Women who had never had an abortion nor had gone through childbirth were more likely to feel misinformed.

Scholars know that the medication abortion process is distinct from surgical abortions, with the features of medication abortion (e.g., lack of medical presence, time required for abortion completion, personal experiences with pain and bleeding) influencing women's perception and satisfaction (Newton et al., 2016). Yet, this research on women's satisfaction with medication abortion is often conflicting (Kimport et al., 2012) and limited (Hedqvist et al., 2016). Given that women increasingly prefer medication abortion over surgical abortion (Newton et al., 2016), the need for studying women's experiences post-medication abortion becomes imperative.

Importance of analyzing unsolicited blogging narratives about one's abortion

To understand women's medication abortion experiences, it is important to study platforms where women engage in unsolicited talk. Unsolicited talk is ideal for collecting formative research that can be studied to explore individual and cultural experiences (Baxter, 2011). First, the audience of these texts is a "generalized other" (Mead, 1982), or culture, rather than a specific individual with whom the author has a relationship (Langellier & Peterson, 2004). The absence of a specific audience encourages narrators to provide an unadulterated account of their experience, rather than tailor their story to specific individuals (e.g., a friend who has had a certain stance on the abortion issue). Similarly, anonymity allows for potentially muted or stigmatized groups to post information without fear of sanctioning. In a culture where abortion remains highly contested and talk about having had an abortion is often muted or stigmatized (Altshuler et al., 2017), it is likely that women may prefer to self-disclose their medication abortion experiences online rather than via face-to-face channels. Furthermore, because women traditionally constitute a co-culture who have historically been muted and must strategically use communication to participate in a dominant patriarchal society (M. Orbe, 2005; M. P. Orbe, 1998), scholars must study platforms where women are sharing unsolicited stories in back-channel outlets (e.g., online blogs).

Online blogs as a platform for unsolicited talk

One backchannel platform of unsolicited talk is online blogs. Blogs provide a computer-mediated platform where people can self-disclose their personal thoughts, feelings, and experiences to others online. The proliferation of blogs in the last decade has transformed the way that we, as a society, "share, create, and curate information with individuals and communities" (Becker & Freburg, 2014, p. 415). Blogs often resemble online personal journal entries that enable writers to freely express themselves in ways that may be less face-threatening or stigmatizing (M. Jones & Alony, 2008). One of the many applications and uses of blogs is to share experiences and events through storytelling.

Relational Dialectics Theory (RDT)

Because talking about one's abortion experience remains stigmatized and muted (Cockrill & Nack, 2013), examining women's stories after having had a medication abortion may illuminate the competing discourses surrounding this debated moral and social issue (e.g., largely evident in the two polarized movements: Right to Choice v. Right to Life), as well as some of the larger dominant discourses from the polarized political movements that influence how women tell their own medication abortion story. Given this goal, RDT (Baxter, 2011) is a relevant framework to assess the competing cultural norms and expectations, which are also referred to as discourses. At any given moment, discourses may be dominant/centripetal or marginalized/centrifugal (i.e., anything that deviates from the dominant discourse). Scholars use RDT as a framework to examine the interplay between certain discourses that then construct social meaning and reality for individuals. Within the theory, there are four types of utterances (i.e., speaking chains) from which dialectical tensions (i.e., centripetal vs. centrifugal) may stem: *distal already-spokens* – utterances reflecting the cultural meaning and discourses that cultural members give voice to in their talk; *proximal already-spokens* – utterances conveying past meanings and discourses within a given relationship; *proximal not-yet-spokens* – immediate response from the hearer in the interaction; and *distal not-yet-spokens* – anticipated responses of a generalized other within the culture. The purpose of this paper is to examine how, if at all, these four types of utterance chains are present within women's medication abortion narratives.

A second aspect of RDT (Baxter, 2011) is to understand how social reality is created discursively through power. Power is located in the struggle between marginalized/centrifugal and dominant/centripetal discourses. There are three ways that power can be located within discourses: diachronic separation, synchronic interplay, and discursive transformation. Diachronic separation occurs when discourses emerge in different texts or locations. Synchronic interplay is when discourses negate (total rejection of a competing discourse), counter (offer limited legitimacy to a discourse), and/or entertain (consider multiple worldviews/discourses or general ambivalence toward discourses) one another. Finally, discursive transformations occur when the interplay of competing discourses creates new meanings rather than remaining in opposition to one another (Baxter, 2011). This current study will focus on examining the synchronic interplay among the centripetal and centrifugal discourses.

A case study of women who have experienced medication abortion

To analyze women's personal narratives and the larger discourses influencing their talk about their own medication abortion, we conducted a case study of the website www.abortionchangesyou.com. We selected this website for several reasons: it is not openly politicized, bloggers do not interact with others, bloggers post anonymously, bloggers do not need to create an account in order to post, and the platform is a space for unsolicited stories with no reward or

compensation to those who post. Furthermore, from a strategic storytelling standpoint (Tyler, 2007), it is important to study women's blogs from an organization that recognizes and respects each woman's individual narrative, as opposed to propagating narratives that openly align with the agenda of only one political movement. The woman who created this website has had an abortion herself and openly shares this information on the "About Us" page. The naming of her own abortion experience grounds co-cultural theorizing (M. Orbe, 2005; M. P. Orbe, 1998) such that other women who feel muted may be empowered and capable of finding similar language strategies.

In this case study, we explore the complexity and consequentiality of women's language choices with anonymously telling their own medication abortion story, as well as offer the potential to capture the interplay of individual, organizational, and social discourses surrounding the abortion debate. The current divisiveness surrounding the socio-political climate in the U.S. about abortion provides further exigency and credence for this research. Our critical analysis is rooted in the interpretive paradigm with the purpose of explaining, describing, and illustrating the stories that women share on this website (Tracy, 2013). The following research questions guide our iterative analysis:

RQ1: What topics are women disclosing to the "generalized other" in their blog?

RQ2: What (if any) sites of struggle characterize women's abortion narrative?

Methods

We conducted a case study approach (Arden Ford et al., 2014) of one website, www.abortionchangesyou.com. Case studies are a contextual examination used to understand a phenomenon within a particular context "and with respect to multiple perspectives within that context" (Arden Ford et al., 2014, p. 118). By employing a case study approach, we were able to draw on multiple perspectives (e.g., 98 different blog stories) that were rooted in a specific context. This methodological choice is common in other communication research, where the unit of analysis is an organization and the goals are to provide an in-depth understanding of the unique particulars and complexities of the case within a larger social context (Norander & Brandhorst, 2017).

Our case study included 98 blogs from women who have had a medication abortion and shared their story on the website. We included all blogs posted between October 2007 – February 2018. This date range reflects the time period between the submission of the first medication abortion blog on the website in 2007, and the point at which we extracted our data for analysis in 2018. Women's blogs ranged in length from one paragraph to three pages of text, single-spaced (the average number of words for the 98 blogs was 655 words). All 98 blogs included content about one's own medication abortion; the vast majority (91 women; 93%) also discussed the events and emotions experienced before and after their medication abortion.

Data analysis and synthesis

The case study approach allows for different data analysis strategies (Norander & Brandhorst, 2017). Because the purpose of our case study is to develop a thick description of the case, using an interpretive analytic strategy is most prudent. We selected Baxter's (2011) contrapuntal analysis to study the meanings circulating around individual and relational identities evidenced within the language choices of the women blogging about their own medication abortion. Given the larger competing discourses about the legality of abortion in the U.S., we felt that the struggle of competing and contradictory discourses would likely be apparent in women's personal blogging narratives. Further, contrapuntal analysis (Baxter, 2011) offered a critical perspective to our analysis as we studied the voices of marginalized women (e.g., women who have had a medication abortion) whose perspectives are often muted and stigmatized in society.

To understand the competing discourses and how meaning was constructed through their interplay, we conducted the first stages of thematic analysis to identify the discourses evident within each blog post (Braun & Clarke, 2006). This process required the three coders to independently familiarize themselves with the entire data set: reading the blogs several times and conducting line-by-line coding that captured the essence of the story in each line. Many of the inductive analytic codes applied to the text were descriptive (e.g., uncertainty; not ready), process (e.g., discovering pregnancy, taking the pills), or in vivo codes (e.g., wanted baby; alone; Saldaña, 2013). The coders met regularly for five months to discuss the codes independently applied to each blog post. During this time, codes emerged into themes as processes were identified in the data and repetitively noticed by all three coders (e.g., changing self perception, silence, responsibility, good parenting). Discrepancies in coding were discussed during coding meetings and resolved through group consensus (Strauss & Corbin, 1990).

During the third and fourth months of data analysis, we went back to the data set to identify where discourses competed (e.g., culpability; justification). Here, we paid particular attention to where the bloggers used instances of negating (e.g., claiming another discourse as irrelevant or rejecting it), countering (e.g., offering a particular discursive position in replacement of another), and entertaining (e.g., not completely rejecting a discourse, but instead noting the potential possibilities with different discourses; Baxter, 2011). Women used negating when saying, "can't," "not," "couldn't," and "never." Examples of countering were most apparent when women used the word "but." Entertaining often occurred when women used the words "possibility" and "could have." Finally, we identified where and how competing discourses interpenetrated (Baxter, 2011). Dialogically contractive discursive practices are silenced discourses. Examples of these discursive practices included negating talk, such as: "can't talk about the abortion," or "there was no other choice." In contrast, dialogically expansive discursive practices are discourses that are encouraged and amplified. Women used these discourses when saying things like: "I don't want the procedure, but I don't want the baby" or "hoping for a brighter future now that it is over."

Data were analyzed until the point of theoretical saturation (i.e., no new thematic categories were present in the blog posts; Strauss & Corbin, 1990), which occurred after the 54th blog post. However, we continued to analyze the remaining blog posts in an effort to verify that our analysis of the discourses evident in the 54 posts accurately reflected all of the posts within the entire data set. Further, we wanted to extract the best exemplars from the entire case study and desired that quotations within all posts be considered for representation. Clear and concise exemplars of competing discourses within women's narratives were then selected and agreed upon by all coders.

Trustworthiness and rigor

Evaluation of the quality of case study research should be determined by criteria associated within the naturalistic paradigm (Arden Ford et al., 2014). Trustworthiness is the criterion that assesses the credibility, transferability, dependability, and confirmability of the data collection and analysis processes (Lincoln & Guba, 1985). We upheld these principles when conducting this study by beginning with a careful design that clearly defined its purpose, research questions, and notion of "boundedness" (i.e., establishing the limits and context of the case; Arden Ford et al., 2014). Second, we spent sufficient time developing and analyzing the case: our analysis transpired over five months. Third, we upheld the principles of reflexivity by using inductive coding for all blog posts and writing individual and group memos throughout the entire coding process as a way to remain transparent and keep a data audit. Fourth, we had a team of three female coders, which allowed for the presence of multiple feminine perspectives.

Findings

Our research questions focused on the topics that women discussed in their personal online blogging narrative posted to www.abortionchangesyou.com (RQ1), and what (if any) sites of struggle were evident in these narratives (RQ2). Our contrapuntal analysis (Baxter, 2011) rendered four sites of dialectical tension: *only choice* vs. *other alternatives, unprepared* vs. *knowledgeable, relief* vs. *regret*, and *silence* vs. *openness*. Each site of struggle characterized a different noteworthy moment within a woman's medication abortion experience: the decision, the medication abortion process, identity after the abortion, and managing the stigmatizing silence before and after the abortion. When recounting their decision to have an abortion, women referenced the struggle of *only choice* vs. *other alternatives*. As women discussed the medication abortion process, the competing discourse of *unprepared* vs. *knowledgeable* was evidenced. Women's narratives about their identity after the abortion indicated the dialectical struggle of *relief* vs. *regret*. Finally, the challenges with managing the tension between *silence* vs. *openness* pervaded women's narratives. Below we discuss each site of struggle using exemplar quotes from women's blogs. Quotes were not edited from their original post.

The decision: Only choice vs. other alternatives

Part of women's narratives included a detailed account of their decision to have a medication abortion. This decision was described as being rife with contradiction, and not a flippant choice. Women enumerated various reasons that were influential in their decision-making process: bad timing, financial instability, relationship problems, lack of family support, not married, too young, too many other children, not prepared to be a parent yet, and/or best decision given the circumstances. After stating one of the aforementioned reasons, 92 women (94%) also explained that abortion was the only or best option given the circumstances. For example, one woman said: "I felt the child growing inside of me. I was rubbing my stomach without me even knowing. I felt the doubt in my heart, but kept telling myself this is the best decision I needed to make" (6–18-17). A different woman recounted:

> "I always leaned more towards keeping the baby and my boyfriend more towards abortion. I knew I could have the baby but it would be difficult. We both work jobs that barely pay over minimum wage and we both were scared to grow up and care for a child" (10-24-17).

Collectively, these exemplars illustrate how any possibility of keeping the baby was negated by one of the reasons that warranted the need for having a medication abortion. Many of the reasons women cited for choosing abortion align with the discourses from the Right to Choice movement: "A pregnancy to a woman is perhaps one of the most determinative aspects of her life. It disrupts her body. It disrupts her education. It disrupts her employment. And it often disrupts her entire family life" (*Roe v. Wade*).

However, the decision to have a medication abortion was not always independently made by the woman. In fact, 52 women (53%) reported that the father to their child or other family members (e.g., parents) negated women's own desires to keep the baby. For example, one woman said:

> "I remember my husband telling me, 'well, don't expect me to be too happy with the idea of having it if you decide to keep it. I won't be too loving.' That was a knife through my heart and I made the tough decision to go through with the abortion" (7-6-12).

Other family members also influenced women's medication abortion decision, albeit her own desires to keep her baby:

> "But my father on the other hand was a different story. He is an old school Puerto Rican who told me that I had to leave if I kept the baby. I had 2 weeks to get an abortion or else he would disown me forever" (3-8-2018).

In both accounts, women communicated their personal choice to have their baby; yet, their choice was negated by family and friends who advocated that abortion was necessary. Centrifugal discourses about others influencing or pressuring women to have an abortion are marginalized discourses.

Finally, when making their decision, 48 women (49%) reported vacillating between keeping their baby and having a medication abortion. Ultimately, outside circumstances or other people influenced their decision to abort. As mentioned earlier, 92 women (94%) shared that abortion was the best or

only option available given the circumstances. In many of these narratives, women did not believe nor realize that other alternatives, besides abortion, were tenable options until after having the abortion. For instance, one woman said:

> "They all tell you 'it's your choice' in the moment, but you don't feel that it is. Being unable to afford it, unable to tell your loved ones, not having the help or feeling unable to support a child. When your partner doesn't want it like you do. All these things push you, blind you to a decision that you don't realize will destroy you" (8-23-17).

Similarly, another woman recounted: "I was kind of excited but I was so scared to tell my family …. I told my mom and her first response was I hope you're getting an abortion. You're going to be a terrible mom" (11-5-17). Both exemplars illustrate the distal and proximal already-spoken discourses that influenced each woman's decision to have a medication abortion. Ultimately, these centripetal discourses (coming from society, the pro-choice movement, other people in their lives, or their own fears) negated the centrifugal discourse that other alternatives (adoption or keeping their baby) were justifiable options available to them.

The medication abortion process: Unprepared vs. knowledgeable

Medication abortions where women undergo most of the process individually at home with limited assistance from a medical provider are becoming more commonplace (Biggs et al., 2019; H. E. Jones et al., 2017). While this process is generally reported to be safe and adhere to evidence-based guidelines (H. E. Jones et al., 2017), little is known about women's personal experiences with having this type of abortion. All women in this case study reported having had a medication abortion. Forty-eight women (49%) provided detailed accounts of their actual medication abortion experience at home. Women said things like: "I felt her come out" (1-8-16). Some women detailed the hardships of this process by saying: "I was in so much pain on the bathroom floor" (3–15-18); "the pills made me vomit, lose control of my bowels, sweat, faint, pass out, and go into full labor" (10-9-09); and "I lay on my bed in the fetal position, holding my stomach" (9-5-15). Other women did not self-report such negative experiences: "The actual process of taking the pill was frightening but not as bad as I imagined" (9-8-15) and "I just popped some pills and got a period" (7-1-15).

In analyzing women's talk about the medication abortion process, a second site of struggle was identified: *knowledgeable vs. unprepared*. In this struggle, women discussed how they were told certain information about the medication abortion process (e.g., when to take the pills, what the pills do, the need to contact a provider if complications arise), but ultimately this information was insufficient, limited, or misleading. Fourteen women (14%) reported being inadequately prepared about what to expect during the medication abortion process. For example, one woman said:

> "They lied to me and said they would give me some pills that would make it just like a late period with a little cramping … The pain of the contractions was so intense I felt like my intestines were pulled out slowly. I collapsed screaming on my bathroom floor, sweat, tears, blood, vomit, and shit all over me" (10-9-09).

Similarly, a different woman recounted:

> "They told me, if you by chance are in pain you can take these pain relievers. If by chance I'm in pain? That sounded like the process would be easy and not so painful. Well NO that was not the case, within 30 minutes I felt really bad cramping. It just kept getting worse and worse. I was crying and moaning from the pain. I literally thought I was dying" (9-2-17).

In both instances, women's personal abortion experiences did not align with the proximal-already-spoken messages (e.g., "it's just a pill") that they were told by their medical providers.

When women's personal experiences contradicted what they were originally told by health care providers, family, or friends women felt deceived. One woman communicated her frustration by saying: "They told me it wouldn't hurt and I wouldn't feel a thing. THAT WAS SUCH A LIE. I felt everything, I heard everything, I seen everything. I ended up blacking out from the pain and puking all over myself" (11-5-17). Similarly, another woman said:

> "We were told we would go back to normal and it won't affect us but they were wrong!!! All I feel is emptiness and hatred. I used to be the happiest most positive girl. All I want is to take it back" (12-15-14).

Even if women did not explicitly report feeling deceived, many women stated that they were inadequately prepared about what to expect. For instance, one woman said: "I knew to expect blood clotting, but nothing could've prepared me for seeing her body. It was the color of my own skin, and was actually starting to look like a person" (1-8-16). Within women's narratives, they expressed a desire for more detailed information about things such as: potential side effects, the intensity of cramping and bleeding, what to do after passing the baby, and potential negative emotions (e.g., fear, uncertainty, sadness, pain) felt after the abortion. When this comprehensive information was not communicated to them prior to taking the pills at home, women reported feeling misled, misinformed, and even deceived. These types of experiences and feelings after having had a medication abortion remain centrifugal discourses that are muted within the abortion debate.

Identity after medication abortion: Relief vs. regret

A third site of dialectical struggle was found in women's talk about their identity after the medication abortion. Most women (N = 81; 83%) reported that their medication abortion changed them, which is not surprising given the name of the website: *Abortion Changes You*. Of noteworthy significance is understanding *how* women talked about these changes and the tension evident in this part of their narrative. Of the 81 women (83%) who stated feeling *changed* after their medication abortion, 75 women (77%) reported being changed in a negative way. Here, women said things like: "I really thought that I could somehow go back to the way things were before finding out I was pregnant. But I cannot. I am not the same person, and my husband is certainly not the same either" (7–11-11). Negative changes often occurred when women's

actual abortion experience did not align with their preconceived ideas about what to expect. These ideas were informed by larger discourses from society, as well as messages from others (e.g., health care providers). Three women indicated a positive change after their abortion by noting something like:

> "Abortion did change my life … As soon as the stomach cramps (only slightly worse than regular menstrual pains) went away, I felt like a whole new person. I couldn't believe how much energy I had again. It was like waking out of a deep depression" (7-1-15).

Positive changes were denoted by experiencing an initial sense of relief with no longer being pregnant. Finally, three women were ambivalent or didn't report their change as positive or negative. One woman said: "I truly believe there is no right and wrong with this situation, it is a life changer but it's your choice" (9-7-10).

Women discussed various issues when talking about change: impact on their emotional health as a result of the abortion, differences in their relationship with their partner/spouse, and new perspectives on their general views of abortion. However, conflicting emotions were evident across all women's blog posts. For instance, one woman said:

> "I went home and confessed to my mother … She helped pull the gigantic blood clots from my body … No one told me it would be like this; the clinic simply gave me what I asked for without telling me what it entailed" (7-20-16).

Similarly, another woman recounted: "I thought maybe after the due date I would feel better, but it doesn't end there. It NEVER ends! The pain and emptiness stays there forever" (4–30-17). In these different accounts, the women alluded to their initial expectations of what the medication abortion would entail or what others told them would happen after their abortion. When a woman's actual medication abortion experience did not align with these messages, women felt disempowered, vulnerable, lost, upset, and sometimes deceived.

When discussing the changes experienced after the abortion, many women talked about emotional changes. One woman said:

> "At first it all seemed like a weight had been lifted and everything was okay then I started to feel really sad and low and now all I do is think about how many weeks pregnant I would have been and what my baby would look like and I miss so much" (4-26-10).

As mentioned, processing one's abortion experience was emotional and took time. Some women wrestled with experiencing negative and difficult emotions after having their abortion. In fact, 37 women (38%) explicitly stated problems with anxiety, depression, drug abuse, and suicidal thoughts as a result of the abortion. For example, one woman said: "I am haunted by the image of my tiny baby. I always will be. I cut myself and even wanted to die" (3–22-13). Another woman recounted: "Looking at my kids thinking of another beautiful child. Couldn't live with myself. Wishing God would take my life" (12–16-11). Collectively, these exemplars illustrate women's emotional changes about processing of their medication abortion.

Finally, 75 women (77%) explicitly stated that they regretted their decision to have an abortion. However, the term regret was rife with contradiction and also included talk about initial relief. For instance, one woman said: "I know I did the right thing for myself and it would be a lot harder for me right now. But I still would give anything to go back in time and keep my baby" (11–19-12). Regret was regarded as a process that was realized over time and through one's life experience. One woman stated: "Had I known how badly I would feel now, I would have kept the baby, even if I had to go through it alone" (10–21-15). Another woman elaborated upon this process by saying:

> "Knowing what I know now at almost a year later I would not have the abortion. That was my child and I should have done what I needed to do to give them a great life. I thought I had no options but I did. I should have put my child first. No matter how early the abortion is its still a growing life and i wish i had done things differently" (4-30-17).

In both accounts, women defined regret as the emotional pain, suffering, remorse, and guilt felt after the medication abortion. Yet, these emotions were often coupled with initial feelings of relief from no longer being pregnant. In sum, the decision to have a medication abortion was significant, transformative, and lifechanging for these women. One woman noted this change by saying: "From the outside, our life looks exactly the same as it would have. But on the inside, everything has changed for me" (10–21-15). Collectively, these accounts expose how the different emotional changes resulted in a lived, dialectical tension between their life before the abortion and their life after the abortion.

Managing the comprehensive stigmatizing silence: Silence vs. openness

Across women's narratives, there existed an overarching dialectical tension of *silence* vs. *openness*, which was difficult for many women to manage when interacting with others. In this struggle, women shared how their medication abortion was often a solo, private experience that was not openly shared with others. Many women decided *not* to inform certain family members about their pregnancy and abortion. Women noted feelings of shame, embarrassment, worry, or fear as some of the reasons for not telling others. Along with stating these emotions, women said things like: "I never told the father and I don't intend to" (8-4-17); "I don't know if I will ever tell my husband and children about what I did" (2–11-12); or "I couldn't talk to my family" (3–16-17). The initial decision to remain silent made it difficult to talk openly with others about their feelings and experiences after their medication abortion. Silence was also experienced in other ways: one woman was glad she was home alone during her abortion so no one could hear her, while a different woman left the abortion clinic and began crying and said, "why is there so much silence here?" as she was taking her pill alone in her bathroom at home.

Even if women did allow certain family members to become privy to their abortion decision, openly discussing their feelings after the abortion remained difficult. When talking with others, one woman said: "I love my husband but it is beyond difficult for me to talk to him about this,

because I know he wants nothing more than to just move on from this" (4–28-18). A different woman recounted: "My close friends know here but I don't really feel I can talk to them about it. I don't feel like i can talk to anyone about it" (2-9-13). Despite these women's desires to talk about their abortion, others (e.g., the baby's father, their husband, family members) refused to engage in conversation with them. As a result, women said things like: "I feel like I have no one to speak to about it since he doesn't think about it the way I do" (9-8-15), and "I try to talk about it with my family and the baby's dad but they all tell me it's in the past" (10–28-17).

Oftentimes, certain dates (such as their child's due date) or friends with other babies who are of similar age to their "would-have-been child" led to triggering events where women desired to express their feelings with others, but felt like they couldn't talk openly. For instance, one woman said: "But I haven't really been able to share the true regret and near constant jealously of my loved ones engagements or pregnancies" (11–21-16). Another woman stated: "I knew I had to have an abortion, but these feelings I have right now I never imagined I'd have. I don't want to go out, I don't want to tell anyone, all I feel like doing is crying" (7-8-18). Thus, the isolation and silence leading up to her own medication abortion continued to pervade after the abortion, creating additional communication challenges with freely expressing her emotions with family and friends.

Silence was often described as being frustrating and challenging. In fact, 59 women (60%) reported feelings of isolation and alienation. As a result, some women personally attacked themselves. For example, one woman said: "I feel like I'm living a lie I get up get ready for work get my family up like normal the days go on like normal but I'm not normal I killed my baby I'm a monster!!" (3–14-17). Similarly, a different woman wrote: "As a mom I feel like a monster and I have to act like nothing happened" (4–18-17). These demeaning language choices (e.g., monster, killer) are present in the distal-already-spoken societal discourses about abortion. Women's awareness of these larger discourses led some women to write about their intentional use of selective language choices when talking about their abortion with others. One woman shared: "I tried to find an OBGYN that could see me ASAP. I went in and told them I had a miscarriage because I was ashamed of the truth of what I did" (3–21-18). Finally, some women reported struggling in silence by saying things like: "I am in desperate need of assistance and I am too embarrassed to attend an in person support group" (11–21-16), and "And when I got home, I had to hold it all in. I was so ashamed of my choice. I couldn't let anyone know" (2–11-11). Even though these women were able to anonymously write about their abortion on this website, they felt muted by their loved ones because of the centripetal discourses of shame and embarrassment associated with abortion.

Discussion

A national study that assessed women's support for and interest in alternative models of abortion provision found that about half of U.S. women are supportive of and nearly one-third are interested in medication abortion (Biggs et al., 2019). The growing interest and practice in this type of abortion provision warrant scholars to understand women's experiences. Our study is the first in the U.S. to conduct a case analysis of women's online blogging narratives about having had a medication abortion. We focused on understanding the discursive dynamics and contradictions that influenced and shaped women's talk about their own experiences. Our analysis rendered four sites of dialectical tension: *only choice* vs. *other alternatives, unprepared* vs. *knowledgeable, relief* vs. *regret*, and *silence* vs. *openness*. Each site of struggle characterized a different stage of women's medication abortion narrative: the decision, the medication abortion process, after-abortion identity, and the general stigmatizing silence associated with abortion.

As other scholars have noted (Kimport & Doty, 2019), we found that women relied upon language choices that aligned with the existing ideological frameworks from both the Right to Life and Right to Choice movements. For instance, some women used the words "fetal tissue," while other women used the word "baby" when referencing their pregnancy. Women also explicitly mentioned distal already-spoken messages from both movements about how they were told "it's just a pill" or "I've killed my baby." Such language choices are not idle linguistic distinctions, but rather indicate a woman's awareness of the different semantics and terminology surrounding the larger cultural narratives about abortion. This awareness was particularly evident when women discussed the overarching silence stigmatizing one's abilities to openly talk with family and friends about their medication abortion experience. Thus, women's talk about their own personal experiences, their justification for having an abortion, and their own sense-making after the medication abortion were shaped by the available heuristics and frames from larger cultural discourses and political movements (Kimport & Doty, 2019).

Cultural narratives of abortion are powerful and construct meaning and truth (Ludlow, 2008). While a woman's personal story about her medication abortion is individual and now occurs in a more private setting (e.g., at home), this experience remains social and political, defined, and reified by larger cultural narratives and semantics (Beynon-Jones, 2017; Cockrill & Nack, 2013). The sexual liberalism script that reflects positive attitudes toward nontraditional sexual behaviors influences individual's attitudes about abortion (Tokunaga et al., 2015), as well as their own narratives about medication abortion. We found evidence of these larger discourses within women's talk about their own medication abortion, and in particular, their rationale for their decision, their description of the medication abortion process, their reflections on their identity after the abortion, and the overall stigmatizing silence resulting in a muted voice and the public illegitimacy of their own narrative. For instance, many of the justifiable reasons recounted by women in this case study for having an abortion align with the centripetal discourses of the Right to Choice movement regarding bodily rights and a woman's freedom of choice. Among women having abortions in the U.S., finances and lack of readiness are the most commonly cited reasons for choosing abortion (Finer et al., 2005).

The presence of larger cultural narratives can result in dialectical tensions as one seeks to construct her own abortion narrative and considers disclosing that narrative to others. In

particular, many women described experiencing both relief and regret after their abortion. Historically, these two emotions have been juxtaposed and positioned as binary emotions that are socially and politically aligned (Ehrlich & Doan, 2019). The Right to Choice movement discourse aligns with the notion that abortion proffers emotional relief, whereas the Right to Life movement discourse positions itself with abortion resulting in regret. This polarized alignment and framing results in both movements speaking different languages and never fully listening nor engaging with the other (Wiederhold, 2014). One proposed origin of this framing dates back to the legal reasoning of the 2007 U.S. Supreme Court case *Gonzales v. Carhart*, where the federal partial-birth abortion ban was upheld. However, our analysis of women's narratives post-medication abortion exposes the complex duality of these two emotions often being experienced in tandem, as opposed to being simplistic binaries. The either-or, unidimensional script from both the Right to Choice and Right to Life movements – abortion provides either relief or results in regret – fueled a sense of tension for many of the women as they processed their identity after the abortion and considered openly disclosing those private experiences with others. Thus, these women's narratives illustrate that one's individual experiences with having had a medication abortion may result in a both/and: initial relief coupled with later regret. A reliance upon political movement discourses to construct one's own narrative may continue to marginalize or invalidate one's own private medication abortion experience when the larger scripts remain politically charged and polarized (LaRoche & Foster, 2018).

The stigma and risk that characterize the topic of abortion are influenced and shaped by the larger centrifugal discourses from both the Right to Choice and Right to Life movements (Beynon-Jones, 2017; Cockrill & Nack, 2013). For example, Cockrill and Nack (2013) found that women seeking an abortion often attempt to manage the stigma of abortion through non-disclosure, stating their reasons for having an abortion as "exceptional" and necessary, or condemning the Right to Life perspectives about abortion. In a different study on Southside Chicago African-American adolescent females, the majority of sexually active teens never talked with their parents about the topic of abortion, and almost 20% expressed fears of harm or eviction if their parent were to learn of an abortion in their past (Sisco et al., 2014). In our case study, we found that women also experienced stigma, silence, and fear that led them to remain private and/or secretive with certain individuals throughout their medication abortion experience. Silence before or during the medication abortion process resulted in women experiencing additional challenges later on with talking openly about one's experiences. Altogether, these findings align with communication scholars who have found that when private health information disclosures are deemed as being threatening or stigmatizing, one's private health information remains concealed (Baxter & Akkoor, 2011; Ebersole & Hernandez, 2016). This is important because secrecy of one's abortion is associated with poorer coping (Major & Gramzow, 1999; Major et al., 1997), and may result in further isolation and lack of social support from others (Cockrill & Biggs, 2017).

Recent movements such as Shout Your Abortion and #YouKnowMe have tried to dispel the stigma and silence surrounding abortion. However, these movements remain politically aligned and purport the "American Dream" abortion narrative: I was able to go to college/graduate/get a good job due to my abortion. These more recent public narratives frame abortion as a restitution or quest experience (Frank, 1995), where women are portrayed as being able to return to normalcy and good health, or regard their abortion story as one part of their personal journey that they were able to overcome. While such discourses were evident in some women's blogs and have been shown to reduce abortion stigma when openly disclosed (Cockrill & Biggs, 2017), many women's narratives within this case study characterized chaos narratives (Frank, 1995) where the abortion experience interrupted their daily lives and left them feeling out of control. Most notably, over 50% of the sample reported that the father to their child or other family members used negating language as a means to justify a woman's need for an abortion, albeit her own desires to keep her baby. In addition, 75 women (77%) regretted their decision, and 37 women (38%) reported struggling with mental illness and suicidal thoughts after the abortion. While previous scholarship has also found evidence of some women experiencing negative outcomes after an abortion due to a lack of decision-making power and limited social support (Kimport et al., 2011), as well as possible significant relationships between abortion and mental health problems (see Fergusson et al., 2013; Reardon, 2018), these centrifugal discourses remain muted and marginalized in the U.S. abortion debate.

Limitations and directions for future research

As with all scholarship there are limitations. Most notably, there is a lack of generalizability due to the limited scope: we only analyzed women's medication abortion narratives anonymously posted to one website. However, it is important to note that the purpose of this project was to make analytic generalizations based on gathering an in-depth descriptive understanding of these women's medication abortion narratives. Second, all qualitative case studies are limited by the sensitivity and integrity of the investigators. We attempted to surmount this obstacle by having three qualitatively trained female researchers who completed independent coding and collectively participated in the contrapuntal analysis process. Third, case study research is criticized for not having a clear set of systematic procedures (Yin, 2014). To address this concern, we sought to clarify and provide transparency with the methodological techniques used. Fourth, the anonymity of women's blog submissions to the website did not allow us to gather and report the social demographics of the women who anonymously shared their abortion narratives, which again hinders the generalizability of our findings. Finally, the population of women who write an anonymous post about their abortion experience may be different from those who do not.

All of these limitations provide avenues for future research. Most importantly, this single case study demonstrates the need for a broader, pluralistic, mixed-method research strategy that

assesses women's medication abortion narratives, particularly given its increased popularity amongst women seeking this type of abortion provision. Such research could interview women who have had a medication abortion, as well as use surveys to assess different variables such as demographic factors, health literacy, and privacy management strategies employed when talking about one's medication abortion.

Conclusion

n sum, our findings show that the medication abortion experience is rife with tension and contradiction. This complexity and duality are not evident in much of the larger cultural discourses and political debates about abortion. Many women in this case study noted that their decision to have a medication abortion was not a flippant decision or an easy choice where women remained unscathed. Women's narratives about their medication abortion experience were complex, and no singular narrative fully encapsulated or defined what women experienced during and after their medication abortion. Therefore, it is critical to transcend the silence in order to expose both sides of the debate and understand how these larger discourses influenced women's personal language choices when constructing their own abortion narrative and anonymously sharing it with others online. The tensions and dialectical struggles experienced after having a medication abortion and attempting to share it with others remain silent from public discourse and debate (Hallgarten, 2018). Presently, this silence positions one's abortion story as an either-or, binary experience that is politically aligned with one movement or another. The larger discourses prevalent within both the Right to Life and Right to Choice movements impact the liminality of women who are contemplating a medication abortion and affect their own narrative reconstruction and sense-making after their private medication abortion.

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EXHIBIT 19

Population Council

NON-PROFIT

Population Council

For more on population control, see John Holdren (https://www.influencewatch.org/person/john-holdren/)

The Population Council is a nonprofit founded in 1952 by John D. Rockefeller III to address supposed world overpopulation. The council conducts demographic research and analysis to support and promote the global use of artificial birth control and abortion; biomedical research to discover and develop new contraceptive drugs and technologies; and demographic analysis in support of population control experiments, policies, and programs in underdeveloped countries.[1]

The Population Council grew from a conference convened by Rockefeller which was attended by "population activists," the director of Planned Parenthood Federation of America (https://www.influencewatch.org/non-profit/planned-parenthood-federation-of-america/), and several well-known eugenicists, among others.[2] Lamenting that "modern civilization had reduced the operation of natural selection by saving more 'weak' lives and enabling them to reproduce," resulting in "a downward trend in... genetic quality," the conferees agreed that an organization needed to be created that would be devoted to the "reduction of fertility."[3][4] Rockefeller formally launched the council with a personal grant of $100,000 and served as the organization's first president. American Eugenics Society (AES) members Frederick Osborn and Frank Notestein were chosen as the council's next two presidents.[5] Early donors to the council included the Rockefeller Brothers Fund (https://www.influencewatch.org/non-profit/rockefeller-brothers-fund/) and the Ford Foundation (https://www.influencewatch.org/non-profit/ford-foundation/), but the U.S. and foreign governments would become the council's biggest financial backers.[6]

The Population Council has been responsible for the development of several controversial contraceptives and abortifacients used throughout the world. In 1962, for instance, the council had been warned by its own research doctors about the acute adverse side effects of the original models of the intrauterine device (IUD). Nonetheless, the council collaborated with the Ford Foundation and the International Planned Parenthood Federation (IPPF) (https://www.influencewatch.org/non-profit/planned-parenthood-federation-of-america/) on large-scale IUD programs throughout the 1960s in India, Pakistan, South Korea, and Taiwan. Reported side effects included severe pain, protracted bleeding, pelvic inflammatory disease, and perforated uteruses.[7]

The original French manufacturer of the RU-486 abortifacient pill donated the rights to manufacture and market the drug in the U.S. to the Population Council in 1994. The council then transferred the rights in exchange for undisclosed royalties to Danco, which *The Washington Post* has called a "secretive and obscure" company in the Cayman Islands.[8] Now called Mifeprex, RU-486 was responsible for about 40 percent of the nearly 900,000 abortions performed in the U.S. in 2016.[9]

The council was also responsible for the development of the hormonal contraceptive implant Norplant. In 1999, the company licensed to manufacture Norplant agreed to a $50 million settlement in response to a class-action lawsuit brought by more than 30,000 women who say they suffered severe side effects using the device.[10]

History

EARLY YEARS

The Population Council was incorporated in November 1952 by John D. Rockefeller III, and funded initially by the Rockefeller Brothers Fund, Ford Foundation, Markle Foundation, the National Institutes of Health, and Rockefeller personally.[6] The new council funded demographic and biomedical research and made grants to researchers and institutions to study "knowledge, attitudes, and practices related to family planning" and artificial birth control in countries throughout the world.[11] Early grants supported studies in embryonic development, funded research into "differential fertility among social classes," and paid for sterilization experiments on "women with bad hereditary history."[12] In 1956, the council established a biomedical research lab at the Rockefeller Institute for research on the human reproductive system and to facilitate the development of new contraceptives.[11]

Historian Donald T. Critchlow wrote that the Population Council "cultivated elite connections and avoided public controversy by identifying itself as a neutral, scientific organization." From its very beginning, however, "the council was policy oriented" and "played a principal role in establishing an international network of population experts who shared a set of assumptions about population dynamics and a consensus as to population intervention."[13]

Founding member of the council and secretary of the American Eugenics Society (AES) Frederick Osborn was Rockefeller's successor as president in 1957. Osborn was a leading proponent of "reform eugenics," which sought to distance itself from the racism and anti-Semitism of the eugenics movements popular in the U.S. prior to World War II and embraced by the Nazi regime in Germany. Osborn "did not hesitate to endorse compulsory eugenic sterilization of the mentally ill or restrictions on immigration, and to voice caution against miscegenation."[14] Osborn had written earlier that, "It is evident that the social conditions which affect reproduction might be modified in a number of ways, so that the dynamic influences of population change would be more in line with conscious social objectives. Eventually, if our dream of human progress is to be realized, rational social action must replace the operation of blind forces in this as in other fields."[15] Under Osborn's leadership, the council made regular direct grants to the AES.[12]

THE IUD

Osborn's colleague at the AES, Frank Notestein, became the council's third president in 1959. Impatient with the cost and bureaucracy involved with widespread dissemination of the birth control pill in undeveloped countries, Notestein and Rockefeller convened an international conference in 1962 on intrauterine devices (IUDs) to gather information on the contraceptive method and encourage further development. Despite hearing from doctors about frequent adverse side effects like pain, protracted bleeding, pelvic inflammatory disease, and perforated uteruses, the council collaborated with the Ford Foundation and the International Planned Parenthood Federation (IPPF) on large-scale IUD programs in Pakistan, Taiwan, South Korea, and India where enthusiastic and often authoritarian leaders made population control a national priority. By 1968, the council had invested more than $2.5 million in manufacturing and distributing the new "Lippes Loop" IUD worldwide.[16]

By 1965, the first program launched in Taiwan revealed that 28 percent of test women had their IUDs removed because of pain or excessive bleeding and 10 percent had become pregnant. This suggested that across Taiwan and South Korea, tens of thousands of women would soon be suffering adverse consequences. In India, writes historian Matthew Connelly, "the number would be orders of magnitude greater." Meanwhile, a new local IUD plant was preparing to produce twenty thousand devices a day and the Indian government announced its plan to supply twenty-nine million women with IUDs over a five-year period.[17]

A year later, significantly adverse side effects of the IUD had become systemic in Taiwan, South Korea, India, Pakistan, Puerto Rico, and the United States. By 1967 in India, 58 percent of women reported some pain after IUD insertion, 24 percent reported severe pain, and 43 percent had prolonged bleeding. That same year, Notestein acknowledged that "mistakes have been made, but the overall gains have been valuable and highly significant."[18]

"BEYOND FAMILY PLANNING"

In 1969, the Population Council's fourth president, Bernard Berelson, published an article entitled "Beyond Family Planning" in the council's quarterly *Studies in Family Planning*.[19] Ostensibly, an effort to promote discussion about the "problem" of continued population growth, the document offered legitimacy to the most draconian policy suggestions, such as adding "fertility control agents" to water supplies in urban areas, temporary sterilization of all young women "via time-capsule contraceptives," and compulsory sterilization of men with three or more children. While Berelson did not necessarily recommend these extreme measures, he included them in his essay as "programs or policies more or less responsibly suggested," and he encouraged further research.[20] Ten years later Berelson would write, "The familiar choice presented in the policy literature—that voluntarism is good and 'coercion' bad—is clearly simplistic. We are all of us 'coerced' daily by both culture and law, in countless accepted ways [...] the term itself is neutral: the issue turns on what end is served by a coercive policy and the participatory conditions under which it is implemented."[21]

Revealing perhaps his true motive for considering harsher measures, Berelson suggested in "Beyond Family Planning" that the "more extreme of controversial proposals tend to legitimate more moderate advances." Berelson noted that abortions were getting easier to perform by "the so-called suction device now being utilized in Eastern Europe and the U.S.S.R.," and might not require hospitalization. These advances would, in turn, allow for even more possibilities like an abortion "camp" where the procedure could be conducted on numerous women simultaneously.[22]

About the same time that Bereleson published "Beyond Family Planning," Population Council's biomedical division director Sheldon Segal was training doctors at the All-India Institute of Medical Sciences (AIIMS) in Delhi how to determine sex in humans "for its general usefulness in reproductive biomedicine." While Segal claimed he never intended his training to facilitate sex-selective abortions, the procedures he taught were already being used to do that.[23] Testifying before Congress in 2016, reporter and author Mara Hvistendahl alleged that a few years after Segal's training "AIIMS became the site of shocking medical experiments." Hvistendahl continued, "Doctors offered poor pregnant women in Delhi sex determination and then tracked whether they aborted—and wrote up the results in a medical journal. Of course, women tended to abort if they were carrying girls. That was how sex selection was introduced to India."[24] Segal would later go on record as a proponent of sex determination as a means of population control.[25]

Fearing boycotts led by American pro-life groups, Roussel-Uclaf, the French company which developed the RU-486 chemical abortifacient pill, chose not to bring the drug to the American market itself and sought to find an American company to buy the rights to RU-486. This proved a long and fruitless effort as the French company was unable to find a single American company willing to take on the politically risky drug. Impatient with the lack of progress, then-U.S. Representative Ron Wyden (D-Oregon) threatened the seizure of Roussel-Uclaf's patent rights. In May 1994, Roussel-Uclaf donated RU-486 rights to the Population Council, which would be responsible for running clinical trials, obtaining Food and Drug Administration (FDA) approval, and finding a manufacturer. [2627]

While waiting for FDA approval, the Population Council transferred rights to manufacture and distribute RU-486 to Danco Laboratories in exchange for undisclosed royalties. *The Washington Post* reported that "secretive and obscure" Danco was formed in the Cayman Islands in 1995.[8] Danco then contracted with Chinese firm Hua Lian to produce the compounds for RU-486, a deal which, according to a research director at the Shanghai Family Planning Commission, was encouraged by the Rockefeller Foundation.[28]

Marketed by Danco as Mifeprex, the "Abortion Pill" was responsible for 6 percent of all abortions in 2001 and 31 percent by 2014, according to the pro-abortion Guttmacher Institute (https://www.influencewatch.org/non-profit/guttmacher-institute/).[29] That percentage has already grown to more than 40 percent since a 2016 FDA ruling extending the use of the abortion drug through 10 weeks of pregnancy.[9]

NORPLANT

Norplant is a contraceptive consisting of six silicone capsules containing the hormone levonorgestrel that are inserted under the skin of a woman's upper arm. Levonorgestrel thickens cervical mucus so that sperm cannot get through to any eggs and also prevents the regular release of eggs. These effects can last for up to five years. The product was developed by Sheldon Segal and Horatio Croxatto of the Population Council in 1966. As with the IUDs, clinical trials were held outside the U.S. in 17 countries in Latin America, Asia, and Africa.[3031] In 1990, the FDA approved Norplant.

The council sold the rights to manufacture and market Norplant to Wyeth-Ayerst Laboratories, a division of the American Home Products Corporation. By 1992, Norplant sales reached $141 million and a year later the device had been implanted in 1 million women in the U.S.[31] Over the next few years, however, tens of thousands of women brought lawsuits against Wyeth-Ayerst charging that the company downplayed the severe side effects of Norplant. By 1999, Wyeth-Ayerst agreed to a settlement in which the company admitted no wrong but agreed to pay $1,500 to each of approximately 36,000 women. Sales of Norplant plummeted, and Wyeth-Ayerst discontinued sales in 2000.[3233]

Activities

The Population Council funds and conducts biomedical research on contraceptive and HIV-prevention drugs and delivery systems; contraceptive product development; policy research and analysis to provide governments and international organizations "evidence-based" justification for contraception and abortion; and demographic analysis in support of population control experiments, policies, and, programs in underdeveloped countries.[1]

The council administers its programs in 50 countries through offices in Africa, Asia, Latin America, and the Middle East.[34] In 2016, the Population Council took in $84.5 million in support, the majority, approximately 60%, from governments. In that year, 46% of Population Council contributions came from the U.S. government through the Agency for International Development (USAID), Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH). The council also received 21% of its support from foundations, corporations, nongovernmental organizations, and individuals, and another 4% from multilateral organizations. In 2016, the council spent $85.2 million on "program services," which included Reproductive Health (37%), HIV and AIDS (27%), and Poverty, Gender, and Youth (17%).[35]

The Population Council developed the non-hormonal copper ParaGard IUD in 1984 and the levonorgestrel-releasing Mirena IUD in 2000.[36] ParaGard is also widely regarded as the most effective "emergency contraceptive" — even more so than the "morning-after" pill. Advocates of using ParaGard in this manner, typically do not mention or downplay the product's abortifacient potential, preventing the implantation of a fertilized egg.

The council has a long history of providing research, analysis, and advocacy to efforts at legitimizing and expanding access to abortion in underdeveloped countries. Population Council participated in the Consortium for Safe Abortions in India, which launched a program of "community-level sensitization using murals, community theater, home health visits, and local media to raise awareness" about the legal right to abortion and the location of abortion providers. The council reported that the program

"successfully dispelled misperceptions about abortion-related issues" and significantly increased the availability of abortion in rural areas.[37] Similarly, working with the National Pro-Choice Alliance for Mexico, the council "played a key role in the passage of the 2007 law decriminalizing early abortion in Mexico City.[38]

CURRICULUM PROGRAM

In collaboration with pro-abortion organizations including International Planned Parenthood Federation and International Women's Health Coalition, the Population Council in 2009 published *It's All One*, a curriculum for sex education teachers "from Africa to the Pacific, from Asia to the Americas, from Europe to the Arab World." Topics include gender, sexual health, HIV, sexuality, relationships, communication, intimate-partner violence, puberty, reproduction, contraception, and abortion. Recommended activities include having students pair-off to role-play situations such as, "communicating one's HIV status, sharing what feels pleasurable and what does not, or deciding whether and how to communicate one's experience of same-sex attraction."[39]

Leadership

As of 2023, Patricia C. Vaughan and James Sailer are the Interim co-Presidents of the Population Council following the previous president, Julia Bunting, stepping away from her position. [40]

Patricia C. Vaughan serves as the interim co-president as well as General Counsel for the Population Council. Vaughan previously served as board chair of the Kenya-based African Population Health and Research Center as well as the South Africa-based Solutions for Innovative Policies, Programs and Technologies, NPC. She also serves on the Council on Foreign Relations (https://www.influencewatch.org/non-profit/council-on-foreign-relations/) (CFR). [41]

James Sailer is the Interim co-president of the Population Council as well as the executive director of the organization's Center for Biomedical Research. He was previously worked as vice-president of corporate affairs for the Population Council as well as the former Board Chair for international non-government organization (NGO) coalition InsideNGO. [42]

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Nonprofit Information

- **Accounting Period:** December - November
- **Tax Exemption Received:** December 1, 1953

Available Filings

2021 Dec

Form Type	Form 990
Total revenue	$58,213,127
Total functional expenses	$60,962,900
Total assets (EOY)	$168,124,790
Total liabilities (EOY)	$29,200,620
Unrelated business income?	N
Total contributions	$44,753,562
Program service revenue	$112,836
Investment income	$2,283,339
Comp. of current officers, directors, etc.	$2,174,686
Form 990	

2020 Dec

Form Type	Form 990
Total revenue	$57,674,221
Total functional expenses	$61,473,136
Total assets (EOY)	$165,937,710
Total liabilities (EOY)	$34,866,284
Unrelated business income?	N

Total contributions	$43,773,375
Program service revenue	$127,349
Investment income	$1,761,612
Comp. of current officers, directors, etc.	$2,324,655
Form 990	

2019 Dec

Form Type	Form 990
Total revenue	$82,631,863
Total functional expenses	$71,080,422
Total assets (EOY)	$169,859,882
Total liabilities (EOY)	$37,917,673
Unrelated business income?	N
Total contributions	$54,165,671
Program service revenue	$82,171
Investment income	$3,473,373
Comp. of current officers, directors, etc.	$2,919,661
Form 990	PDF (HTTPS://PROJECTS.PROPUBLICA.ORG/NONPROFITS/DOWNLOAD-FILING?PATH=04_2021_PREFIXES_06-13%2F131687001_201912

2018 Dec

Form Type	Form 990

Total revenue	$97,604,680
Total functional expenses	$82,590,271
Total assets (EOY)	$145,312,264
Total liabilities (EOY)	$38,681,586
Unrelated business income?	N
Total contributions	$70,001,047
Program service revenue	$134,800
Investment income	$2,981,831
Comp. of current officers, directors, etc.	$2,533,591
Form 990	PDF (HTTPS://PROJECTS.PROPUBLICA.ORG/NONPROFITS/DOWNLOAD-FILING?PATH=02_2020_PREFIXES_05-13%2F131687001_201812

2017 Dec

Form Type	Form 990
Total revenue	$91,365,529
Total functional expenses	$86,668,211
Total assets (EOY)	$140,903,775
Total liabilities (EOY)	$41,299,941
Unrelated business income?	N
Total contributions	$71,764,136
Program service revenue	$67,711

Investment income	$1,800,315
Comp. of current officers, directors, etc.	$2,617,615
Form 990	PDF (HTTPS://PROJECTS.PROPUBLICA.ORG/NONPROFITS/DOWNLOAD-FILING?PATH=02_2019_PREFIXES_11-13%2F131687001_201712_

2016 Dec

Form Type	Form 990
Total revenue	$82,733,727
Total functional expenses	$85,432,557
Total assets (EOY)	$142,820,494
Total liabilities (EOY)	$52,748,972
Unrelated business income?	N
Total contributions	$72,427,240
Program service revenue	$0
Investment income	$1,856,838
Comp. of current officers, directors, etc.	$2,863,685
Form 990	PDF (HTTPS://PROJECTS.PROPUBLICA.ORG/NONPROFITS/DOWNLOAD-FILING?PATH=IRS%2F131687001_201612_990_201711281498237

2015 Dec

Form Type	Form 990
Total revenue	$79,012,374
Total functional expenses	$84,157,365

Total assets (EOY)	$144,875,451
Total liabilities (EOY)	$54,254,931
Unrelated business income?	N
Total contributions	$71,368,781
Program service revenue	$0
Investment income	$3,706,919
Comp. of current officers, directors, etc.	$3,074,268
Form 990	PDF (HTTPS://PROJECTS.PROPUBLICA.ORG/NONPROFITS/DOWNLOAD-FILING?PATH=2017_03_EO%2F13-1687001_990_201512.PDF)

2014 Dec

Form Type	Form 990
Total revenue	$88,192,984
Total functional expenses	$86,700,897
Total assets (EOY)	$138,846,469
Total liabilities (EOY)	$32,791,971
Unrelated business income?	N
Total contributions	$75,254,425
Program service revenue	$0
Investment income	$4,437,539

Comp. of current officers, directors, etc.	$2,888,531
Form 990	PDF (HTTPS://PROJECTS.PROPUBLICA.ORG/NONPROFITS/DOWNLOAD-FILING?PATH=2015_09_EO%2F13-1687001_990_201412.PDF)

2013 Dec

Form Type	Form 990
Total revenue	$81,701,469
Total functional expenses	$87,349,595
Total assets (EOY)	$139,324,151
Total liabilities (EOY)	$29,917,362
Unrelated business income?	N
Total contributions	$74,820,045
Program service revenue	$0
Investment income	$2,609,105
Comp. of current officers, directors, etc.	$2,657,069
Form 990	PDF (HTTPS://PROJECTS.PROPUBLICA.ORG/NONPROFITS/DOWNLOAD-FILING?PATH=2014_09_EO%2F13-1687001_990_201312.PDF)

2012 Dec

Form Type	Form 990
Total revenue	$66,071,100
Total functional expenses	$78,369,608
Total assets (EOY)	$130,952,524

Total liabilities (EOY)	$31,803,832
Unrelated business income?	N
Total contributions	$55,236,787
Program service revenue	$0
Investment income	$2,804,602
Comp. of current officers, directors, etc.	$2,645,870
Form 990	PDF (HTTPS://PROJECTS.PROPUBLICA.ORG/NONPROFITS/DOWNLOAD-FILING?PATH=2013_09_EO%2F13-1687001_990_201212.PDF)

2011 Dec

Form Type	Form 990
Total revenue	$70,889,544
Total functional expenses	$85,080,839
Total assets (EOY)	$135,947,611
Total liabilities (EOY)	$32,055,273
Unrelated business income?	N
Total contributions	$59,340,421
Program service revenue	$0
Investment income	$1,700,869
Comp. of current officers, directors, etc.	$2,475,622

Form 990 PDF (HTTPS://PROJECTS.PROPUBLICA.ORG/NONPROFITS/DOWNLOAD-FILING?PATH=2012_10_EO%2F13-1687001_990_201112.PDF)

Additional Filings (PDFs)

- 2010 Dec Form 990 (https://projects.propublica.org/nonprofits/download-filing?path=2011_09_EO%2F13-1687001_990_201012.pdf)
- 2009 Dec Form 990 (https://projects.propublica.org/nonprofits/download-filing?path=2011_02_EO%2F13-1687001_990_200912.pdf)
- 2008 Dec Form 990 (https://projects.propublica.org/nonprofits/download-filing?path=2009_10_EO%2F13-1687001_990_200812.pdf)
- 2007 Dec Form 990 (https://projects.propublica.org/nonprofits/download-filing?path=2009_01_EO%2F13-1687001_990_200712.pdf)
- 2006 Dec Form 990 (https://projects.propublica.org/nonprofits/download-filing?path=2008_03_EO%2F13-1687001_990_200612.pdf)
- 2005 Dec Form 990 (https://projects.propublica.org/nonprofits/download-filing?path=2007_12_EO%2F13-1687001_990_200512.pdf)
- 2004 Dec Form 990 (https://projects.propublica.org/nonprofits/download-filing?path=2005_12_EO%2F13-1687001_990_200412.pdf)
- 2003 Dec Form 990 (https://projects.propublica.org/nonprofits/download-filing?path=2004_12_EO%2F13-1687001_990_200312.pdf)
- 2002 Dec Form 990 (https://projects.propublica.org/nonprofits/download-filing?path=2003_12_EO%2F13-1687001_990_200212.pdf)
- 2001 Dec Form 990 (https://projects.propublica.org/nonprofits/download-filing?path=2002_11_EO%2F13-1687001_990_200112.pdf)

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EXHIBIT 20

2002 Citizen Petition of AAPLOG to FDA
(Aug. 8, 2002)
("2002 Citizen Petition")

BEFORE THE DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Citizen Petition re: Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Days' Gestation	**)**

CITIZEN PETITION AND REQUEST FOR ADMINISTRATIVE STAY

The American Association of Pro Life Obstetricians and Gynecologists ("AAPLOG"), the Christian Medical Association ("CMA"), and Concerned Women for America ("CWA") (collectively, "the Petitioners") submit this Petition pursuant to 21 C.F.R. §§ 10.30 and 10.35; 21 C.F.R. Part 314, Subpart H (§§ 314.500-314.560); and Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355).[1] The Petitioners urge the Commissioner of Food and Drugs to impose an immediate stay of the approval by the Food and Drug Administration ("FDA" or "agency") of Mifeprex™ (mifepristone; also, "RU-486"),[2] thereby halting all distribution and marketing of the drug, pending final action on this Petition. In addition the Petitioners urge the Commissioner to revoke FDA's approval of Mifeprex and request a full FDA audit of the Mifeprex clinical studies.[3]

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[1] Federal Food, Drug, & Cosmetic Act of 1938 ("FD&C Act"), Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et seq.*).

[2] The New Drug Application for Mifeprex, which was filed by the Population Council, was approved on September 28, 2000. Mifeprex is distributed by Danco Laboratories, a licensee of the Population Council.

[3] The Petitioners will, at times, cite to documents contained in FDA's January 31, 2002 public release of documents (approximately 9,000 pages in 94 files) made pursuant to a Freedom of Information Act request ("FDA FOIA Release") filed by the non-profit organization, Judicial Watch. These bracketed citations will reflect the page numbering FDA has stamped on the bottom of each page, for example: [FDA FOIA Release: MIF 000001-05]. The FDA webpage posting the 94 files is: <http://www.fda.gov/cder/archives/mifepristone/default.htm>. Since the initial release FDA has edited some of the 94 files. However, the stamped page numbers have not changed. Additionally, many footnotes refer to Appendix A to this Petition, which contains a selected bibliography.

I. ACTION REQUESTED

The Petitioners respectfully request that the Commissioner immediately stay the approval of Mifeprex, thereby halting all distribution and marketing of the drug pending final action on this Petition. They urge the Commissioner to revoke market approval for Mifeprex in light of the legal violations and important safety concerns explained below. In addition, they request a full FDA audit of all records from the French and American clinical trials offered in support of the Mifeprex NDA.

II. INTEREST OF THE PETITIONERS

While it is true that the Petitioners have consistently opposed abortion and continue to do so, a careful examination of the claims made in this petition should alert people of conscience on either side of this issue that women are being harmed. Regardless of one's position on abortion, FDA's violations of its standards and rules have put women's health and lives at risk. The Petitioners are non-profit organizations that share a great concern about women's health issues. The American Association of Pro-Life Obstetricians and Gynecologists ("AAPLOG") is a recognized interest group of the American College of Obstetricians and Gynecologists ("ACOG"), currently representing over 2,000 obstetricians and gynecologists throughout the United States of America. The Christian Medical Association, founded in 1931, is a professional organization with thousands of physician members representing every medical specialty. Concerned Women for America ("CWA"), founded in 1979, is the largest public policy women's organization in the United States with members in every State and a total membership exceeding 500,000.

III. STATEMENT OF GROUNDS

A. SUMMARY OF THE PETITIONERS' ARGUMENTS

Good cause exists to grant an immediate stay of the agency's September 28, 2000 Mifeprex approval.[4] Good cause also exists for the subsequent revocation of that approval.[5] As established herein, (1) the approval of Mifeprex violated the Administrative Procedure Act's prohibition on agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;[6] (2) FDA's approval of Mifeprex violated 21 U.S.C. § 355 because the drug does not satisfy the safety and labeling requirements of that section; and (3) the agency approved Mifeprex despite the presence of substantial risks to women's health.

This Petition represents the latest attempt by members of the medical community and other concerned observers to warn FDA of the dangers posed by Mifeprex abortions to the health of women.[7] Women undergoing Mifeprex abortions risk, among other problems, uncontrolled fatal hemorrhage and serious bacterial infections. Mifeprex abortions particularly endanger women with ectopic pregnancies and those whose pregnancies have progressed beyond 49 days.[8]

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[4] When FDA approved the Population Council's NDA for mifepristone, it approved the drug for use in conjunction with misoprostol. In this Petition, "Mifeprex Regimen" will refer to the combined use of Mifeprex and misoprostol to effect an abortion.

[5] *See* 21 C.F.R. § 314.530 ("Withdrawal Procedures").

[6] 5 U.S.C. § 706(2)(A).

[7] On February 28, 1995, Americans United for Life and other groups and individuals filed a Citizen Petition with FDA requesting it to "refuse to approve any NDA for RU 486 for use as a pharmaceutical abortifacient that does not contain adequate evidence that the drug has undergone nonclinical and clinical safety and effectiveness trials." The petitioners also set forth a number of factors for the agency to consider. Americans United for Life *et al.*, Citizen Petition (Feb. 28 1995)[FDA FOIA Release: MIF 006144-6248]; *see also*, Letter, Ronald G. Chesemore, Associate Commissioner for Regulatory Affairs, FDA, to Gary L. Yingling, McKenna & Cuneo (March 20, 1995) (one-page letter suggesting that the petition was prematurely filed and claiming to be a "full response")[FDA FOIA Release: MIF 006250].

[8] The gestational age of a pregnancy is based on the first day of a woman's last menstrual period, which is designated as Day 1 of the pregnancy. On Day 49, a woman is deemed to be seven weeks pregnant, which means she has experienced 49 days of amenorrhea (time elapsed since the beginning of her last menstrual period).

Warnings about these dangers, together with FDA's own concerns about the safety of the abortion regimen, went unheeded. On September 28, 2000, FDA approved the new drug application ("NDA") for Mifeprex.[9] The initial reports of life-threatening and fatal adverse events appear to bear out the safety concerns underlying the pre-approval warnings. The Petition highlights a number of agency actions that were arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law. These serious departures from standard agency practice allowed the NDA for Mifeprex, a drug that is not safe for its intended use, to be approved by FDA.[10]

First, the approval of Mifeprex violated the legal requirements of FDA's Accelerated Approval Regulations found in Subpart H.[11] Mifeprex is not a drug for the treatment of a serious or life-threatening illness. It does not demonstrate the potential to address an unmet medical need because a less dangerous and more effective alternative for performing abortions already exists. It appears that FDA's decision to use Subpart H was motivated by its concern that, without restrictions, the drug could not be used safely. Rather than attempting to compensate for

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Ovulation for the small percentage of woman with a perfect 28 day cycle typically takes place between Days 12 and 14 and fertilization typically takes place 24 to 48 hours later.

[9] *See* U.S. Department of Health and Human Services, *HHS News*, Press Release P00-19, "FDA Approves Mifepristone for the Termination of Early Pregnancy," September 28, 2000. A selection of FDA documents relevant to its approval of Mifeprex may found at: <http://www.fda.gov/cder/drug/infopage/mifepristone>; and on a second page: <http://www.fda.gov/cder/foi/nda/2000/20687_mifepristone.htm>.

[10] FDA's unlawful approval of Mifeprex may not be unprecedented. The medical-scientific community and the mainstream press have called attention to a number of other instances in which one could question whether drugs and medical devices have been improperly approved. *See, e.g.*, Richard Horton, "Lotronex and the FDA: A Fatal Erosion of Integrity," *Lancet* 357 (May 19, 2001): 1544-1545; David Willman, "How a New Policy Led to Seven Deadly Drugs," *Los Angeles Times* (Dec. 20, 2000): at A1; Kit R. Roane, "Replacement Parts: How the FDA Allows Faulty, and Sometimes Dangerous, Medical Devices onto the Market," *U.S. News & World Report* (July 29, 2002): 54-59 (discussing FDA's recent approval policies regarding medical devices).

[11] 21 C.F.R. §§ 314.500-314.560. FDA's Accelerated Approval Regulations are set forth at 21 C.F.R. Part 314, Subpart H ("Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses") ("Accelerated Approval Regulations" or "Subpart H"). The Accelerated Approval Regulations were promulgated by FDA after notice and comment: New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, *Proposed Rule*, 57 Fed. Reg. 13234 (April 15, 1992) ("*Subpart H Proposed Rule*") and New Drug, Antibiotic, and Biological

the inherent dangerousness of Mifeprex by inappropriately resorting to the Subpart H approval mechanism, FDA should simply have refused to approve Mifeprex. (*See* Section III.D., *infra*.)

Second, Mifeprex was not proven to be "safe and effective" as required by law.[12] The scientific quality of the trials used to support the NDA was undeniably deficient according to Congress's statutory requirements and FDA's well-established standards.[13] The trials were not blinded, randomized, or concurrently controlled. FDA failed to explicitly waive its rules or offer a reasoned explanation for defying its own standards. (*See* Section III.E., *infra*.)

Third, the Mifeprex Regimen requires that Mifeprex be used in conjunction with another drug, misoprostol. FDA, however, has never approved misoprostol as an abortifacient. Although FDA normally opposes the promotion of off-label uses, in connection with the Mifeprex NDA, the agency sanctioned and itself participated in the promotion of the off-label use of misoprostol. Mifeprex, the label of which creates the false impression that misoprostol is approved for use as an abortifacient, is misbranded. (*See* Section III.F., *infra*.)

Fourth, and most critically, the Mifeprex Regimen is dangerous. FDA sought, without success, to convince the drug sponsor to place safety restrictions on Mifeprex. When that failed, on June 1, 2000, FDA itself proposed restrictions intended to reduce the unacceptable health risks associated with mifepristone abortions. Nevertheless, the agency, under concerted pressure from abortion advocates and politicians, ultimately approved mifepristone for use in a deregulated regimen that lacks key safeguards. For example, the regimen does not include a requirement that transvaginal ultrasound be used to date pregnancies and rule out ectopic

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Product Regulations; Accelerated Approval, *Final Rule*, 57 Fed. Reg. 58942 (Dec. 11, 1992) ("*Subpart H Final Rule*") (available at: <http://www.fda.gov/cder/fedreg/fr19921211.txt>).

[12] *See* 21 U.S.C. § 355.

[13] *See* 21 C.F.R. § 314.126.

pregnancies, which cannot be treated with the Mifeprex Regimen. In addition, FDA failed to restrict access to mifepristone to physicians trained in the provision of Mifeprex and surgical abortions and capable of treating complications arising from abortions. Concerns about the dangers of Mifeprex were confirmed when Danco and FDA announced publicly on April 17, 2002, a number of serious adverse events, including two deaths. (*See* Section III.G., *infra*.)

Fifth, the drug's sponsor has neglected to require Mifeprex providers to adhere to the limited restrictions contained in the approved regimen. The sponsor's inaction is surprising in light of the fact that these restrictions are being flouted openly. Section 314.530 authorizes FDA to withdraw the approval of a Subpart H drug if a drug's sponsor does not fulfill its responsibility of ensuring compliance with the restrictions on the use of the drug. (*See* Section III.H., *infra*.)

Sixth, the safeguards employed in the U.S. Clinical Trial are not mirrored in the regimen that FDA approved. Transvaginal ultrasounds, for example, although employed in the U.S. Clinical Trial, are not required under FDA's approved regimen. Nor are the trial requirements governing emergency care reproduced in the approved regimen. (*See* Section III.I., *infra*.)

Seventh, FDA's waiver of its rule, 21 C.F.R. § 314.55, requiring the testing of all new drugs for their potential effects on children, has jeopardized the health and safety of American teenage girls who may have abortions. FDA expressly contemplated the pediatric use of Mifeprex, but waived, without an adequately reasoned justification, the requirement that the drug undergo pediatric testing. (*See* Section III.J., *infra*.)

Eighth, FDA did not require the sponsor of Mifeprex to honor its commitments for Phase IV studies, which provide the opportunity to study in-depth the drug's safety and effectiveness after approval. When FDA approved Mifeprex, the agency permitted the Population Council to replace the six Phase IV study commitments it had made in 1996 with two much narrower

commitments. The modified studies will not adequately address outstanding questions, such as the effects of mifepristone abortions on women outside the tested age range of 18 to 35 years. (*See* Section III.K., *infra*.)

In sum, FDA, in approving Mifeprex, acted in a manner inconsistent with its statutory authorization, regulations, and well-established policies. FDA did not provide a contemporaneous explanation of its numerous departures from past practice.[14] Its aberrant actions coupled with the absence of explanations violated a fundamental principle of administrative law; an agency must either adhere to prior policies or fully explain why it is not doing so.[15] The approval of Mifeprex was, therefore, arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. It must be reversed.

B. FDA APPROVAL OF THE MIFEPREX REGIMEN

1. The Introduction of Mifepristone into the United States

Roussel Uclaf, a French pharmaceutical firm, first developed and tested mifepristone ("RU-486") as an abortifacient. By April 1990 the drug had become permanently available in

[14] An agency must explain its reasons for acting in a particular manner. *See, e.g., Securities & Exchange Commission v. Chenery Corp.*, 332 U.S. 194, 196-97 (1947) (noting that a court should not "be compelled to guess at the theory underlying the agency's action," but rather "[i]f the administrative action is to be tested by the basis upon which it purports to rest, that basis must be set forth with such clarity as to be understandable."). *Post hoc* rationalizations cannot salvage the agency's action with respect to Mifeprex. *See, e.g., Martin v. Occupational Safety and Health Review Commission*, 499 U.S. 144, 156-57 (1991) (*post hoc* rationalizations of counsel "do not constitute an exercise of the agency's delegated lawmaking powers"); *Investment Company Institute v. Camp*, 401 U.S. 617, 628 (1971) ("Congress has delegated to the administrative official and not to appellate counsel the responsibility for elaborating and enforcing statutory commands.").

[15] *See, e.g., Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 852 (D.C. Cir. 1970) ("[A]n agency changing its course must supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored, and if an agency glosses over or swerves from prior precedents without discussion it may cross the line from the tolerably terse to the intolerably mute.") (footnote omitted) (citing approvingly *Motor Vehicle Manufacturers Ass'n v. State Farm Mutual Automobile Ins. Co.*, 463 U.S. 29, 57 (1983)); *JSG Trading Corp. v. USDA*, 176 F.3d 535, 544 and 545 (D.C. Cir. 1999) (remanding agency action where "the agency manifestly failed to explain its abrupt departure from prior precedent" and noting that the agency "was obligated to articulate a principled rationale for departing from [its prior] test") (citations omitted); *Gilbert v. National Labor Relations Board*, 56 F.3d 1438, 1445 (D.C. Cir. 1995) ("It is, of course, elementary that an agency must conform to its prior decisions or explain the reason for its departure from such precedent.").

France. According to Dr. André Ulmann, the Roussel project manager for the development of RU-486, Roussel prohibited the commencement of any new studies in the United States and took the position that "under no circumstance[s]" would it permit a new drug application to be filed with FDA.[16] In fact, "the chairman of Hoechst [the parent company to Roussel] had officially declared that mifepristone was not compatible with the ethics of the company."[17]

Undeterred by Hoechst's reluctance to bring the drug to the United States, on January 22, 1993, President Clinton directed Department of Health and Human Services ("HHS") Secretary Donna Shalala to assess initiatives to promote the testing and licensing of mifepristone or other antiprogestins in the United States.[18] Further signaling that approval of mifepristone by FDA was a top priority of his Administration, President Clinton reportedly "wrote to Hoechst asking the company to file a new drug application with the FDA (an unprecedented situation in the pharmaceutical industry!), which Hoechst intransigently refused to do."[19]

In early 1993, Secretary Shalala and FDA Commissioner David Kessler "communicated with senior Roussel Uclaf officials to begin efforts to pave the way for bringing RU-486 into the American marketplace."[20] On May 16, 1994, the Population Council reached an agreement with Roussel Uclaf, pursuant to which the European drug maker transferred "without remuneration,

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[16] *See* André Ulmann, M.D., "The Development of Mifepristone: A Pharmaceutical Drama in Three Acts," *Journal of the American Medical Women's Association* 55 (Supplement 2000): 117-20, at 119. In 1994 Roussel Uclaf joined with the German pharmaceutical firm, Hoechst AG, to form Hoechst Roussel Ltd. In 1995, this entity merged with a third firm, Marion Merrell Dow, to form Hoechst Marion Roussel. In December 1999 Hoechst and Rhône-Poulenc combined to form Aventis, S.A., headquartered in Strasbourg, France.

[17] Ulmann, *infra* Appendix A, at 120.

[18] *See* Memorandum for the Secretary of Health and Human Services, "Importation of RU-486," *Public Papers of the Presidents: Administration of William J. Clinton, 1993* (Jan. 22, 1993) at 11.

[19] Ulmann, *infra* Appendix A, at 120 (emphasis in original).

[20] HHS Fact Sheet, "Mifepristone (RU-486): Brief Overview," (rel. May 16, 1994). Available at: <http://www.hhs.gov/news/press/pre1995pres/940516.txt>.

its United States patent rights for mifepristone (RU-486) to the Population Council . . . ."[21] Secretary Shalala was instrumental in bringing about the transfer of the patent rights to the Population Council[22] and even set a deadline – May 15, 1994 – for the transfer.[23]

After obtaining the American patent rights to mifepristone, the Population Council conducted clinical trials in the United States and filed a new drug application in 1996. The Population Council established a non-profit corporation, American Health Technologies ("AHT"), to assist in the effort to bring the drug to the market.[24] The Population Council ultimately granted Danco Laboratories, LLC ("Danco"), which was incorporated in the Cayman Islands in 1995, "an exclusive license to manufacture, market, and distribute Mifeprex in the United States."[25] Danco, after a difficult search,[26] selected the Chinese drug manufacturer,

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[21] HHS Press Release, "Roussel Uclaf Donates U.S. Patent Rights for RU-486 to Population Council," (rel. May 16, 1994). Available at: <http://www.hhs.gov/news/press/pre1995pres/940516.txt>.

[22] *Id*. ("Shalala commended Roussel Uclaf and the Population Council for coming to closure after months of complex negotiations amid repeated urging from the Clinton administration.")

[23] *See* William J. Eaton, "Path Cleared for Abortion Pill Use Medicine: French Maker of RU-486 Gives Patent Rights to a Nonprofit Group," *Los Angeles Times*, May 17, 1994, at A1 ("Negotiations between the French manufacturer and the Population Council dragged on for more than a year until Shalala set a May 15 deadline, producing the agreement . . . .").

[24] Dr. Susan Allen, who once served as president and CEO of American Health Technologies, joined the staff of the Reproductive and Urologic Drug Products Division in FDA's Center for Drug Evaluation and Research in 1998 as a medical officer and was promoted to team leader for reproductive drugs in January 1999. *See* "RU-486 Action Date Is Sept. 30; Allen Named Reproductive Division Director," *The Pink Sheet* 62 (June 12, 2000): at 14. Dr. Allen became acting director of the Division in January 2000 and permanent director on June 18, 2000. *See id. The Pink Sheet* also commented, "Allen is presumably recused from the mifepristone review as a result of her prior experience with the product." *Id*.

[25] Danco, "The History of Mifeprex,"available at <http://www.earlyoptionpill.com/history.php3>. (Danco has dubbed mifepristone "the Early Option Pill" for marketing purposes.) Little information about Danco is available. *See* Robert O'Harrow, "RU-486 Marketer Remains Elusive," *Washington Post* (Oct. 12, 2000): at A18 ("Secretive and obscure, Danco is one of the most enigmatic companies in the pharmaceutical industry."). Danco is apparently a successor entity to Advanced Health Technology. *See* "RU-486 Action Date Is Sept. 30; Allen Named Reproductive Division Director," *The Pink Sheet* 62 (June 12, 2000): at 14 (reporting that Advanced Health Technologies had become Neogen, which, in turn, had become Danco, according to the Population Council and Danco, "with some management and investor changes").

[26] In 1995 Danco contracted with a Hungarian pharmaceutical firm, Gideon Richter, to manufacture mifepristone for American distribution. After Gideon Richter reneged on the contract in February 1997, Danco sued Gideon Richter for breach of contract and began searching for a new producer. *See* "Ru-486: U.S. Partners Sue European Manufacturer," *Kaiser Daily Reproductive Health Report* (June 12, 1997) (available at: <http://www.kaisernetwork.org/reports/1997/06/a970612.1.html>). This was one of a number of lawsuits stemming

Shanghai Hua Lin Pharmaceutical Company, to manufacture the drug.[27] Abortion advocates eagerly awaited the approval of mifepristone in the United States because, among other reasons, they anticipated that it would enhance women's access to abortion.[28]

2. FDA Approval of Mifepristone

The Population Council filed a new drug application for "mifepristone 200 mg tablets" on March 18, 1996.[29] FDA initially accorded the drug standard review, but in a letter dated May 7, 1996, FDA's Center for Drug Evaluation and Research notified the Population Council that mifepristone would receive priority review.[30] On September 18, 1996, FDA issued a letter

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from attempts to bring mifepristone to the United States. *See* "Ru-486: Litigation Could Cause Delay For U.S. Introduction," *Kaiser Daily Reproductive Health Report* (Dec. 17, 1996) (available at: <http://www.kaisernetwork.org/reports/1996/12/a961217.9.html>) (describing some of the legal problems encountered by the Population Council in bringing the drug to market).

[27] Pamela Wiley, "Chinese Plant to Make RU-486 for U.S.," (Oct. 15, 2000) (available at: <http://www.nurseweek.com/news/00-10/1015-486.asp>).

[28] *See* Margaret Talbot, "The Little White Bombshell," *New York Times Magazine* (July 11, 1999): at 39-43 ("'One of my real, and I think realistic, hopes for this method,' says Carolyn Westhoff, an OB-GYN at Columbia University medical school who offers medical abortion as part of a clinical trial, 'is that it will help get abortion back into the medical mainstream and out of this ghettoized place it's been in.' And if that is indeed the scenario we're looking at – a scenario in which abortion is folded far more seamlessly into regular medical practice – then it has implications not only for women's experience of abortion but for the politics of abortion as well."); *id.* ("Not only are mifepristone abortions, by nature, more discreet than their surgical equivalents (like vacuum aspiration), but the practitioners who prescribe them will almost certainly constitute a larger and a more varied group than the dwindling corps of OB-GYNs willing to do surgical abortions.") In fact, access to medical abortion, will continue to depend on the availability of surgical abortion, which serves as a back-up in FDA's approved Mifeprex regimen. Thus, it is spurious to suggest that Mifprex abortions can safely be made available in places in which surgical abortion is not offered.

[29] The application was dated March 14, 1996 and received by FDA on March 18, 1996. *See* Letter, FDA/CDER to Ann Robbins, Population Council (Sept. 18, 1996): at 1 ("1996 Mifepristone Approvable Letter").

[30] *See* Letter, FDA/CDER to Ann Robins, Population Council (May 7, 1996)[FDA FOIA Release: MIF 006431]. The Population Council filed its complete response on March 30, 2000, which gave FDA until September 30, 2000 to act on the application. In fiscal year 2000 a "standard" designation would have given FDA at least ten months to consider the application. FDA accorded mifepristone "priority review," which typically required FDA to act within six months. *See* FDA/CDER, "PDUFA Reauthorization Performance Goals and Procedures" (Nov. 16, 1997) (available at: <http://www.fda.gov/cder/news/pdufagoals.htm>) ("Fiscal Year 2000"). Of 98 approvals in 2000, only 20 were Priority Review drugs. *See* FDA/CDER, *Report to the Nation* (2000): at 6. FDA's use of priority review appears inappropriate when considered in light of the agency's current guidance on the issue, which states that priority review is appropriate when "[t]he drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease." *See* FDA/CDER, "Review Management: Priority Review Policy," Manual of Policies and Procedures (MAPP) 6020.3, at 1 (Apr. 22, 1996) (text bracketed as in original).

stating that the application was approvable and requested more information from the sponsor.[31] FDA issued a second approvable letter for mifepristone, dated February 18, 2000, setting forth the remaining prerequisites for approval.[32] The 2000 Mifepristone Approvable Letter announced that FDA had "considered this application under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) and [had] concluded that restrictions as per [21] CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product."[33]

On September 28, 2000, FDA approved mifepristone ("Mifeprex™") "for the medical termination of intrauterine pregnancies through 49 days' pregnancy."[34] Mifeprex was approved under Subpart H, which, FDA explained, "applies when FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with certain skills or experience."[35] The approved regimen requires at least three office visits.[36] FDA required the Population Council to include, on the Mifeprex Label, a "black box warning for special problems, particularly those that may lead to death or serious injury."[37]

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[31] 1996 Mifepristone Approvable Letter at 1.

[32] 2000 Mifepristone Approvable Letter at 1.

[33] 2000 Mifepristone Approvable Letter at 5.

[34] Letter, FDA/CDER to Sandra P. Arnold, Population Council (Sept. 28, 2000): at 1 ("Mifeprex Approval Letter"). In conjunction with the Mifeprex Approval Letter, FDA issued a memorandum that expanded upon the basis for and the restrictions on the approval of Mifeprex. *See* Memorandum, FDA/CDER to "NDA 20-687 MIFEPREX (mifepristone) Population Council" (Sept. 28, 2000): at 6 ("Mifeprex Approval Memo").

[35] Mifeprex Approval Memo at 6.

[36] Pursuant to the approved regimen, on "Day One: Mifeprex Administration" the patient reads the Medication Guide, signs the Patient Agreement, and ingests 600 mg of Mifeprex; on "Day Three: Misoprostol Administration" the patient ingests 400 micrograms of misoprostol orally (unless abortion has occurred and been confirmed by clinical examination or ultrasonographic scan); and, on or about "Day 14: Post-Treatment Examination" the patient returns to the practitioner for verification through a clinical examination or ultrasound that the pregnancy has been successfully terminated. *See* Mifeprex Label ("Dosage and Administration")(available at: <http://www.fda.gov/cder/foi/label/2000/20687lbl.pdf>).

[37] Mifeprex Approval Memo at 2 (citing 21 CFR 201.57(e), which authorizes FDA to require such a warning). The terms "label," "labeling," and "package insert" are often used interchangeably in food and drug law literature. In this Petition, "Label" describes the fine-print "package insert" that accompanies a drug when it is purchased. However, the FD&C Act defines "label" as "a display of written, printed, or graphic matter upon the immediate container of any article . . . ." 21 U.S.C. § 321(k). The term "labeling," which will also appears in this Petition,

FDA also outlined the Population Council's post-approval, Phase IV study commitments[38] and waived, without explanation, FDA's regulations providing that all new drugs must be tested for safety and effectiveness in children.[39]

C. BACKGROUND ON FDA'S DRUG APPROVAL PROCESS

1. FDA's Default Rules for Establishing Drug Safety and Effectiveness

FDA's regulations state that "[t]he purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."[40] FDA's default criteria for establishing safety and effectiveness are commonly referred to as the agency's "gold standard."[41] At the core of this default standard is FDA's recognition, reflecting the development of the scientific method and its application to pharmacology, that human bias and misperceptions are pervasive and that every precaution must be taken to avoid them. "The history of experimental medicine and research psychology," Michael Greenberg writes, "had demonstrated that uncontrolled, unblinded clinical trials were systematically vulnerable to experimenter bias, placebo effects, and the like."[42] Consequently, rigorous policies have been set forth by FDA and,

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encompasses "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). "Labeling" may even describe promotional materials used by the drug manufacturer including "[b]rochures, booklets, mailing pieces, . . . price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, . . . and reprints and similar pieces of printed, audio or visual matter descriptive of a drug and references published (for example, the Physician's Desk Reference) for use by medical practitioners, pharmacists, or nurses . . . ." 21 C.F.R. § 202.1(l)(2). FDA has provided more information on this terminology at: <http://www.fda.gov/cder/handbook/adverdef.htm>.

[38] *See* Mifeprex Approval Memo at 7.

[39] *See* FDA Mifeprex Approval Letter at 3.

[40] 21 C.F.R. § 314.126(a).

[41] *See* Jennifer Kulynych, "Will FDA Relinquish the 'Gold Standard' for New Drug Approval? Redefining 'Substantial Evidence' in the FDA Modernization Act of 1997," *Food and Drug Law Journal* 54 (1999): 127-149, at 129. We will refer to these criteria as the "default standard."

[42] Michael D. Greenberg, "AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process," *Legislation and Public Policy* 3 (2000): 295-350, at 308.

more recently, by the International Conference on Harmonisation ("ICH") to eliminate bias from the evaluation of drug safety and effectiveness.[43]

FDA has been criticized for its zealous implementation of this policy,[44] but there is widespread recognition of the value of the default standard. The 1962 statutory amendments to the FD&C Act "authorized the agency to review all NDAs, not only to assess drug safety, but also to determine whether a manufacturer has provided 'substantial evidence' from 'adequate and well-controlled investigations' that a drug is effective for its intended use."[45] In implementing regulations, FDA "required that the evidence include at least one (and usually two) well-controlled (preferably 'blind') trials showing statistically significant results for treatment of humans with the new drug."[46] "[B]arring unusual circumstances, the agency ordinarily requires two successful and well-controlled clinical trials for new drug approval."[47] FDA's mandate for clinical trials "has two very important elements:"

> (1) a "controlled" trial, in which an experimental drug is compared to a placebo, or a known effective treatment in order to establish the comparative efficacy of the drug, and (2) a "double-blind" trial, which involves random assignment of research subjects to the

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[43] FDA, "International Conference on Harmonisation; Guidance on General Considerations for Clinical Trials," *Notice*, 62 Fed. Reg. 66113 (Dec. 17, 1997) (*FDA Guidance (ICH: E8): General Considerations*). The homepage, (www.ich.org), for the ICH describes the organization as follows: "The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health."

[44] *See, e.g.*, Henry I. Miller, "Failed FDA Reform," *Regulation* 21 (Summer 1998): 24-30.

[45] Kulynych, *infra* Appendix A, at 129 (citing 21 U.S.C. § 355(d)).

[46] Greenberg, *infra* Appendix A, at 307 (citing 21 C.F.R. § 314.126 (1999). FDA comprehensively revised NDA evaluation rules in what is commonly referred to as the "NDA Rewrite." *See Final Rule*, "New Drug and Antibiotic Regulations," 50 Fed. Reg. 7452 (Feb. 22, 1985). Section 314.126 was promulgated in that final rule. *Id*. at 7506-7.

[47] Kulynych, *infra* Appendix A, at 130.

> experimental and control groups, under conditions in which neither the doctors nor the research subjects know who is getting the experimental drug and who the control.[48]

Each of the mandated features helps to eliminate bias in trial results. First, in "double-blinded" studies neither the patient nor the provider team (physician, nurse, etc.) knows the identity of the drug administered. If that is not possible, the person evaluating the trial results will not know which treatment has been administered to which subject. Second, a "randomized" study requires a random determination of which subject receives which treatment. This determination is often effected through computer-generated assignments done before clinical testing begins. Finally, comparison-control (also known as "comparator-control") requires that the experimental drug be compared *concurrently* to the current best treatment, or, alternatively, to a placebo. A placebo is used when the drug being tested represents the first treatment of its kind for the particular indication and no established treatment exists.

2. FDA Initiatives to Expedite the Approval of Drugs for the Very Sick

Largely in response to FDA's perceived slowness in approving drugs for human immunodeficiency virus ("HIV") patients, the agency undertook several initiatives to either expedite the ability of seriously or terminally-ill patients to have access to experimental drugs or to provide processes "intended to move drugs to market more quickly by compressing clinical development and FDA review times."[49] In 1988, FDA adopted an interim rule establishing Subpart E of 21 C.F.R. Part 312 ("Drugs Intended to Treat Life-Threatening and Severely-

[48] Greenberg, *infra* Appendix A, at 307-8 (footnotes omitted).

[49] Sheila R. Shulman and Jeffrey S. Brown, "The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?" *Food and Drug Law Journal* 50 (1995): 503-531, at 503-4.

Debilitating Diseases").[50] Subpart E embodied several of the new procedures that FDA had used to bring the HIV medication, AZT (zidovudine), to market quickly.[51] Subpart E also created a "collaborative framework in which early and repeated consultation between the FDA and pharmaceutical manufacturers served to facilitate clinical trials, and to insure ex ante that prospective research designs would meet with subsequent regulatory approval."[52] "Taken together," the innovations found in Subpart E, "served to radically alter the new drug approval process with regard to life-threatening illnesses, particularly for AIDS."[53]

On April 15, 1992, FDA took its procedural innovations further when it proposed an "Accelerated Approval" process (*i.e.*, Subpart H). Shulman and Brown believe that Subpart H "represent[ed] the most significant departure from the traditional FDA standards for drug approval."[54] Subpart H's "major point of departure" from previously existing approval regimes was its focus on granting drug approval "on the basis of the drug's effect on a surrogate endpoint that is reasonably likely to predict clinical benefit over time."[55] A "surrogate end point" or "surrogate marker" is "a laboratory parameter or physical sign that is used in a clinical trial as a substitute for a clinically meaningful end point, such as mortality."[56] The value of surrogate

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[50] *See Interim Rule*, "Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses," 53 Fed. Reg. 41,516 (Oct. 21, 1988). The Subpart E rules may be found at 21 C.F.R. §§ 312.80-88.

[51] *See* Greenberg, *infra* Appendix A, at 321.

[52] Greenberg, *infra* Appendix A, at 321 (citation omitted).

[53] Greenberg, *infra* Appendix A, at 323.

[54] Shulman and Brown, *infra* Appendix A, at 514.

[55] Shulman and Brown, *infra* Appendix A, at 514. Likewise, Greenberg observed that the "essential element of the accelerated approval regulations [*i.e.*, Subpart H] was the provision that 'surrogate endpoints' could be employed as the empirical basis for FDA approval of a new drug." Greenberg, *infra* Appendix A, at 323 (citation omitted).

[56] Dennis F. Thompson, "Surrogate End Points, Skepticism, and the CAST Study," editorial, *Annals of Pharmacotherapy*, 36 (Jan. 2002): 170-71, at 170 (citations omitted).

endpoints lies in their ability to predict clinical outcomes.[57] As "examples of surrogate end points that have been proven to be excellent predictors of clinical outcomes and, hence, have saved both money and precious time expediting drugs to the patient care arena," Dean Dennis Thompson cites "a diverse group of antihypertensive drugs approved on the basis of reduced blood pressure effects [that] has shown clear benefits in reducing cardiovascular events and mortality."[58] With the passage of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"), Congress effectively codified Section 314.510, the surrogate endpoint provision of Subpart H.[59]

Neither Shulman and Brown nor Greenberg focused on a second type of drug approval included in Subpart H – codified now at 21 C.F.R. § 314.520.[60] This second avenue for Subpart H approval is reserved for circumstances in which "FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted."[61] Pursuant to this provision "FDA may approve a treatment subject to special

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[57] *See* Thompson, *infra* Appendix A, at 170.

[58] Thompson, *infra* Appendix A, at 170.

[59] This codification was part of Congress's major reauthorization and modernization of the Federal Food, Drug & Cosmetic Act. Section 506(b) of FDAMA (21 U.S.C. § 356) "in effect, codifie[d] in statute FDA's Accelerated Approval Rule . . . , made final in 1992, which allows expedited marketing of certain new drugs or biological products intended to treat serious or life-threatening illnesses and that appear to provide meaningful therapeutic benefits to patients compared with existing treatments." FDA Centers for Drug Evaluation and Research and for Biologics Evaluation and Research, *Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review*, at 2 (Sept. 1998) (footnote omitted). While clearly codifying Subpart H's surrogate endpoint provision at 21 U.S.C. § 356(b)(1), Congress does not appear to have enacted a parallel provision to Section 314.520, which pertains to "restricted use" drugs, under which Mifeprex was approved.

[60] Section 314.520 (Approval with restrictions to ensure safe use.) states:

> (a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the drug product, such as:
> (1) Distribution restricted to certain facilities or physicians with special training or experience; or
> (2) Distribution conditioned on the performance of specified medical procedures.
> (b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

[61] *Subpart H Final Rule*, 57 Fed. Reg. at 58942.

distribution or use restrictions that address outstanding safety issues."[62] Section 314.520 balanced FDA's desire to bring clinically beneficial drugs to the market with the agency's concern that "[s]ome drugs, however, are so inherently toxic or otherwise potentially harmful that it is difficult to justify their unrestricted use."[63] The agency explained "that some clinically beneficial drugs can be used safely only if distribution and use are modified and restricted."[64]

Section 314.520 is intended for drugs that are vitally necessary, but which may impose greater than normal risks for the patient.[65] FDA was willing "to approve such high risk drugs for early marketing if the agency can be assured that postmarketing restrictions will be in place to counterbalance the known safety concerns."[66] Postmarketing restrictions would be designed "to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction."[67] FDA intended to employ restrictions on distribution "only in those rare instances in which the agency believes carefully worded labeling for a product granted accelerated approval will *not* assure the product's safe use."[68] In the absence of restrictions, which "may vary with the circumstances of each drug[,] . . . the drug would be adulterated under Section 501 of the act, misbranded under Section 502 of the act, or not shown to be safe under Section 505 of the act."[69] In short, "[w]ithout such restrictions, the drugs would not meet the statutory criteria,

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[62] Geoffrey M. Levitt, James N. Czaban, and Andrea S. Paterson, "Chapter 6: Human Drug Regulation" in *Fundamentals of Law and Regulation: An In-Depth Look at Therapeutic Products* (David G. Adams, Richard M. Cooper, and Jonathan S. Kahan, eds.), vol. II (Washington, D.C.: Food and Drug Law Institute, 1997): at 200.

[63] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[64] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[65] Of course, "[v]irtually all drug[s] can be toxic to humans, and no drug is completely free of risk," but, as the seriousness of an illness and the effect of the drug on that illness increase, "the greater the acceptable risk from the drug." *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[66] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13237.

[67] *Subpart H Final Rule*, 57 Fed. Reg. at 58952.

[68] *Subpart H Final Rule*, 57 Fed. Reg. at 58952 (emphasis added).

[69] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13237.

could not be approved for distribution, and would not be available for prescribing or dispensing."[70] Mifeprex was the third of four drugs approved pursuant to Section 314.520.[71]

D. FDA'S APPROVAL OF MIFEPREX UNDER ITS ACCELERATED APPROVAL REGULATIONS (SUBPART H) WAS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

FDA's accelerated approval regulations (Subpart H) apply to certain new drug products "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)"[72] When it proposed Subpart H in 1992, FDA observed that the following types of illness would fall within the reach of Subpart H:

> The terms "serious" and "life-threatening" would be used as FDA has defined them in the past. The seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Thus, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's dementia, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Further, many chronic illnesses that are generally well-managed by available therapy can have serious outcomes. For example, inflammatory bowel disease,

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[70] *Subpart H Final Rule*, 57 Fed. Reg. at 58951. The agency continued: "The agency, as a matter of longstanding policy, does not wish to interfere with the appropriate practice of medicine or pharmacy. In this instance, the agency believes that rather than interfering with physician or pharmacy practice, the regulations permit, in exceptional cases, approval of drugs with restrictions so that the drugs may be available for prescribing or dispensing." *Id*. at 58951-52.

[71] On June 7, 2002, the drug Lotronex (alosetron hydrochloride) was reintroduced to the market after a *Supplemental* NDA was approved pursuant to Subpart H's redistricted distribution provision. *See* Letter, FDA/CDER, Florence Houn, M.D., Director, Office of Drug Evaluation III to Olivia Pinkett, Product Director, Regulatory Affairs, GlaxoSmithKline (June 7, 2002): at 1 ("This supplemental application, considered for approval under 21 CFR 314, Subpart H at your request, narrows the original approved indication to use of the drug in a population for whom the benefits of the drug may outweigh the risks and provides for a risk management program. . . . You have indicated your agreement with approval under restricted conditions.").

[72] 21 C.F.R. § 314.500. The rule was amended in 1999 to remove the words "and antibiotic." *See* Conforming Regulations Regarding Removal of Section 507 of the Federal Food, Drug, and Cosmetic Act, *Final Rule*, 64 Fed. Reg. 396, 402 (Jan. 5, 1999).

> asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus, erythematosus, depression, psychoses, and many other diseases can be serious for certain populations or in some or all of their phases.[73]

According to FDA, the agency has approved 38 NDAs, including the Mifeprex application, under Subpart H.[74] Of these approvals, 20 were for the treatment of HIV and HIV-related diseases, nine were for the treatment of various cancers and their symptoms, four were for severe bacterial infections, one was for erythema nodosum leprosum (leprosy), one was for hypotension, and, finally, one was for the termination of unwanted pregnancies.[75]

Pregnancy, without major complications, is not a "serious or life-threatening illness" for purposes of Subpart H. It is, rather, a normal physiological state experienced by most females one or more times during their childbearing years, and it is rarely accompanied by complications that threaten the life of the mother or the child. Following delivery, almost all women return to a normal routine without disability. Thus, pregnancy is not the kind of exceptional circumstance that falls within the scope of Subpart H. The fact that the Mifeprex Regimen is intended for healthy women provides further evidence of this point.

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[73] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13235. In the *Subpart H Final Rule*, FDA asserted that "serious and life-threatening illnesses" would be readily identifiable: "FDA discussed the meaning of the terms 'serious' and 'life-threatening' in its final rules on 'treatment IND's' (52 FR 19466 at 19467, May 22, 1987) and 'subpart E' procedures (54 FR 41516 at 41518-41519, October 21, 1988). The use of these terms in this rule is the same as FDA defined and used the terms in those rulemakings. It would be virtually impossible to name every 'serious' and 'life-threatening' disease that would be within the scope of this rule. In FDA's experience with 'treatment IND's' and drugs covered by the 'subpart E' procedures there have not been problems in determining which diseases fall within the meaning of the terms 'serious' and 'life-threatening,' and FDA would expect no problems under this accelerated approval program." *Subpart H Final Rule*, 57 Fed. Reg. at 58945.

[74] These estimates are based on the version of FDA's webpage, dated February 5, 2002, listing Subpart H approvals, *infra* Appendix A.

[75] *See* FDA/CDER webpage, "NDAs Approved under Subpart H," *infra* Appendix A. A copy of the most recently available version is reproduced in Appendix C (available at: <http://www.fda.gov/cder/rdmt/accapp.htm>). *See also* "NDA Supplements Approved under Subpart H" (available at: <http://www.fda.gov/cder/rdmt/accappr1.htm>) (supplemental approvals are not included in the figures set forth in the text because they refer to FDA actions regarding drugs that have already been approved).

In fact, the Population Council argued strenuously that its application for mifepristone did not fall within the scope of Subpart H.[76] In a letter to FDA written approximately three weeks before the final approval of the mifepristone NDA, the Population Council's Sandra P. Arnold protested, ". . . it is clear that the imposition of Subpart H is unlawful, unnecessary, and undesirable. We ask FDA to reconsider."[77] Arnold argued correctly that "[n]either pregnancy nor unwanted pregnancy is an illness, and Subpart H is therefore inapplicable for that reason alone."[78] She continued, stating, "Neither is pregnancy nor unwanted pregnancy a 'serious' or 'life-threatening' situation as that term is defined in Subpart H."[79] In the next paragraph, after directly quoting the *Supbart H Final Rule*, Ms. Arnold asserted that "[t]he plain meaning of these terms does not comprehend normal, everyday occurrences such as pregnancy and unwanted pregnancy."[80] She added that, unlike HIV infection, pulmonary tuberculosis, cancer, and other illnesses, "pregnancy and unwanted pregnancy do not affect survival or day-to-day functioning as those terms are used in Subpart H."[81] She continued that, "although a pregnancy 'progresses,'" the development of a pregnancy "is hardly the same as the worsening of a disease that physicians call progression."[82]

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[76] The Population Council appears to have been concerned about getting the drug approved "without invoking the Subpart H regulatory provisions that signal 'big deal' to the pharmaceutical industry." Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 6, 2000): at 4 [FDA FOIA Release: MIF 001333-49]("Sandra Arnold Letter"). Sandra Arnold was "Vice President, Corporate Affairs" of the Population Council.

[77] Sandra Arnold Letter at 1.

[78] Sandra Arnold Letter at 1-2.

[79] Sandra Arnold Letter at 2.

[80] Sandra Arnold Letter at 2.

[81] Sandra Arnold Letter at 2.

[82] Sandra Arnold Letter at 2. Ms. Arnold also warned the agency that extending the scope of Subpart H to include pregnancy and unwanted pregnancy by exercising agency "judgment" was not defensible; the exercise of such judgment should go to whether or not "a particular disease actually is serious, not [act as] a means of stretching the meaning of serious to cover entirely new categories of non-serious situations." *Id*.

Additionally, Mifeprex fails to meet the second requirement set forth in Section 314.500 that drugs approved under Subpart H "provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)" As was noted above, the Mifeprex Approval Memo contends "that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H [and] [t]he meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure."[83] By defining the "therapeutic benefit" solely as the avoidance of the current standard of care's delivery mechanism, FDA effectively guarantees that a drug will satisfy this second prong of Subpart H as long as it represents a different method of therapy.[84] It does not appear that such considerations formed the basis of any other Subpart H approval.

When FDA adopted Subpart H, it cited as "readily understood illustrations of the intent of the [meaningful therapeutic benefit] requirement" an "improved response compared to available therapy" and the "ability to treat unresponsive or intolerant patients."[85] Based on these illustrations, Mifeprex does not fall within the intent of the requirement. First, there is a less dangerous, more effective alternative to Mifeprex available for the termination of pregnancies: namely, surgical abortions. Dr. Jeffrey Jensen conducted a study to compare the safety and

[83] Mifeprex Approval Memo at 6.

[84] The view that merely making a different mode of therapy available *per se* produces a benefit is inconsistent with the position the agency has articulated elsewhere. MAPP 6020.3, which defines eligibility for FDA priority review, suggests that drug therapies are not inherently superior to non-drug therapies. Specifically, a drug may be afforded priority review if it would provide a significant improvement when compared with "marketed products . . . including non-"drug" products/therapies." *See* FDA/CDER, "Review Management: Priority Review Policy," MAPP 6020.3, at 1 (Apr. 22, 1996).

[85] *Subpart H Final Rule*, 57 Fed. Reg. at 58947.

efficacy of medical abortion with that of surgical abortion.[86] The study compared 178 patients who, as participants in the U.S. clinical trial in support of the Mifeprex NDA, underwent mifepristone/misoprostol abortions, with 199 patients who later received surgical abortions at the same clinical site. The primary procedure failed (*i.e.*, there was a subsequent surgical intervention) in 18.3 percent of the mifepristone/misoprostol patients and 4.7 percent of the surgical patients.[87] Of the mifepristone/misoprostol patients who failed their primary procedure, 12.5 percent required surgical intervention for acute bleeding, 43.8 percent for persistent bleeding, 15.6 percent for incomplete abortion, and 28.1 percent for ongoing pregnancy.[88] By contrast, the sole cause for surgical intervention among the surgical patients who failed their primary procedure was persistent bleeding.[89] In addition, mifepristone/misoprostol patients "reported significantly longer bleeding" and "significantly higher levels of pain . . . , nausea . . . , vomiting . . . , and diarrhea" than their surgical counterparts.[90]

Second, Mifeprex does not treat a subset of the female population that is unresponsive to, or intolerant of surgical abortion. To the contrary, because "medical abortion failures should be managed with surgical termination" the option for surgical abortion must be available for any Mifeprex patient.[91] As the U.S. trial conducted in support of the NDA indicated, the possibility

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[86] Jeffrey T. Jensen, Susan J. Astley, Elizabeth Morgan, and Mark D. Nicols, "Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study," *Contraception* 59 (1999): 153-159 ("Jensen Study")[FDA FOIA Release: MIF 000438-44].

[87] *See* Jensen Study, *infra* Appendix A, at 155, Table 2.

[88] *See* Jensen Study, *infra* Appendix A, at 156, Table 3.

[89] *See* Jensen Study, *infra* Appendix A, at 156, Table 3.

[90] Jensen Study, *infra* Appendix A, at 156.

[91] Mifeprex Label ("Warnings").

for failure is substantial.[92] Thus, any patient who would be intolerant of surgical abortion, if such a class of patients exists, cannot use the Mifeprex Regimen.

As discussed below, FDA approved Mifeprex pursuant to Section 314.520 in order to impose safety restrictions to counteract the risks it had identified. FDA, confronted by the sponsor's refusal to establish voluntary restrictions on distribution,[93] viewed Subpart H as the only available regulatory vehicle that had the potential to make Mifeprex safe.[94] The inappropriate application of Section 314.520 served the agency's immediate need of conditioning the drug's approval on certain safety measures. However, Mifeprex fails to satisfy the Subpart H requirements because, although it presents great risk to the user, it neither treats a serious or life-threatening illness nor provides a therapeutic benefit above existing treatments. A drug with such characteristics should not have been approved.

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[92] FDA, "Medical Officer's Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments," at 11 (Table 1) (reporting a failure rate of 8% for pregnancies less than or equal to 49 days' duration) ("Medical Officer's Review").

[93] Early in the approval process, FDA anticipated that the Population Council would cooperate, thus obviating the need for Subpart H restrictions: "[B]ecause the applicant has voluntarily proposed a system of limited distribution, imposition of further distribution restrictions under the Agency's Subpart H regulations does not appear warranted." *See* Memorandum, FDA/CDER to NDA 20-687 File (Sept. 16, 1996): at 2 [FDA FOIA Release MIF 000560-62]. The voluntary restrictions placed on the drug Accutane, a drug for severe acne, illustrate that a cooperative drug sponsor may be able to obviate the need for Subpart H restrictions. Because Accutane can cause birth defects, the restrictions are designed to ensure that women taking the drug are not and do not become pregnant. The "System to Manage Accutane Related Teratogenicity™ (S.M.A.R.T.™)," controls the distribution of the drug through the issuance of yellow Accutane Qualification Stickers. These stickers are distributed to physicians who meet a number of qualifications and they, in turn, distribute them to patients, who must undergo two tests to confirm they are not pregnant and must commit to use two forms of contraception. Pharmacists may fill prescriptions for the drug only if they bear the qualification sticker, were issued within the past week, and prescribe no more than 30 days' worth of the drug. *See* Accutane Label.

[94] This interpretation of the agency's actions is supported by FDA spokeswoman Crystal Rice, who said "that outside of Subpart H, the FDA does not have another regulatory program to mandate safety restrictions on drug marketing for drugs used to treat 'serious or life-threatening illnesses'" and "that 'other agreements [or restrictions on the drug] not under Subpart H worked out between FDA and a sponsor would be essentially voluntary.'" "Danco Medical Director Explains Mifepristone's FDA Approval Not Fast-Tracked or Accelerated, Despite Media Reports," *Kaiser Daily Reproductive Health Report* (March 29, 2001) (available at: <http://report.kff.org/archive/repro/2001/3/kr010329.5.htm>).

E. THE CLINICAL TRIALS DID NOT PRESENT "SUBSTANTIAL EVIDENCE" THAT THE MIFEPREX REGIMEN IS SAFE AND EFFECTIVE

FDA's approval of the Mifeprex NDA ran counter to Congress's statutory requirements, the agency's regulations and guidance documents, and FDA's well-established standards for the quality and quantity of scientific evidence needed to support an agency finding that a new drug is safe and effective. The clinical trials submitted by the Population Council to support its NDA did not use the full set of design features FDA typically requires to produce unbiased investigations of drug safety and effectiveness. Because these trials were not blinded, randomized, or concurrently controlled, they did not establish the safety and effectiveness of the Mifeprex Regimen. Inexplicably, FDA failed to perform a statistical analysis of the data from the American trial. Furthermore, FDA's approval of Mifeprex pursuant to Subpart H compounds the deficiencies in the trials because sponsors of Subpart H drugs must demonstrate that the drug for which approval is being sought provides a "meaningful therapeutic benefit over existing therapy." Because Mifeprex was approved in reliance on French and American trials that did not compare the Mifeprex Regimen with the existing standard of care for ending pregnancies (*i.e.*, surgical abortion), the trials cannot support this Subpart H approval.

1. The Clinical Trials Underlying FDA's Approval of Mifeprex

FDA based its approval of Mifeprex on safety and effectiveness data derived from two French clinical trials ("French Clinical Trials") and one U.S. clinical trial ("U.S. Clinical Trial").[95] Neither the French Clinical Trials nor the U.S. Clinical Trial was blinded, randomized,

[95] *See* Mifeprex Approval Memo, *infra* Appendix A, at 1.

or concurrently controlled – the hallmarks of unbiased, scientific analysis generally relied upon by FDA.

a. The French Clinical Trials

The French Clinical Trials, which formed the basis for the Population Council's original NDA submission in 1996, were open-label, multi-center studies.[96] One of these trials consisted of 1,286 patients at 24 centers in France ("French Trial I").[97] The trial was limited to women who had pregnancies of no more than 49 days' gestational age, as established by ultrasound, if available, or by the patient's estimate.[98] On the first day of the procedure, the patient received 600 mg of mifepristone orally "in the presence of a study investigator."[99] Approximately 48 hours later, she returned and, unless the abortion had already taken place, ingested 400 micrograms of misoprostol "in the presence of a study investigator."[100] The patient remained under observation for four hours or more after the ingestion of misoprostol and returned for "a final assessment of the pregnancy termination procedure" eight to 15 days later.[101]

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[96] FDA's Reproductive Health Drugs Advisory Committee ("FDA Advisory Committee"), which met in July 1996 to consider the mifepristone NDA, based its conclusion primarily on the French trial along with preliminary data from the U.S. Clinical Trial. *See* FDA Advisory Committee, *Hearings on New Drug Application for the Use of Mifepristone for Interruption of Early Pregnancy*, at 6, 132-33 (July 19, 1996) (*FDA Hearings Transcript*)[FDA FOIA Release: MIF 005200-90]. Committee member Dr. Mary Jo O'Sullivan asked why the Committee meeting was being held "at this time when the data is not finalized." *Id.* at 37. Dr. C. Wayne Bardin, who was responsible for overseeing the Population Council's NDA preparation, responded that "we have sufficient data . . . [f]rom the non-U.S. data to allow us to submit an application to the FDA." *Id.*

[97] *See* FDA, Statistical Review and Evaluation, at 2-4 (May 21, 1996) ("Statistical Review"). This French trial is referred to as FFR/91/486/14.

[98] *See* Statistical Review, *infra* Appendix A, at 2. "Since the ultrasound estimate of gestational age was more reliable than the patient's estimate . . . gestational age based on the ultrasound examination was used if available." *Id.* Investigators, in violation of study protocol, included some women with pregnancies of more than 49 days. *See* Statistical Review, *infra* Appendix A, at 3.

[99] *See* Statistical Review, *infra* Appendix A, at 2.

[100] *See* Statistical Review, *infra* Appendix A, at 2.

[101] *See* Statistical Review, *infra* Appendix A, at 2.

The efficacy analysis of French Trial I encompassed only 1,205 patients, while the safety analysis included all 1,286 participants.[102] The regimen resulted in "complete expulsion" in 95.4 percent of the 1,189 participants whose pregnancies were 49 days or less.[103] The rate of complete expulsion declined with increased gestational age.[104] Sixty-one women had complete expulsions before taking misoprostol.[105] Almost 86 percent of patients in French Trial I experienced at least one adverse event as a result of the procedure.[106]

The second French clinical trial ("French Trial II") enrolled 1,194 patients at 11 centers.[107] The trial was limited to women who had pregnancies of no more than 63 days' gestational age, as established by ultrasound, if available, or by the patient's estimate.[108] The regimen used in French Study II was essentially the same as that described above in connection with French Study I, except that an additional 200 micrograms of misoprostol was administered if complete expulsion did not occur within three hours after taking the initial 400 microgram dose of misoprostol.[109] Patients who received the second dose of misoprostol remained under observation for a total of five hours.[110]

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[102] *See* Statistical Review, *infra* Appendix A, at 3.

[103] *See* Statistical Review, *infra* Appendix A, at 3. Patients for whom expulsion of the embryo was complete at the end of the process were categorized as successes, while patients with incomplete expulsions (2.8%), ongoing pregnancies (1.5%), and those who needed surgical procedures for bleeding (.3%) were classified as failures. *See id.* at 3 and 9 (Table 1).

[104] *See* Statistical Review, *infra* Appendix A, at 3 ("[T]here was a statistically significant . . . inverse relationship between gestational age and the success rate as the success rate generally declined with increasing gestational age.").

[105] *See* Statistical Review, *infra* Appendix A, at 3. Twenty-six of these women received misoprostol anyway, because the investigators did not realize that they had had complete abortions. *See id.*

[106] *See* Statistical Review, *infra* Appendix A, at 4.

[107] *See* Statistical Review, *infra* Appendix A, at 4-7. This French trial is designated as FF/92/486/24.

[108] *See* Statistical Review, *infra* Appendix A, at 4-5.

[109] *See* Statistical Review, *infra* Appendix A, at 5.

[110] *See* Statistical Review, *infra* Appendix A, at 5.

The efficacy analysis of French Trial II encompassed only 1,104 patients, while the safety analysis included all 1,194 participants.[111] The regimen resulted in "complete expulsion" in 92.8 percent of the participants.[112] The rate of complete expulsion declined with increased gestational age.[113] Twenty-six women had complete expulsions before taking misoprostol.[114] Almost 93 percent of patients in French Trial II experienced at least one adverse event as a result of the procedure.[115]

Among the deficiencies that characterized both French Clinical Trials was the absence of an appropriate control group. Consequently, as an FDA statistician concluded after reviewing the data from the French Clinical Trials: "In the absence of a concurrent control group in each of these studies, it is a matter of clinical judgment whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy."[116]

b. The U.S Clinical Trial

The U.S. Clinical Trial was carried out from September 13, 1994 to September 12, 1995 at various qualified university hospitals and clinics.[117] Patients had to satisfy a number of criteria

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[111] *See* Statistical Review, *infra* Appendix A, at 5.

[112] *See* Statistical Review, *infra* Appendix A, at 6. As in French Study I, patients for whom expulsion of the embryo was complete at the end of the process were categorized as successes, while patients with incomplete expulsions (4.0%), ongoing pregnancies (2.3%), and those who needed surgical procedures for bleeding (.9%) were classified as failures. *See id.* at 5 and 12 (Table 4).

[113] *See* Statistical Review, *infra* Appendix A, at 6.

[114] *See* Statistical Review, *infra* Appendix A, at 6.

[115] *See* Statistical Review, *infra* Appendix A, at 7.

[116] Statistical Review, *infra* Appendix A, at 7-8.

[117] *See* Medical Officer's Review, *infra* Appendix A, at 6. More specifically, the U.S. Clinical Trial consisted of "two prospective, open-label, multicenter clinical trials in the United States according to two identical protocols." Medical Officer's Review, *infra* Appendix A, at 6 and 9. In this Petition, the trials will be referred to as "the U.S. Clinical Trial," because the protocols employed were identical, the results of the two trials were analyzed jointly, and the results were published in the same article. *See* Irving M. Spitz, M.D., C. Wayne Bardin, M.D., Lauri

to be included in the study.[118] All patients were screened by pelvic examination and ultrasound to ensure that their pregnancies were not too advanced for the procedure.[119] On their first visit, patients took 200 mg of mifepristone orally "[i]n the presence of the investigator."[120] Patients returned 36 to 60 hours later to ingest 400 micrograms of misoprostol orally in the presence of the investigator, unless the investigator determined that the termination was already complete.[121] Following ingestion of misoprostol, patients were observed for a minimum of four hours.[122] Patients were instructed to return again 12 days later for a follow-up assessment.[123] A patient's pregnancy was terminated surgically "at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion."[124]

Benton, M.D., and Ann Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," *New England Journal of Medicine* 338 (Apr. 30, 1998): 1241-47 ("Spitz Article") ")[FDA FOIA Release: MIF 006692-97]. The members of the FDA Advisory Committee who were still working for FDA at the time of publication received a copy of the Spitz Article. *See* Medical Officer's Review, *infra* Appendix A, at 29. Although FDA considered data from the entire U.S. Clinical Trial, it appears that the agency formally approved Mifeprex based only on the portion of the U.S. Clinical Trial data that was generated among women whose pregnancies were no more than 49 days' gestational age. *See* Mifeprex Approval Memo, *infra* Appendix A, at 1 ("The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period."). *See also* Mifeprex Label ("Clinical Studies").

[118] Among the inclusion criteria were requirements that a patient be at least 18 years old, be in good health, have an intrauterine pregnancy of no more than 63 days (confirmed by a pelvic examination *and* ultrasound), and have agreed to a surgical abortion if the mifepristone-misoprostol abortion failed. Medical Officer's Review, *infra* Appendix A, at 7-8. The study excluded women with certain health problems, such as liver, respiratory, or renal disease, cardiovascular disease, chronic hypertension, anemia, clotting problems, pelvic inflammatory disease, and ectopic pregnancies. *See id.* at 8. In addition, women who were over 35 and smoked, had IUDs, were breastfeeding, were unlikely to comply with study requirements, or who "[l]ived or worked more than one hour from the emergency care facility" were excluded. *See id.* at 8-9.

[119] *See* Medical Officer's Review, *infra* Appendix A, at 8.

[120] Medical Officer's Review, *infra* Appendix A, at 9.

[121] *See* Medical Officer's Review, *infra* Appendix A, at 9.

[122] *See* Medical Officer's Review, *infra* Appendix A, at 7.

[123] *See* Medical Officer's Review, *infra* Appendix A, at 7.

[124] Medical Officer's Review, *infra* Appendix A, at 16.

The U.S. Clinical Trial consisted of 2,121 subjects.[125] Of these patients, 2,015 were evaluated for efficacy,[126] which "was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure."[127] The remaining 106 patients did not return for the third visit.[128] The mifepristone-misoprostol combination was effective in 92 percent of patients with pregnancies no greater than 49 days, 83 percent of patients with pregnancies between 50 and 56 days, and 77 percent of women with pregnancies between 57 and 63 days.[129] All 2,121 subjects were evaluated for safety.[130] Ninety-nine percent of patients experienced adverse events and most of these experienced multiple adverse events.[131] Twenty-three percent of the adverse effects experienced by each gestational age group were "severe."[132]

Finally, FDA did not conduct a statistical review of the results of the U.S. Clinical Trial. FDA's statistical reviewer explained this failure by noting that "[a] statistical evaluation of the European studies was completed previously "and "[t]he clinical results of the supporting U.S.

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[125] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[126] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[127] Medical Officer's Review, *infra* Appendix A, at 16. The failure to establish a pre-trial, statistical definition for drug efficacy was a defect in trial design.

[128] *See* Medical Officer's Review, *infra* Appendix A, at 16. It would have been appropriate to include these 106 patients in the efficacy analysis as "failures," if for no other reason than that they did not appear for all three required visits. Although "[f]or 92 of these patients, there was some information suggesting a successful outcome," *id.* at 10, there was neither definitive evidence of complete abortion nor, apparently, any information with respect to whether these women subsequently experienced any adverse effects. In fact, during their second visit, five of these 106 women were diagnosed as having continuing pregnancies. *Id.* at 10. *See also* Spitz Article, *infra* Appendix A, at 1246 ("The ultimate outcome of these pregnancies is unknown, despite our repeated attempts to contact the women.").

[129] *See* Medical Officer's Review, *infra* Appendix A, at 11 (Table 1).

[130] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[131] *See* Medical Officer's Review, *infra* Appendix A, at 11.

[132] *See* Medical Officer's Review, *infra* Appendix A, at 11.

studies . . . are similar enough to the results of the European studies that, in the opinion of the medical reviewer, a statistical evaluation of the results of the U.S. studies is not required."[133]

2. Requirements for Proving Drug Safety and Effectiveness

FDA has developed a rigorous default standard for scientific demonstrations of safety and effectiveness of human drug products.[134] Section 505(d)(5) of the FD & C Act provides, in relevant part, that FDA shall refuse to approve a new drug application when "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."[135] Section 505(d) defines "substantial evidence" to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved . . . ."[136] FDA has stated that "substantial evidence" requires a showing of clinically significant evidence of effectiveness rather than mere statistical evidence of significance.[137] No such showing was made for Mifeprex, which has been demonstrated to be less effective than surgical abortion for all segments of the population.

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[133] FDA, "Statistical Comments on Amendment 024," Memorandum to File NDA 20-687 (Feb. 14, 2000). This document is available along with the agency's Statistical Review. *See* Statistical Review, *infra* Appendix A.

[134] *See* the discussion of the development and requirements of FDA's "gold standard," *supra* Section III.C.1.

[135] 21 U.S.C. § 355(d)(5).

[136] 21 U.S.C. § 355(d) ("the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.").

[137] *See Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 155 (D.C. Cir. 1986) ("It is important to note that the Commissioner does not contend that the effectiveness shown must amount to a 'medical breakthrough', as ARW complains, but contends in his brief that he would be satisfied with even a modest clinical or therapeutic effect.").

Section 314.126 of FDA's rules states that "[r]eports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs."[138] The rule states that a major purpose of an adequate and well-designed study is to "permit[ ] a valid comparison with a control to provide a quantitative assessment of drug effect."[139] According to Section 314.126(b), an adequate and well-controlled study serves to ensure that the subjects of the trial have the disease or condition being studied,[140] that the method of assigning patients to treatment and control groups minimizes bias (*e.g.*, using randomization),[141] and, that "[a]dequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data" (*e.g.*, blinding).[142] The criteria that the rule establishes "have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation."[143]

Agency guidance provides that FDA may approve an NDA based on only one, not two, effectiveness trials for drugs in one of the following three categories:

> 1) when effectiveness may be demonstrated adequately with existing studies of another claim or dose (e.g., approval for pediatric use on the basis of studies in adults); 2) when a controlled trial of a specific new use is supported by evidence from adequately controlled trials from related uses, dosages, or endpoints; and 3) when a single multicenter trial provides statistically convincing and clinically meaningful evidence of effectiveness, supported by confirmatory research.[144]

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[138] 21 C.F.R. § 314.126(a) ("Adequate and well-controlled studies.").

[139] 21 C.F.R. § 314.126(b)(2) (describing "placebo concurrent control," "dose-comparison concurrent control," "no treatment concurrent control," "active treatment concurrent control," and "historical control").

[140] 21 C.F.R. § 314.126(b)(3).

[141] 21 C.F.R. § 314.126(b)(4).

[142] 21 C.F.R. § 314.126(b)(5).

[143] 21 C.F.R. § 314.126(a).

[144] Kulynych, *infra* Appendix A, at 146 (citing FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) at 5-17 (*FDA Effectiveness Guidance*).

Mifepristone did not fall within any of these categories. The first and second categories were inapposite because mifepristone had not been approved for any use in any population in the United States; additionally, no evidence from adequate and well-controlled trials had ever been presented to FDA regarding any use for mifepristone. Because neither the French Clinical Trials nor the U.S. Clinical Trial was randomized, blinded,[145] or comparator-controlled, none of these trials could provide the type of data necessary for the third category either. Furthermore, these studies lacked "clear, prospectively determined clinical and statistical analytic criteria."[146]

Even though FDA takes the position elsewhere that the extent to which a trial's design controls for various types of bias "is a critical determinant of its quality and persuasiveness,"[147] neither the French Clinical Trials nor the U.S. Clinical Trial were randomized, concurrently controlled, or blinded. A control group "allow[s for] discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment."[148] Control groups also enable investigators to

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[145] Blinding is the normal method by which those who evaluate a medication's effectiveness and side effects, are kept unaware of whether they are evaluating the comparator drug (sometimes a placebo), or the new medication (or procedure) under study. If possible, the patient is also blinded and not allowed to know which treatment she is receiving ("double-blinding"). According to standard scientific and medical practice and the standards to which FDA holds pharmaceutical sponsors, all clinical research studies investigating the effects of new drugs should be subjected to an assessment by a blinded evaluator. Conducting a concurrently-controlled, randomized trial comparing surgical abortion with the mifepristone-misoprostol regimen is readily achievable. There are study designs that would have also allowed for blinding. Had blinding proved too difficult to perform, the requirement could have been waived based upon a satisfactory showing by the sponsor.

[146] *FDA Effectiveness Guidance*, *infra* Appendix A, at 12.

[147] FDA, "Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials," (Rockville, Md.: May 2001) at 3 (§ 1.2.1) (*FDA Guidance (ICH: E10): Choice of Control Group*). FDA's publication of "E10" is available at: <http://www.fda.gov/cder/guidance/4155fnl.pdf>.

[148] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2) (Introduction, "Purpose of Control Group").

determine "what would have happened to patients if they had not received the test treatment or if they had received a different treatment known to be effective."[149]

A trial that employs a concurrent control group drawn from the same population yields the most robust data. Concurrent control groups are chosen from the same population as the test group and are "treated in a defined way as part of the same trial that studies the test treatment, and over the same period of time."[150] When concurrent control groups are used, the treatment and non-treatment groups are similar in all baseline and non-treatment variables that could influence the outcome or introduce bias into the study.[151]

By contrast, in a trial using external or historical controls "the control group consists of patients who are not part of the same randomized study as the group receiving the investigational agent; i.e., there is no concurrently randomized control group."[152] FDA cautions:

> "The external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome). Use of the latter comparator is particularly treacherous (such trials are usually considered uncontrolled) because general impressions are so often inaccurate."[153]

In such a trial, "[t]he control group is thus not derived from exactly the same population as the treated population."[154] If, as is most common, the external control group is composed of "a well-documented population of patients observed at an earlier time," the trial is said to be

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[149] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2).

[150] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2).

[151] *See FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2). "Bias here . . . means the systematic tendency of any aspects of the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value." *Id*.

[152] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1).

[153] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 5 (§ 1.3.5).

[154] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1).

"historically" controlled.[155] Blinding and randomization are also not available to minimize bias when external or historical controls are used.[156]

According to FDA, the "[i]nability to control bias is the major and well-recognized limitation of externally controlled trials and is sufficient in many cases to make the design unsuitable."[157] A legal commentator recently cautioned courts about the scientific validity of experiments and trials that have no concurrent control.[158] She explained that "historically controlled subjects have not been subjected to exactly the same conditions as the test subjects."[159] Consequently, "one must be wary of" non-concurrently controlled studies (*i.e.*, historical, external, or uncontrolled studies) because their conclusions can be manipulated more easily than if concurrent controls are used.[160]

3. FDA's Acceptance of the French and U.S. Clinical Trial Data Violated Section 314.126(e) of the Agency's Rules

Section 314.126(e) of FDA's rules states unequivocally that "[u]ncontrolled studies or partially controlled studies *are not acceptable* as the *sole* basis for the approval of claims of effectiveness."[161] The section authorizes the use of uncontrolled trials merely to present supporting evidence for controlled trials; uncontrolled trials, if they are "carefully conducted and

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[155] *See FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1) ("but it could be a group at another institution observed contemporaneously, or even a group at the same institution but outside the study.").

[156] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 27 (§ 2.5.2).

[157] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.2).

[158] Erica Beecher-Monas, "The Heuristics of Intellectual Due Process: A Primer for Triers of Science," *New York University Law Review* 75: 1563-1657, 1628.

[159] Beecher-Monas, *infra* Appendix A, at 1628, n.357.

[160] Beecher-Monas, *infra* Appendix A, at 1628, n.357 (" 'you can prove anything with selective controls,' so one must be wary of historical controls," Beecher-Monas quoting Jon Cohen, "Cancer Vaccines Get a Shot in the Arm," 262 Science 841, 843 (1993)).

[161] 21 C.F.R. § 314.126(e)(emphasis added).

documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug."[162]

FDA recognizes a limited role for external, historically controlled studies. The agency takes the position that "[h]istorical (external) controls can be justified in some cases, but particular care is important to minimize the likelihood of erroneous inference."[163] Similarly, Section 314.126 cautions that "[b]ecause historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent controlled populations, historical control designs are usually reserved for special circumstances."[164] FDA cites as an example, "studies of diseases with high and predictable mortality (for example, certain malignancies),"[165] in which a decision might be made to offer all trial participants a potentially effective drug. Externally controlled studies also may suffice because "the effect of the drug is self-evident (general anesthetics, drug metabolism)."[166]

The French and U.S. Clinical Trials, which did not employ either external or historical control groups, were uncontrolled. During the Advisory Committee Hearings, FDA's Dr. Ridgley C. Bennett, who summarized the data from the French Clinical Trials, stated:

> There are very few studies comparing medical methods and vacuum aspiration for termination of early pregnancy. To date, no large randomized controlled trials have compared mifepristone plus misoprostol with suction curettage abortion. However, large published series have demonstrated morbidity rates associated with mifepristone plus prostaglandin to be similar to those of suction-curettage.[167]

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[162] 21 C.F.R. § 314.126(e).

[163] *FDA Guidance (ICH: E8): General Considerations*, *infra* Appendix A, 62 Fed. Reg. at 66117 (§ 3.2.2.2). According to FDA guidance, the "main advantage" of an externally controlled trial "is that all patients can receive a promising drug, making the study more attractive to patients and physicians." *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 27 (§ 2.5.6).

[164] 21 C.F.R. § 314.126(b)(2)(v) ("Historical control.").

[165] 21 C.F.R. § 314.126(b)(2)(v).

[166] 21 C.F.R. § 314.126(b)(2)(v).

[167] FDA Hearings Transcript, *infra* Appendix A, at 130. Jensen and his fellow researchers conducted "[a] prospective, noncurrent, single center cohort comparison." S*ee* Jensen Study, *infra* Appendix A, at 153. The study

"Published series" and uncontrolled studies cannot serve as a substitute for the well-controlled clinical trials that FDA requires. A concurrent control group would have been feasible because the trial participants were prepared to receive surgical abortion in the event of a failed mifepristone abortion.

The unusual circumstances that sometimes justify relying on externally controlled trials are not applicable with respect to pregnancy termination, generally, or the termination using mifepristone and misoprostol, specifically. Randomized, concurrently-controlled, blinded trials would have allowed investigators to compare not only the relative rates of complete termination and expulsion, but also the nature, intensity, and duration of the numerous side effects. In the absence of concurrent controls and blinding, the duration and intensity of cramping, nausea, bleeding, pain, and any emotional or psychological effects of the treatments would be subject to investigator and patient bias. The design of the U.S. Clinical Trial precluded unbiased comparison groups that could have helped analysts arrive "at a complete understanding of potential advantages, disadvantages and differences" between medical and surgical abortion.[168] FDA's *de facto* waiver of Section 314.126(e) constituted a gross departure from its past practice and announced standards for the conduct of adequate and well-controlled clinical trials.[169]

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compared the data from Mifeprex patients at one of the sites that participated in the U.S. Clinical Trial with data from patients who subsequently underwent surgical abortions at the same site. Although the methodological quality of this study is arguably superior to either the French or U.S. Clinical Trials, had it been offered as trial data it also would have been a weak substitute for a randomized controlled trial establishing equivalent or superior efficacy to surgical abortion.

[168] *See* Jensen Study, *infra* Appendix A, at 156. Dr. Cassandra Henderson, a member of the FDA Advisory Committee, wondered about this point as well: "Since this regimen is not without any side effects and we know that spontaneous abortion is not an infrequent occurrence, is it appropriate to use historical controls in trying to evaluate the efficacy of this regimen and not a randomized placebo trial?" FDA Hearings Transcript, *infra* Appendix A, at 131 (FDA's Dr. Ridgely C. Bennett gave the following puzzling response: "Well, I think it would be difficult to do a randomized trial of this nature. But I think it is fair to use a historical control for efficacy.").

[169] There is no evidence that FDA formally issued a waiver under Section 314.126(c) of the requirement for well-controlled studies or that the Population Council ever requested such a waiver.

4. Subpart H's Standard for Proving Drug Effectiveness

The approval of a drug under Subpart H does not lower the applicable standards for proving the drug's effectiveness. As FDA stated when it adopted Subpart H, "[a]ll drugs approved [under Subpart H] will have had effectiveness demonstrated on the basis of adequate and well-controlled studies."[170] In fact, Subpart H is available only for drugs "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients *over existing treatments* (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)."[171] Neither the French nor the U.S. Clinical Trials yielded scientifically valid comparisons with the existing therapy, surgical abortion, to support a finding of a "meaningful therapeutic benefit over existing treatments." FDA should have required the concurrent testing of mifepristone with surgical abortion to test the proposition that mifepristone has a meaningful therapeutic benefit over the standard method for terminating pregnancies. FDA did not require the drug sponsor to perform such trials for Mifeprex, which departs from FDA's normal treatment of Subpart H drugs generally and for the other drugs approved under the restricted distribution provisions in Section 314.520.

Mifeprex appears to be the only drug that FDA has approved under Section 314.520 of Subpart H without requiring compliance with the statutory and regulatory requirements that safety and efficacy be scientifically demonstrated through blinded, comparator-controlled, and randomized clinical trials capable of providing data for subjection to rigorous statistical analysis.

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[170] *Subpart H Final Rule*, 57 Fed. Reg. at 58953.

[171] 21 C.F.R. § 314.500 (emphasis added). The class of "existing treatments" to which there must be a comparison, as specified in this rule section, is not limited to pharmaceuticals. For example, a potential chemotherapeutic agent might be compared to radiation therapy.

Aside from Mifeprex, only four drugs have been approved pursuant to Section 314.520, the restricted distribution prong of Subpart H. Each of these drugs, Xeloda,[172] Thalomid,[173] Actiq,[174] and Tracleer,[175] was an appropriate candidate for approval under Section 314.520. Moreover, in each case, studies were performed that allowed for a meaningful statistical analysis of the effectiveness of this drug in comparison with the current available standard of care. FDA's decision to require randomized, comparator-controlled, blinded trial design for each drug, even in the face of urgent need for the treatments at issue, supports the claim that FDA's treatment of the mifepristone NDA was aberrant.

Xeloda™ (capecitabine) was approved for use in treating patients with widely metastatic ("Stage IV") terminal breast cancer, for whom all other modalities of chemotherapy have failed or are contraindicated.[176] The average lifespan of a patient with multi-drug resistant tumors participating in the clinical trials for this drug was only 8.5 months. Because Xeloda was only modestly effective (25% of the recipients improved for an average of five months), exhibited significant toxicity, and was a last resort treatment for dying patients, FDA approved it under Section 314.520 with use restrictions and commitments to further study the drug. Subsequent randomized, concurrent controlled, blinded evaluator trials demonstrated Xeloda's statistical superiority to the standard of care for metastatic colon and breast cancers.[177]

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[172] NDA 20896.

[173] NDA 20785.

[174] NDA 20747.

[175] NDA 21290.

[176] *See* "NDAs Approved under Subpart H," *infra* Appendix A. The current version of the Subpart H approval chart (updated Aug. 8, 2002) indicates that Xeloda is a "surrogate endpoint" drug, rather than a restricted distribution drug. However, the two previous postings of the chart state the opposite. Furthermore, FDA's approval letter states that the NDA "[was] approved under 21 CFR 314.520." Letter, FDA/CDER to Cynthia Dinella, Group Director, Regulatory Affairs, Hoffman-La Roche Inc. (Apr. 30, 1998).

[177] *See* Xeloda package insert.

Thalidomide (Thalomid™) was approved under Section 314.520 for the treatment of leprosy, a disfiguring, chronically disabling, and often lethal skin infection.[178] Thalidomide is a drug the severe toxicity of which, particularly to fetuses, is well-documented. Children exposed to this drug *in utero* suffer dramatic birth defects, namely the partial absence of hands, feet, arms and legs. The public outcry following the discovery that thalidomide causes these alarming malformations helped to spur the scientific modernization of FDA drug approval policy and practices in the 1960s. Clinical trials involving leprosy are difficult and require long periods of time because the disease is very rare in the United States. Three randomized, double-blinded comparator-controlled clinical trials were performed to support the Thalomid NDA.[179]

Oral fentanyl citrate (Actiq™) was approved under Section 314.520 as a powerful sedating narcotic painkiller, primarily for use to relieve the suffering of dying cancer patients.[180] Actiq can be lethal, particularly to children, because it quickly abolishes a patient's drive to breathe, unless the patient is already accustomed to narcotic analgesics. Moreover, Actiq, a powerful narcotic, has a high potential for abuse and diversion into the illegal drug market. Actiq was evaluated in a "double blinded, placebo controlled" study for the treatment of breakthrough cancer pain and was shown to "produce statistically significantly more pain relief compared with placebo."[181] Actiq is restricted for use only by oncologists and pain specialists who are familiar with the management of the side effects and complications of the drug's use as approved.

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[178] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[179] *See* Thalomid package insert.

[180] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[181] Actiq package insert.

Tracleer™ (bosentan tablets) was approved pursuant to Section 314.520 for use in treating pulmonary hypertension, a life threatening and frequently progressive condition of excessively high blood pressure in the lung blood vessels resulting from chronic scarring and injury of the lung tissue.[182] Tracleer can cause liver damage and major birth defects. Two randomized, double-blinded, placebo-controlled clinical trials demonstrated the superiority of the drug over a placebo. Tracleer was compared to a placebo because there is no alternate standard of care for pulmonary hypertension. Despite its potential toxicity, Tracleer was approved subject to usage restrictions under Section 314.520 because it is the only treatment available for a life threatening and debilitating condition.[183]

5. FDA Failed to Require a Comprehensive Audit of French Clinical Trial Data after Discovering Violations of Good Clinical Practices

In June 1996, FDA inspected the trial records of a "French government-supported abortion clinic" that participated in the French Clinical Trials. FDA issued a Form 483 detailing problems uncovered during the inspection. The problems identified by the investigator suggested carelessness, fraud, evidence tampering, and the systematic under-reporting of serious adverse events. The inspection "revealed a failure to maintain complete and accurate records." The violations that were discovered included: "laboratory reports that were missing" for 11 patients, "missing ultrasound documents" for 20 patients, "pages missing from the case record files and unreported aspirations," inclusion of 4 ineligible patients, and "consent forms were dated after the start of study for some subjects, and the investigator had signed consent form

[182] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[183] *See* Tracleer package insert.

sometimes in advance, up to 4 days before the subjects had signed."[184] There were also "under-reported side effects" such as "a patient bleeding with two subsequent aspirations; convulsions reported as fainting; and expulsion which was actually a surgical evacuation; bleeding, nausea and contractions, or bleeding and pelvic pain."[185] After elaborating on the deficiencies found, the FDA inspector concluded: "Notwithstanding these objectionable conditions, [redacted name of an FDA official] assured Dr. Aubeny that he would not recommend that the studies not be included in the evaluation of the NDA application."[186]

FDA should not have allowed tainted data to support the Mifeprex NDA. A complete audit of all French Clinical Trial data is warranted to determine whether another set of clinical trials must be performed to replace the tainted French trial data.

F. THE AGENCY'S DE FACTO APPROVAL OF MISOPROSTOL'S NEW USE WAS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

When FDA approved Mifeprex, it also took action with respect to a second drug – misoprostol. Taken alone, mifepristone is ineffective as an abortifacient.[187] In order to achieve an abortion rate greater than 90 percent, the administration of mifepristone is followed approximately two days later by a prostaglandin to complete the abortion. In the U.S. Clinical

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[184] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 1 [FDA FOIA Release: MIF 004135-45].

[185] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 1.

[186] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 9.

[187] Although some studies using mifepristone alone have produced completion rates as high as 60 to 80 percent, it is widely recognized that, on its own, mifepristone is not a viable substitute for surgical abortion. *See, e.g.,* Mitchell D. Creinin, "Early Medical Abortion with Mifepristone or Methotrexate: Overview," *Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations* (Washington, D.C.: National Abortion Federation, 2001) at 3 (reporting that "[f]or gestations up to 49 days, complete abortion occurs in approximately 60% to 80%" of women using mifepristone alone); Helena von Hertzen, M.D., "Research on Regimens for Early Medical Abortion," *Journal of the American Medical Women's Association* 55 (Supplement 2000): 133-36.

Trial, the prostaglandin used was misoprostol, which was distributed by G.D Searle & Co. ("Searle") as the anti-ulcer drug Cytotec™.[188] Ultimately, FDA based its approval of Mifeprex on the combined action of a mifepristone and misoprostol regimen. On the day FDA approved mifepristone, it notified Searle that "[t]he drug mifepristone is now approved in a regimen with misoprostol for termination of pregnancy of 49 days or less."[189]

Searle, which opposed the use of its drug in conjunction with Mifeprex as an abortifacient,[190] did not file a Supplemental NDA for the use of misoprostol as part of an abortion regimen.[191] Absent such an application, FDA lacked the basis for sanctioning a new indication for misoprostol. As Peter Barton Hutt, former FDA general counsel, observed, the agency's treatment of misoprostol "set[ ] an extraordinary precedent" because FDA was "seemingly

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[188] After a series of corporate transactions, Searle is now part of Pharmacia Corporation, which is headquartered in Peapack, New Jersey. In 1985, G.D. Searle & Co. became the pharmaceutical unit of Monsanto. In April 2000, Monsanto merged with Pharmacia & Upjohn to create the Pharmacia Corporation. Pharmacia & Upjohn had been created in 1995 when Pharmacia AB and the Upjohn Company merged. On July 15, 2002, Pfizer Inc. announced that it would purchase Pharmacia.

[189] Letter, Dr. Lilia Talarico, M.D., Director, FDA/CDER, Division of Gastrointestinal and Coagulation Drug Products, Office of Drug Evaluation III to Dr. Mary Jo Pritza, G.D. Searle & Co. (Sept. 28, 2000): at 1 [FDA FOIA Release: MIF 008847-48]. The Talarico Letter came in response to the August 8, 2000 application by Searle to obtain approval for changes that would have bolstered the Cytotec label's discussion of adverse effects (presumably in anticipation of FDA's approval of the mifepristone NDA). FDA chided Searle for attempting to make the proposed changes and summarily rejected them. *Id*. at 1. When it announced the Mifeprex approval, FDA referred to the "approved treatment regimen." *See* FDA, Press Release, "FDA Approves Mifepristone for the Termination of Early Pregnancy" (Sept. 28, 2000). *See also* FDA webpage, *infra* Appendix A, "Mifepristone Questions and Answers 4/17/2002," at Question 4 (referring to the "mifepristone treatment regimen").

[190] In fact, on August 23, 2000, Searle wrote an open letter to all health care practitioners stating that "Cytotec is not approved for the induction of labor or abortion." The letter listed a number of potential "[s]erious adverse events reported following off-label use of Cytotec in pregnant women includ[ing] maternal or fetal death." Michael Cullen, M.D., Medical Director U.S., Searle, Open Letter to Health Care Providers (Aug. 23, 2000)[FDA FOIA Release: MIF 008022]. Officials of the American College of Obstetricians and Gynecologists, among others, decried Searle's lack of cooperation. *See* Ralph W. Hale, M.D., and Stanley Zinberg, M.D., "The Use of Misoprostol in Pregnancy," editorial, *New England Journal of Medicine* 344 (Jan. 4, 2001): 59-60. FDA's approval of the Mifeprex Regimen in the face of Searle's opposition appears to have usurped Searle's rights to control the distribution of its drug.

[191] Because Searle's patent on misoprostol did not expire until July 2000, no other party would have been able to file a timely supplemental NDA for the use of a generic form of misoprostol as an abortifacient.

encouraging a drug's unapproved use."[192] He added that the agency is in an "embarrassing and uncomfortable position."[193] FDA did more than encourage the unapproved use of misoprostol; it *mandated* the unapproved use.

1. Misoprostol's Use as an Abortifacient is a New Indication for which the Requisite Supplemental New Drug Application Was Not Filed

A drug that differs in any material way (including in composition, effect, or intended use) from an approved drug is a new drug that must independently be established to be safe and effective.[194] Furthermore, a drug already being used to treat one disease or part of the body may be a new drug when used to treat another disease or part of the body.[195] Misoprostol's new use as an abortifacient, therefore, marks it as a "new drug."[196]

New drugs must be shown to be safe and effective. Specifically, FDA requires that "[a]ll indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) . . . unless the requirement is waived . . . ."[197]

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[192] Rachel Zimmerman, "Clash Between Pharmacia and FDA May Hinder the Use of RU-486," *Wall Street Journal* (Oct. 18, 2000): at B1.

[193] Zimmerman at B1.

[194] *See Thompson v. Western Medical Center*, Brief for the Petitioners (filed by the Solicitor General of the United States), No. 01-344 (Dec. 2001): at 4 ("See *United States v. Generix Drug Corp.*, 460 U.S. 453, 460-461 (1983) (determination whether a product is a new drug takes into account both active and inactive ingredients); 21 C.F.R. 310.3(h) (discussing factors that make a drug a 'new drug').

[195] A drug may be deemed "new" because of "[t]he newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body." 21 C.F.R. § 310.3(h)(4).

[196] The "newness" of misoprostol in this indication was heightened by the fact that, when Mifeprex was approved, misoprostol was explicitly contraindicated for pregnant women. The misoprostol label included the following black-box warning: "CYTOTEC (MISOPROSTOL) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE IT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT . . . ." In April 2002, the Cytotec label was changed to "remove[ ] the contraindication and precaution that Cytotec should not be used in women who are pregnant." FDA, "Major Changes to Cytotec Labeling" (April 17, 2002). The label now restricts the contraindication to pregnant women who are using Cytotec as a non-steroidal anti-inflammatory drug ("NSAID"). The revised Cytotec label and, more specifically, the "Indications and Usage" section, however, continue to lack any reference to the use of misoprostol in the Mifeprex Regimen.

[197] 21 C.F.R. § 201.57(c)(2). To the best of the Petitioners' knowledge, FDA did not formally waive the requirement for misoprostol as part of an abortion regimen.

A Supplemental NDA provides the necessary evidence in support of a new indication.[198] Absent a waiver, a Supplemental NDA permits FDA to consider the evidence in support of the proposed change and approve related labeling changes in advance.[199] Even though a new use for misoprostol is an integral part of the Mifeprex Regimen, FDA sanctioned this new misoprostol indication without having received and considered a Supplemental NDA.

Among the changes for which FDA approval is necessary are changes to statements in a drug's labeling indicating whether "[t]he drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy."[200] A well-known treatment regimen illustrates how FDA has typically dealt with the labeling of two drugs that have been approved for combined use. The regimen pairs methotrexate and Leucovorin Rescue. Methotrexate, a chemotherapeutic agent, kills cancer cells by depriving them of folic acid which is necessary for DNA synthesis, but, in the process, methotrexate deprives normal bone marrow cells of the folic acid they need. Leucovorin Rescue serves as an antidote to the toxic effects of methotrexate. The labeling for Leucovorin Rescue refers to its use "after high-dose methotrexate therapy in osteosarcoma," which is an approved

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[198] A recent article noted: "To obtain FDA approval for an additional use of a previously approved drug, the sponsor must submit a supplemental application (sNDA, sBLA, or sPMA) demonstrating the safety and efficacy of the drug when used in the new way or for the new indication. The supplemental application typically requires clinical data similar to those in the original application, but does not require the same extensive chemistry, manufacturing and controls, and preclinical pharmacology and toxicology data as in the original application." Shane M. Ward, "*Washington Legal Foundation* and the Two-Click Rule: The First Amendment Inequity of the Food and Drug Administration's Regulation of Off-Label Drug Use Information on the Internet," *Food and Drug Law Journal* 56 (2001): 41-56, at 44 (citations omitted).

[199] *See* 21 C.F.R. § 314.70(b). *See also* Richard A. Merrill, "The Architecture of Government Regulation of Medical Products," *Univ. of Virginia Law Review* 82 (1996): 1753-1866, at 1775 ("FDA takes the position, which no manufacturer has sought to challenge in court, that any potentially significant modification of an approved new drug [application] likewise requires advance agency approval. As a consequence, not only attempts to expand the indications for a drug but other changes in labeling, in inactive ingredients, in the method or location of manufacture, or in packaging must first be the subject of an approved Supplemental New Drug Application.").

[200] *See* 21 C.F.R. § 201.57(c)(1)(iv).

indication for methotrexate.[201] Similarly, methotrexate's labeling refers to an approved use of Leucovorin Rescue.[202]

By contrast, in the Mifeprex labeling, an *unapproved* indication for misoprostol is discussed. In approving such labeling, FDA has taken the aberrant position that the maker of one drug (Mifeprex) can secure approval of a new indication for another company's drug (misoprostol) merely by describing that new use as part of a combined therapy. FDA circumvented its own regulations by failing to require that both drugs in the Mifeprex Regimen be approved for the indication in question – pregnancy termination.[203]

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[201] *See* Leucovorin Calcium for Injection Package Insert ("Indications and Usage") ("Leucovorin calcium rescue is indicated after high-dose methotrexate therapy in osteosarcoma. Leucovorin calcium is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists."). The package insert is available at: <http://www.xanodyne.com/leucovorin_calcium_pl_2002.pdf>.

[202] The methotrexate package insert states that "[m]ethotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor." The package insert is available at: <http://www.rxlist.com/cgi/generic/mtx_ids.htm>.

[203] A recent approval of a biologic product also illustrates the principle that FDA-approved labeling lists only approved indications. On February 19, 2002, FDA approved Zevalin for use in combination with Rituxan (rituximab) to treat low-grade B-cell non-Hodgkins Lymphoma (NHL). Rituxan had been approved previously and was already indicated "for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma." *See* Rituxan Package Insert ("Indications and Usage"). Rituxan and Zevalin are monoclonal antibodies that can significantly shrink tumors by targeting white blood cells (B-cells) including malignant B cells. The "Indications and Usage" section of Zevalin's label describes the drug as being "part of the ZEVALIN therapeutic regimen (see Dosage and Administration)." The "Dosage" section directs that Rituxan be administered and then followed by Zevalin on Day One and then again seven to nine days later. After the Zevalin NDA was approved, detailed information about the administration of the "Zevalin Therapeutic Regimen" was added to the Rituxan label. On February 19, 2002, FDA's Center for Biologics Evaluation and Research approved a supplement to the Rituximab biologics license application "to revise the dosage and administration section of the package insert to include information regarding the use of Rituximab as a component of the Zevalin therapeutic regimen . . . ." Letter, Dr. Karen D. Weiss, M.D., Director, Division of Clinical Trial Design and Analysis, Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, to Alice Wei, IDEC Pharmaceuticals (Feb. 19, 2002) (*see* <http://www.fda.gov/cber/approvltr/rituide021902L.htm>).

2. FDA Sanctioned the Promotion of Misoprostol for an Unapproved Use as Part of the Mifeprex Regimen

The use of misoprostol as an abortifacient is an unapproved or "off-label" use.[204] FDA objects to the *promotion* of off-label uses of drugs by manufacturers.[205] "Off-label" uses of drugs are common as physicians explore new ways of using approved drugs, but normally FDA strives to ensure that physicians and patients are not misled into believing that FDA has approved such uses. In an effort to curb the promotion of off-label uses by pharmaceutical manufacturers, FDA issued regulatory guidance in 1996 pertaining to the dissemination of off-label use information.[206] In this case, however, FDA not only sanctioned, but participated in, the promotion of an off-label use of misoprostol. FDA oversaw the creation of the promotional materials for Mifeprex,[207] which discussed the off-label use of misoprostol.[208] FDA itself disseminated information about

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[204] *See generally* James M. Beck and Elizabeth D. Azari, "FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions," *Food & Drug Law Journal* 53 (1998): 71-104, at 71 n.2, which explains "off-label" use as follows:

> "Off-label" has more accurately been termed "extra label" use. It means only that a product is used for a condition or in a way not appearing on its FDA-regulated labeling, not that the agency has judged the use adversely. *See, e.g.*, *Washington Legal Found. v. Kessler*, 880 F.Supp. 26, 28 n.1 (D.D.C. 1995). . . . Off-label can mean many things. "[U]sing an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease, treating unrelated, unindicated diseases, and treating the indicated disease but varying from the indicated dosage, regimen, or patient population may all be considered off-label use." William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 248 (1993) (footnotes omitted).

[205] *See, e.g., Subpart H Final Rule*, 57 Fed. Reg. at 58,953 ("Under the act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and that FDA has approved.").

[206] *See* FDA, "Advertising and Promotion; Guidances," Notice, 61 Fed. Reg. 52,800 (Oct. 8, 1996) (publishing two guidance documents: "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data" and "Guidance for Industry Funded Dissemination of Reference Texts").

[207] FDA reminded the Population Council in the Mifeprex Approval Letter that, pursuant to 21 C.F.R. § 314.550, the drug sponsor is obligated to submit Mifeprex promotional material for review by the agency prior to dissemination to physicians and the public. *See* Mifeprex Approval Letter at 3.

[208] A Danco Laboratories webpage, for example, contains the following question and answer:

> Q: How Does Mifeprex Work?
>
> A: Mifeprex blocks progesterone, a hormone necessary for a pregnancy to continue. You take Mifeprex followed by a prostaglandin, misoprostol, which causes uterine contractions that help to end pregnancy.
>
> In more detail, Mifeprex blocks progesterone, a naturally produced hormone that prepares the lining of the uterus for a fertilized egg and helps maintain pregnancy. Without progesterone, the lining of the uterus

the off-label use of misoprostol in documents such as the press release announcing the approval of Mifeprex for use in conjunction with misoprostol.[209] Recently it did so again when the agency emphasized the importance of adhering to the approved regimen, including the off-label use of misoprostol.[210]

3. Mifeprex Is Misbranded: Its Labeling Promotes an Unapproved Use of Another Drug

The labeling for Mifeprex is misleading because it directs physicians to use misoprostol for a purpose that FDA never approved.[211] FDA's ability to regulate the marketing and distribution of drugs rests largely on its legal capacity to strictly control the content of a drug's labeling. A fundamental tenet of drug regulation is that FDA requires approval for every indication listed in the labeling of a drug.[212] FDA would undercut its own authority if it did not also apply this rule to uses for a drug referenced on another drug's labeling.

The Mifeprex labeling creates false expectations about misoprostol. Physicians and patients are justified in believing that any use or indication for a drug, included in the "Indication

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> softens, breaks down and bleeding begins. Mifeprex is followed by a prostaglandin that causes the uterus to contract, which helps to complete the process. . . . The prostaglandin used following Mifeprex is misoprostol, a drug already available in the United States.

"Using Mifeprex: Frequently Asked User Questions," Danco Laboratories website at <http://www.earlyoptionpill.com/may_faqs.php3>. The electronic version of the Mifeprex Label contains a hyperlink to the Danco Laboratories website, <www.earlyoptionpill.com>, which contains the above-referenced webpage. (When printed, the hyperlink appears to be ordinary text.)

[209] *See*, FDA, Press Release, "FDA Approves Mifepristone for the Termination of Early Pregnancy" (Sept. 28, 2000) ("Under the approved treatment regimen, a woman first takes 600 milligrams of mifepristone (three 200 milligram pills) by mouth. Two days later, she takes 400 micrograms (two 200-microgram pills) of misoprostol, a prostaglandin.").

[210] *See* FDA webpage, *infra* Appendix A, "Mifepristone Questions and Answers 4/17/2002," at Question 6. In this same document, however, FDA cautions health care providers against "using misoprostol 'off-label,' in other words, using misoprostol vaginally at different doses . . . ." *Id*. at Question 9.

[211] Misoprostol receives more than a passing mention on the Mifeprex Label; the word "misoprostol" appears 34 times (compared to 57 appearances of "mifepristone" and 34 appearances of "Mifeprex").

and Usage" section of an FDA-approved label, has been subjected to the rigorous approval process set forth in Section 505 of the FD&C Act. Section 201.6(a) of the Agency's rules states that misbranding may arise from "a false or misleading representation with respect to another drug."[213] "When a physician, manufacturer, or *other third party* steps in to promote an unapproved use of a drug by advertising or distribution to other physicians, the drug may become unlawful under Section 301(k) the FD&C Act, 21 U.S.C. § 331(k)(1994), which prohibits misbranding, and Section 502(f)(1), 21 U.S.C. § 352(f)(1)(1994), which requires a drug's labeling to bear 'adequate directions for use.'"[214] Mifeprex is, therefore, misbranded.

Mifeprex is also misbranded because it is unsafe when used as directed in the approved labeling. Section 502(j) of the FD& C Act states that "[a] drug or device shall be deemed to be misbranded . . . [i]f it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof."[215] As discussed in the next section, FDA's approved regimen is unsafe because it lacks important safeguards.

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[212] *See* Elizabeth A. Weeks, "Is It Worth the Trouble? The New Policy on Dissemination of Information on Off-Label Drug Use under the Food and Drug Modernization Act of 1997," *Food and Drug Law Journal* 54 (1999): 645-65, at 647 n.13 (citing Merrill, (*infra* Appendix A), at 1853).

[213] *See* 21 C.F.R. § 201.6(a).

[214] Merrill, *infra* Appendix A, at n.318 (emphasis added). *See also* 21 C.F.R. § 314.530(a)(5) (authorizing the Secretary to withdraw approval of a Subpart H drug if "[t]he promotional materials are false or misleading").

[215] 21 U.S.C. § 352(j). *See also* Jeffrey N. Gibbs and Judith E. Beach, "Chapter 7: Adulteration and Misbranding of Drugs" in *Fundamentals of Law and Regulation: An In-Depth Look at Therapeutic Products* (David G. Adams, Richard M. Cooper, and Jonathan S. Kahan, eds.), vol. II (Washington, D.C.: Food and Drug Law Institute, 1997): at 229 ("When the drug is dangerous to the health of the user even when used as recommended on the label, it is misbranded.").

G. WOMEN'S LIVES ARE BEING ENDANGERED BY THE LACK OF SAFEGUARDS IN FDA'S APPROVED REGIMEN

On February 18, 2000, FDA informed the Population Council that "adequate information ha[d] *not* been presented to demonstrate that [mifepristone], when marketed in accordance with the terms of distribution proposed [by the Population Council], is safe and effective for use as recommended."[216] Over the next several months, the Population Council and Danco refused to supplement its distribution plan with a meaningful patient safety component. This prompted FDA, on June 1, 2000, to privately convey to the sponsor a set of proposed restrictions intended to rectify the sponsor's omission. The agency's proposed restrictions were soon leaked to the public. Amidst a vigorous political and editorial backlash, the sponsor not only rejected FDA's proposal but, in what was described by FDA as a "very significant change," repudiated restrictions the sponsor itself had proposed in 1996.[217] FDA succumbed and soon approved a regimen that did not embody restrictions sufficient to address the agency's legitimate safety concerns.

Early in the approval process, FDA expressed its intention to place restrictions on the use of mifepristone.[218] FDA's position was informed, in part, by the international experience with

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[216] 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5 (emphasis added).

[217] *See* FDA Email (June 23, 2000): at 1 (explaining that the Population Council's attorney "affirmed that the 1996 proposals for distribution system as presented by the Pop Council then and agreed to by the [FDA Advisory Committee] and FDA are NOT what the Pop Council wants today. I explained that this change is very significant and that they need to provide their justification/rationale.")[FDA FOIA Release: MIF 002523].

[218] In order to allay concerns of the drug's European owner, FDA pledged, in the course of securing the U.S. patent rights for the Population Council, to "take appropriate measures . . . to assist through the NDA-approval process in the creation of a regime for the distribution and use that will protect against misuse of the drug." Letter, David A. Kessler, Commissioner of Food and Drugs, to the President & CEO of Roussel Uclaf [name redacted] and to Margaret Catley-Carlson, President of Population Council (May 16, 1994): at 1 [FDA FOIA Release: MIF 004992-93].

mifepristone.[219] The NDA submitted by the Population Council on March 14, 1996 included a plan that would have limited distribution of mifepristone to "licensed physicians (with prior training in assessing the length of pregnancy, in diagnosing ectopic pregnancy, and [redacted]), who will attend educational seminars on the safe use of this regimen."[220]

The FDA Advisory Committee, when it met in July 1996, was not satisfied with the restrictions proposed by the Population Council and expressed "serious reservations on how [the proposed drug distribution system] is currently described in terms of assuring safe and adequate credentialing of providers."[221] The Committee recommended additional restrictions designed to ensure "that this drug not be expanded to hands of physicians who are not already skilled in managing pregnancies, terminations, and complications of both."[222] Accordingly, FDA's 1996 Approvable Letter required the submission of "a comprehensive description of the proposed distribution system."[223]

In subsequent submissions, however, the Population Council insisted that the drug was safe and proffered restrictions designed primarily to control the manufacturing and retailing of the drug product. On August 18, 1999, the Population Council proposed to:[224] (i) limit the number and type of distributors; (ii) limit distribution to distributor-registered physicians who

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[219] In Europe, for example, mifepristone is used under more highly controlled conditions than were ultimately required in the United States. *See* Amendment to NDA 20-687, International Product Labeling with English Translations (submitted March 21, 2000) (presenting English translation of mifepristone product label, approved July 6, 1999, used in Austria, Belgium, Denmark, France, Germany, Greece, the Netherlands and Spain)[FDA FOIA Release: MIF 000493-506].

[220] Memorandum, FDA/CDER to NDA 20-687 File (Sept. 16, 1996): at 2 [FDA FOIA Release MIF 000560-62].

[221] FDA Advisory Committee, Minutes of July 19, 1996 Meeting (approved July 23, 1996): at 7 [FDA FOIA Release: MIF 000539-45].

[222] FDA Memorandum, "Highlights of the July 19, 1996 Reproductive Health Products Advisory Committee (AC) Meeting on Mifepristone: Outstanding Issues for FDA to Address" (undated): at 3-4 [FDA FOIA Release: MIF 000534-38].

[223] 1996 Mifepristone Approvable Letter , *infra* Appendix A, at 1.

had provided certain assurances;[225] and, (iii) make available "training materials and information" and medical consultation to health care providers and product information to patients.[226] On January 21, 2000, Danco opined that "[r]egardless of the distribution system for mifepristone, the medical safety of this drug is well documented."[227] and proposed a distribution system that was designed only to ensure that Danco would "exert[ ] positive control over distribution of Mifeprex® through all phases of manufacturing, storage, shipment and administration from manufacturer to patient."[228]

In reaction to the sponsor's recalcitrance, FDA took the position "that restrictions as per CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product."[229] The agency nevertheless continued to encourage the sponsor to take an active role in devising appropriate restrictions on the use of mifepristone. Instead, in March 2000, the Population Council again protested that such restrictions were unwarranted.[230] It submitted a

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[224] *See* Medical Officer's Review, *infra* Appendix A, at 21-23 (setting forth the Population Council's complete response submitted to FDA on August 18, 1999).

[225] The physician would be required to provide a *self*-attestation covering the physician's ability to accurately date pregnancies and determine the patient's blood Rh factor and the physician's access to emergency medical facilities. Registering physicians would also agree to obtain from each patient an acknowledgement that she has received full information and is willing to comply with the treatment regimen, to maintain certain records (including ultrasound and blood test records) for each patient, to report adverse events and information about ongoing pregnancies, and to "[u]se every effort to ensure patients return for their follow up visit 14-20 days after taking the product." *See* Medical Officer's Review, *infra* Appendix A, at 22-23.

[226] *See* Medical Officer's Review, *infra* Appendix A, at 23.

[227] Amendment 039 to the NDA, Cover Letter, Danco to FDA (Jan. 21, 2000): at 1 [FDA FOIA Release: MIF 000525-26]. Danco attempted to attribute any deleterious effects of mifepristone abortions to misoprostol: "More serious adverse events are quite rare and are related to the entire treatment (not mifepristone *per se*), almost always following the use of the prostaglandin." *Id.* at 2.

[228] *See* Amendment 039 to the NDA, Mifeprex Distribution Plan Executive Summary (Jan. 21, 2000): at 3 [FDA FOIA Release: MIF 000530-31].

[229] *See* 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5. *See supra* Section III.C.2 and III.D. for a discussion of Subpart H, Section 314.520, which is reserved for drugs that are so inherently dangerous that their distribution and use must be restricted.

[230] In the course of objecting to the approval of the drug under subpart H, which is "likely to falsely 'mark' mifepristone as a highly toxic and risky drug," the Population Council insisted that "the FDA knows, [Mifeprex] is

distribution plan that it characterized as "detailed and comprehensive" and "surely equal to its purpose."[231] Once again, the plan consisted of restrictions intended only to control the manufacturing and retailing of the drug product.[232] Again FDA objected that "[t]he proposed distribution system as submitted primarily addresses security for the manufacturer and distributor; it must also include safeguards for the patient."[233] The agency requested "that sponsor present a proposal regarding provider qualifications that addresses safety concerns of patients receiving the drug product."[234]

On June 1, 2000, FDA proposed the following set of "Qualifications for Physician Recipients:" (1) the physician must demonstrate that she is licensed to practice medicine; (2) the physician must be "trained and authorized by law" to perform surgical abortions; (3) the physician must have "been trained to and ha[ve] the ability to assess the age of a pregnancy accurately by ultrasound examination, to monitor abortion by ultrasound examination, and to diagnose an ectopic pregnancy by ultrasound examination;" (4) the physician must have "satisfactorily completed training certified by the distributor in the mifepristone treatment procedure, including mechanism of action, appropriate use, proper administration, follow-up, efficacy, adverse events, adverse event reporting, complications, and surgical indications;" and

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exceptionally safe and effective." Responses by Population Council to "FDA Letter, [redacted] to Arnold, Sandra (February 18, 2000)" (Mar. 2000): at 1 [FDA FOIA Release: MIF 000523-24]("March 2000 Response").

[231] March 2000 Response, *infra* Appendix A, at 2.

[232] Specifically, the plan provided for "secure manufacturing and shipping procedures, controlled returns, tracking of distribution of individual packages to the patient level, use of a limited number of distributors [redacted], account registration and other detailed ordering requirements for practitioners, direct distribution only to practitioners (not through retail pharmacies), and the use of signed patient agreements." March 2000 Response, *infra* Appendix A, at 2.

[233] Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1 [FDA FOIA Release: MIF 007811-13].

[234] Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1. FDA wanted the sponsor to provide a set of auditable provider qualifications, a plan for auditing providers to ensure that they were meeting these criteria, and an arrangement for discontinuing distribution to unqualified providers. *See id.* at 2.

(5) the physician must have "continuing access (e.g., admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or [one hour's] drive from the treatment facility."[235] FDA's proposals were intended to address concerns about the safety of the women undergoing mifepristone-misoprostol abortions that the Population Council and Danco had refused to take into account in crafting restrictions for the drug.[236]

The Population Council and Danco objected strenuously to the proposed restrictions and aired their complaints in public.[237] FDA reprimanded the Population Council for leaking the restrictions to the public and misrepresenting the nature of the restrictions.[238] The Executive Vice President of the American College of Obstetricians and Gynecologists submitted an analysis of the leaked restrictions to FDA.[239] The editorial and political reaction,[240] together with the

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[235] *See* FDA, "FDA Proposed Restricted Distribution System for NDA 20-687 on 6/1/00" (June 1, 2000)[FDA FOIA Release: MIF 000522]. *See also* American College of Obstetricians and Gynecologists, "Analysis of the Possible FDA Mifepristone Restrictions" (July 27, 2000): at 1 (setting forth FDA's second proposed restriction, which is redacted in the publicly available copy of FDA's proposal; also providing the redacted portion of the fifth restriction)[FDA FOIA Release: MIF 001366-69].

[236] It should be noted, that even these restrictions would not have been sufficient to make mifepristone-misoprostol abortions safe. Among the key safeguards missing from FDA's proposal were requirements that every prospective patient undergo an ultrasound and that prescribing physicians be required to have admitting privileges at facilities able to provide emergency care.

[237] Paul Blumenthal, M.D., Jane Johnson, and Felicia Stewart, M.D., "The Approval of Mifepristone (RU486) in the United States: What's Wrong with this Picture?" *Medscape Women's Health* 5 (2000) (reproduced in an internal FDA email)[FDA FOIA Release: MIF 00002597-99] ("At a meeting of early abortion providers and abortion advocates, the Population Council and Danco revealed that the U.S. Food and Drug Administration (FDA) had made a series of proposals regarding the labeling and distribution of mifepristone that would severely limit women's access to the drug if and when it is approved.").

[238] *See* Teleconference Meeting Minutes (between FDA staff and representatives of the Population Council and Danco) (June 7, 2000): at 1 ("Meeting Objective: . . . to discuss the misrepresentations by the Press regarding the proposed distribution system, and to agree on the need for serious, candid, and confidential discussions to resolve deficiencies of the application.")[FDA FOIA Release: MIF 002136-37]; FDA internal email (June 23, 2000): at 1 (re: telephone conversation with Population Council attorney, Nancy Buc, on 6/23/00) ("I also said that we were looking to Pop Council to be a responsible entity in manufacturing, distributing, and shepherding this drug and that most responsible entities make proposals rather than expect FDA to write labels and distribution systems and obtain comments through the media.")[FDA FOIA Release: MIF 002523].

[239] *See* Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) to Jane Henney, M.D. (July 24, 2000) and enclosure: ACOG, "Analysis of the Possible FDA Mifepristone Restrictions" (July 27, 2000)[FDA FOIA Release: MIF 001366-69]. ACOG and the American Medical Association ("AMA") also attempted to secure a meeting with

impending approval deadline of September 30, 2000,[241] however, had the desired effect of undermining FDA's resolve.

At a meeting on July 19, 2000, FDA yielded to the Population Council and Danco on a number of important issues.[242] FDA abandoned its proposal for auditable physician qualifications and agreed instead to permit physicians to attest to their own qualifications.[243] Instead of requiring formal training, FDA merely "request[ed] that the physician also attest to having read and understood the training materials and labeling."[244] FDA also agreed not to

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Dr. Jane Henney, FDA Commissioner, and her staff, in order to further discuss their opinion of the restrictions. *See* Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) and E. Ratcliffe Anderson, Jr., M.D. (Executive Vice President, AMA) to Jane Henney, M.D. (July 24, 2000): at 1 ("The undersigned organizations . . . are very concerned about restrictions . . . [FDA] has proposed for . . . mifepristone. . . . We would like the opportunity to meet with you and your staff to discuss this important issue. It's imperative that the FDA fully understands the effect that these proposals would have on the quality of health care. It's equally imperative that the FDA's work be based solely on evidence from the drug's clinical trials, and be entirely from political influence.")[FDA FOIA Release: MIF 001363]. They were permitted only to meet with officials in FDA's Office of Women's Health, an office within the agency that was not involved in reviewing the NDA. *See* Letter, Jane Henney to Hale and Anderson (Aug. 11, 2000): at 1-2 [FDA FOIA Release: MIF 001361]. The questionable scientific basis for this challenge to FDA's proposed restrictions was recently brought to the attention of ACOG by one of the Petitioners. Letter, Donna Harrison, M.D. (Chairperson, AAPLOG Committee on Mifeprex Use) to Ralph Hale, M.D. (Executive Vice President, ACOG) (May 23, 2002) (available at <http://www.aaplog.org/acogmifeprexletter.htm>).

[240] *See, e.g*, Letter, U.S. Senator Barbara Boxer to Dr. Jane Henney (June 9, 2000): at 1 ("According to news reports, the FDA is considering placing draconian restrictions on the accessibility of RU-486 as a condition of its approval . . . . In 1996, the FDA found RU-486 to be safe and effective. Therefore, it is a mystery to me why the FDA would even consider restricting access to it.")[FDA FOIA Release: MIF 006376]; Letter, Mark Green, Public Advocate for the City of New York, to Dr. Jane Henney (Sep. 22, 2000): at 1 ("Earlier this week Planned Parenthood of New York City, NARAL-New York, the Access Project and Physicians for Reproductive Health and Choice joined me in convening a public hearing in New York City on pending action by [FDA] on mifepristone . . . . [I am] also concerned about the restrictions on access to RU-486 that FDA is said to be considering.")[FDA FOIA Release: MIF 001288-1302]; Sheryl Gay Stolberg, "F.D.A. Adds Hurdles in Approval of Abortion Pill," *New York Times* (June 8, 2000): at A21 ("The long-running effort to bring the French abortion pill to women in this country has encountered yet another obstacle: a suggestion by [FDA] that it may place tight restrictions on how the drug, RU-486, is distributed and who can prescribe it."); Letter, U.S. Representative Lynn Woolsey to Dr. Jane Henney (June 22, 2000): at 1 ("However, I am deeply concerned about recent press reports about proposed restrictions.") [FDA FOIA Release: MIF 006372].

[241] As noted above, because FDA had accorded priority review to mifepristone, the approval process was slated for completion by September 30, 2000.

[242] *See* Meeting Minutes, re: Approvability Issues Related to Labeling and Distribution Plan for Mifepristone (July 19, 2000): at 2-4 [FDA FOIA Release: MIF 004661-65].

[243] *See id.* at 2.

[244] *Id.* at 2.

require pre-procedure ultrasounds.[245] Furthermore, FDA stated "that it is not necessary to require the patient to take the drugs in the presence of health care provider."[246]

Among the unresolved issues at the conclusion of the July 19, 2000 meeting was the question of whether prescribing physicians should be limited to those who were able to perform surgical abortions, a provider qualification FDA believed was necessary:

> FDA requests that the ability to perform vacuum aspirations and/or D&Cs be added to provider qualifications. Providers also need to have access to emergency services. The need for surgical intervention is predictable unlike with other drugs. All OB/GYNs and other practitioners of women's health have these skills. The countries with experience with mifepristone have tight provision of complete services and have a long record of good outcomes.[247]

The Population Council later rejected FDA's request,[248] and the agency acquiesced.[249]

Despite its persistent concerns, FDA approved a regimen that posed the very risks to women's health that the agency had previously identified. When it approved Mifeprex, FDA stated that "[u]nder 21 CFR 314.520, distribution of the drug is restricted as follows:"

> Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:
>
> - Ability to assess the duration of pregnancy accurately.
> - Ability to diagnose ectopic pregnancies.
> - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
> - Has read and understood the prescribing information of Mifeprex™.

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[245] *See id.* at 3.

[246] *Id.* at 3.

[247] *Id.* at 3.

[248] *See* Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 6 (arguing that bolstering the provider qualifications in this way would be "not only unnecessary, but also in fact potentially counterproductive for patients")[FDA FOIA Release: MIF 0001373-81].

[249] *See* Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 [FDA FOIA Release: MIF 004587-88].

- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement, and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's records.[250]

In addition, the restrictions include a requirement that distribution be carried out in accordance with the plan submitted to FDA by the Population Council in a March 30, 2000 submission.[251] Even as it assented to a regimen that lacked critical safeguards, FDA took a number of steps that indicated its lingering concerns about the safety of the drug. First, FDA ultimately decided to rely on an infrequently used provision in Subpart H in hopes of ensuring that mifepristone would be used safely and, if necessary, could be withdrawn from market rapidly.[252] Second, the staff insisted that the mifepristone label "include a black boxed warning describing the major requirements and conditions for use."[253] "FDA generally reserves boxed warnings for serious or

[250] Mifeprex Approval Letter at 2.

[251] *See* Mifeprex Approval Letter at 2.

[252] *See* 21 C.F.R. 530 ("Withdrawal Procedures"). *See also* FDA, Memorandum, re: NDA 20-687 (Feb. 17, 2000): at 3 [FDA FOIA Release: MIF 000583-85]. As late as July 19, 2000, the question of whether to use Subpart H was deemed to be an "Outstanding Issue." *See* Meeting Minutes, re: Approvability Issues (July 19, 2000): at 4 [FDA FOIA Release: MIF 004661-65].

[253] FDA, Memorandum, re NDA 20-687 (Feb. 17, 2000): at 2. The Population Council, which opposed the inclusion of such a warning, ultimately persuaded FDA to agreed to a pared-down Black Box Warning, which would merely direct the prescribing physician (i) to plan in advance for emergency care, and (ii) to make available to the patient and provide her with the opportunity to discuss the patient information and patient agreement. *See* Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 1-2 [FDA FOIA Release MIF 0001373-81].

life-threatening risks that best can be minimized by conveying critical information to the prescribing doctor in a highlighted manner."[254]

FDA's willingness to tailor the restrictions on Mifeprex to suit the demands of the Population Council and Danco will continue to manifest itself in serious adverse events among the women who use the Mifeprex Regimen. Some of the most critical flaws in the approved regimen are discussed below along with serious adverse events that have already been reported.

1. The Approved Regimen Is Unsafe Because It Does Not Require Ultrasound

a. Ultrasound Is Necessary to Accurately Date Pregnancies

The gestational age of a woman's pregnancy is a critical factor in determining whether she is an appropriate candidate for a mifepristone abortion. In order to minimize the risks of hemorrhage, incomplete abortion and continuing pregnancy, the gestational age of the pregnancy must be less than or equal to 49 days.[255] The authors of the Spitz Article, for example, found that "[f]ailures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of the pregnancy."[256] Through the combination of mifepristone and

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[254] Judith E. Beach et al., "Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs," *Food and Drug Law Journal* 53 (1998): 403-412, at 403 (available at: <http://www.fdli.org/pubs/Journal%20Online/53_3/art2.pdf>). *See also* 21 C.F.R. § 201.57(e) ("Warnings").

[255] As noted above, the gestational age of a pregnancy is based on the first day of a woman's last menstrual period, which is designated as Day 1 of the pregnancy.

[256] Spitz Article, *infra* Appendix A, at 1241. "The largest increase was in failures representing ongoing pregnancy, which increased from 1 percent in the [less than or equal to] 49-days group to 9 percent in the 57-to-63 days group (P<0.001)." Children born from ongoing pregnancies, after a failed application of the Mifeprex Regimen, may suffer birth defects, fertility problems, or other health problems later in life. Researchers have found evidence linking misoprostol and birth defects such as missing or deformed limbs and misshapen skulls. Much of this research was conducted in Brazil, where numerous women have attempted to induce abortions using misoprostol alone. *See, e.g.,* Sylvia Pagán Westphal, "Birth Defects Caused by Ulcer Drug Abortions," *NewScientist.com* (29 Aug. 2001) ("Several studies in Brazil, where up to 75 percent of clandestine abortions involve misoprostol, suggest the drug causes birth defects such as fused joints, growth retardation and a condition known as Möbius syndrome, which is characterised by paralysis of the face."); Iêda M. Orioli and Eduardo E. Castilla, "Epidemiological

misoprostol, "pregnancy was terminated in 762 of the 827 women pregnant for [less than or equal to] 49 days (92 percent), 563 of the 678 women pregnant for 50 to 56 days (83 percent), and 395 of the 510 women pregnant for 57 to 63 days (77 percent) . . . ."[257] The study also found that "[a]bdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding also increased with advancing gestational age."[258] Due to the significant increase in failures and complications with increasing gestational age, FDA approved Mifeprex only for pregnancies of less than or equal to 49 days' gestation.[259]

The only way to date a pregnancy with the degree of accuracy necessary to exclude women whose pregnancies are beyond 49 days' gestation is by use of transvaginal ultrasound. FDA severely undermined the limitation on gestational age, however, when it failed to require

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Assessment of Misoprostol Tetratogenicity," *British Journal of Obstetrics and Gynaecology* 107 (April 2000): 519-23, at 522 (". . . there is an association of prenatal use of misoprostol as an abortifacient and congenital defects of vascular disruption type."); F.R. Vargas *et al.*, "Prenatal Exposure to Misoprostol and Vascular Disruption Defects: A Case-Control Study," *American Journal of Medical Genetics* 95 (2000): 302-306, at 306 ("add[ing] epidemiological basis to the growing body of evidence that prenatal exposure to misoprostol is related to the occurrence of vascular disruption defects in some exposed fetuses."). FDA determined that data submitted by the Population Council from a survey of fetal abnormalities in 82 pregnancies that were exposed to mifepristone alone or in combination with misoprostol was inconclusive. *See* FDA Mifeprex Approval Memorandum, *infra* Appendix A, at 4. FDA acknowledged, however, the possible link between misoprostol and birth defects. *See* Medical Officer's Review, *infra* Appendix A, at 18 (". . . medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects)."). The need for a study of the possible joint effects of mifepristone and misoprostol on babies born after a failed application of the Mifeprex Regimen was highlighted by the abnormalities discovered in a fetus exposed to misoprostol and mifepristone. *See* Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Number 3877547-X (March. 1, 2002) (French report of numerous deformities in fetus that was exposed to mifepristone and misoprostol but survived until a subsequent surgical abortion was performed; "The anatomopathology examination showed a meningo-encephalocele. The left hand was constituted of only two fingers (oligodactylia), left and right foot were constituted of only one finger (monodactylia). There was a facial dysmorphia.").

[257] Spitz Article, *infra* Appendix A, at 1241.

[258] Spitz Article, *infra* Appendix A, at 1241. In order to treat vaginal bleeding, "[t]wo percent of the women in the [less than or equal to] 49-days group, as compared with 4 percent in each of the other two groups, were hospitalized, underwent surgical intervention, and received intravenous fluids (P=0.008)." *Id.*

[259] FDA's Medical Officer's Review noted: "The success of medical termination of pregnancy decreased with advancing gestational age and the incidence of adverse events increased with advancing gestational age." Medical Officer's Review, *infra* Appendix A, at 18. The review stated further: "This method of pregnancy termination is of limited value because of the relatively short window of opportunity, in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period." *Id.*

the ultrasound dating of pregnancies. FDA's approved regimen relies instead on a patient's recollection of her menstrual history and a physical examination. Dating based on menstrual history is inherently inaccurate because women may not have a perfect 28-day menstrual cycle[260] and because 25 percent of women experience bleeding during the early stages of pregnancy.[261] Gestational dating through physical examination, even when carried out by experienced clinicians, can also be inaccurate.[262] Factors such as patient body size, uterine fibroids, previous parity, and uterine position may impair a clinician's ability to assess uterine size.[263] Transvaginal ultrasound, by contrast, is accurate within plus or minus 3 days at gestational ages of 5 to 7 weeks.[264] "Transvaginal ultrasonographic examination is necessary to ensure accurate gestational

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[260] *See, e.g.,* Leon Speroff, M.D., Robert H. Glass, M.D., and Nathan G. Kase, M.D., *Clinical Gynecologic Endocrinology and Infertility*, 5th ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 219 ("The perfect 28 day cycle is indeed the most common mode, but it totaled only 12.4% of Vollman's cycles. Overall, approximately 15% of reproductive age cycles are 28 days in length. Only 0.5% of women experience a cycle less than 21 days long, and only 0.9% a cycle greater than 35 days. Most women have cycles that last from 24-35 days, but at least 20% of women experience irregular cycles.").

[261] *See* Peter W. Callen, M.D., *Ultrasonography in Obstetrics and Gynecology* 2nd ed. (Phila, Pa: W.B.Saunders Company; Harcourt, Brace, Jovanovich, 1988) at 32 ("Threatened abortion is a common complication that occurs in approximately 25% of clinically apparent pregnancies."); Speroff, *et al*, *Clinical Gynecologic Endocrinology and Infertility*, 5th ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 536 (noting that "pregnancy and pregnancy-related problems such as ectopic pregnancy or spontaneous abortion" can cause uterine bleeding).

[262] Steven R. Goldstein, M.D., Francis R. M. Jacot, M.D., Claude Poulin, M.D., and D. Scott Poehlmann, M.D., "Documenting Pregnancy and Gestational Age," Chapter 4, in Maureen Paul et al., eds., *A Clinician's Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999) ("*A Clinician's Guide*"): at 41 ("Although clinical sizing of the uterus during the first trimester can provide a rough estimate of gestational age, it is imprecise; misestimation of gestational age by uterine sizing alone can occur even in the hands of experienced clinicians.").

[263] *See A Clinician's Guide*, *infra* Appendix A, at 41 ("a number of conditions such as leiomymas, multiple gestation, and obesity may severely limit the accuracy of gestational age assessment by physical examination, warranting preprocedure assessment by ultrasonography in known or suspected cases") (footnotes omitted).

[264] *See* Salim Daya, M.B., "Accuracy of Gestational Age Estimation Using Fetal Crown-rump Measurements," *American Journal of Obstetrics and Gynecology* 168 (March 1993): 903–908; Ivar K. Rossavik, M.D., George O. Torjusen, M.D., and William E. Gibbons, M.D., "Conceptual Age and Ultrasound Measurements of Gestation Age and Crow-Rump Length in *in Vitro* Fertilization Pregnancies," *Fertility and Sterility* 49 (1988): 1012-17. *See also* Mitchell D. Creinin, M.D. and Heather Jerald, "Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria," *American Journal of Obstetrics and.Gynecology* 180 (1999): 35-41. In this study comparisons of gestational age estimates based on the last reported menstrual period to those generated through ultrasound in patients presenting for medical abortion, revealed the former method to be significantly inaccurate in approximately half the cases. The authors observed: "It is interesting that in this population of women seeking abortion the gestational age according to the LMP [last menstrual period] was verified

dating for provision of medical abortion according to current standards in clinical guidelines established by the National Abortion Federation."[265]

b. Ultrasound Is Necessary to Identify Ectopic Pregnancies

Approximately two percent of all pregnancies in the United States are "ectopic pregnancies," in which the pregnancy is located outside the uterus – often in the fallopian tube.[266] Mifeprex does not terminate ectopic pregnancies.[267] Therefore, if a woman who has an ectopic pregnancy undergoes a mifepristone-misoprostol abortion, she is at risk for tubal rupture and subsequent hemorrhage due to delay in diagnosis and delay in treatment. The symptoms of an ectopic pregnancy – vaginal bleeding, pelvic pain, and cramping – are confusingly similar to certain side effects of the Mifeprex Regimen.[268] A woman with an ectopic pregnancy is at risk of suffering massive intra-abdominal hemorrhage, damage to her reproductive organs, permanent

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by the transvaginal ultrasonographic examination only 48% to 56% of the time when a gestational sac was present and only 55% to 64% of the time when an embryonic pole was present . . . . These results, though, do not even include those women who were excluded from the studies because the ultrasonographic examination findings were so different from the dates by LMP that the estimation of gestational age was changed too much for them to be included." *Id*.

[265] Mitchell D. Creinin, M.D. and Heather Jerald, "Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria," *American Journal of Obstetrics and.Gynecology* 180 (1999): at 35-41 (text preceding n. 8) (citation omitted).

[266] Centers for Disease Control, "Ectopic pregnancy – United States, 1990-1992," *Morbidity and Mortality Weekly Report* (*MMWR*) 44 (No. 3) (Jan. 27, 1995): at 46. The number of ectopic pregnancies may be even higher now because sexually transmitted diseases and other causes of ectopic pregnancy are more widespread than they were in 1992 – the latest year for which the Centers for Disease Control have reported the number of ectopic pregnancies. *Id*. at 46-7.

[267] *See, e.g*., Beth Kruse *et al.*, "Management of Side Effects and Complications in Medical Abortion," *American Journal of Obstetrics and Gynecology* 183 (2000): S65-S75, at S72 ("Mifepristone has not proved effective in treating extrauterine pregnancy . . . .").

[268] *See* American College of Obstetricians and Gynecologists, "Medical Management of Abortion," *ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists* 26 (April 2001): at 6 (noting that in medical abortions, "women may even experience symptom resolution consistent with a complete medical abortion and still have a persistent gestational sac or even an ectopic pregnancy") ("ACOG Practice Bulletin"). Vaginal bleeding, for example, is a normal consequence of the Mifeprex Regimen and may continue for weeks after a woman ingests Mifeprex and misoprostol. *See, e.g.,* Spitz, *infra* Appendix A, at 1243 ("Vaginal bleeding is a natural consequence of the abortion process, and it occurred in all the women whose pregnancies were terminated

sterility, and even death if not promptly treated by emergency surgery. The authors of a French mifepristone study in which a participant with an ectopic pregnancy underwent emergency surgery to stop heavy bleeding, concluded that:

> The case of undiagnosed ectopic pregnancy, which ruptured suddenly 2 days after misoprostol intake, indicates that (1) mifepristone plus misoprostol is not an effective treatment of ectopic pregnancies and should not be used for this purpose, and (2) all medical means of detecting an ectopic pregnancy should be used before prescribing mifepristone plus misoprostol.[269]

Although the Mifeprex Label states that the Mifeprex Regimen is contraindicated for women with a "[c]onfirmed or suspected ectopic pregnancy,"[270] FDA did not require that ultrasound be used to exclude women with ectopic pregnancies. Instead, the approved regimen relies solely on a self-certification by the prescribing physician that she has the "[a]bility to diagnose ectopic pregnancies."[271] A physical examination alone cannot accurately identify ectopic pregnancies. Ultrasound, "[i]n addition to providing the best information for gestational age determination . . . can also provide useful diagnostic information regarding a wide variety of pathologies of early pregnancy," including ectopic pregnancies.[272]

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medically. The median duration of bleeding or spotting was 13 days in the [less than or equal to] 49-days group and 15 days in the other two groups (P<0.001).").

[269] Elizabeth Aubény, *et al.*, "Termination of Early Pregnancy (Up to 63 Days of Amenorrhea) with Mifepristone and Increasing Doses of Misoprostol," *International Journal of Fertility & Menopausal Studies* 40 (1995): 85-91, at 91.

[270] *See* Mifeprex Label ("Contraindications").

[271] *See* Mifeprex Prescriber's Agreement.

[272] *A Clinician's Guide*, *infra* Appendix A, at 47-8.

2. FDA's Approved Regimen Is Not Restricted to Properly Trained Physicians who Have Admitting Privileges to Emergency Facilities

FDA's approved regimen lacks any objective qualifications for prescribing physicians and administering health care providers.[273] The health care provider administering the Mifeprex Regime need not undergo training, may not necessarily be an obstetrician or gynecologist, may not have any surgical training or training in the management of abortion complications, and may not even be a physician.[274] For example, the Mifeprex Regimen could be administered by a nurse untrained in any type of abortion and under the remote supervision of a family practitioner who does not regularly practice obstetrics and is incapable of providing emergency care.

Physicians and the health care staff that they supervise require formal training in both pharmaceutical and surgical abortion to minimize the morbidity inherent in performing mifepristone abortions.[275] National Abortion Federation guidelines provide that "[a]ll personnel performing abortions must receive training in the performance of abortions and in the prevention,

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[273] Self-certifications do not provide an effective substitute for imposing objective, auditable requirements. The Mifeprex Prescriber's Agreement, for example, merely requires that the prescribing physician profess to have the "[a]bility to assess the duration of pregnancy accurately." The vacuity of this stipulation is illustrated in remarks made by Dr. Susan Allen (who later became an FDA official) before the FDA Advisory Committee. Dr. Allen stated, "If you also recall when you go through medical school you learn how to date a pregnancy." FDA Hearings Transcript, *infra* Appendix A, at 319.

[274] *See* Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 ("the distribution system would allow for physicians to obtain the drug product after meeting all qualifications, but Mifeprex could be administered by someone who is under the supervision of that physician such as midwives or nurse practitioners")[FDA FOIA Release: MIF 004587-88]; *see also*, Mifeprex Approval Memo, *infra* Appendix A, at 4-5 ("Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician from dispensing the drug to patients, provided state laws permit this.").

[275] A survey of methotrexate abortion providers underscores the necessity of training in both medical and surgical abortion. *See* S. Marie Harvey, Linda J. Beckman, and Sarah J. Satre, "Experiences and Satisfaction with Providing Methotrexate-Induced Abortions among U.S. Providers," *Journal of the American Medical Women's Association* 55 (2000): 161-63, at 162 (In a study comparing methotrexate and surgical abortion, "[m]ost providers felt strongly that all clinic staff should be familiar with both procedures and, thus, the training needs would be equivalent. This thought was echoed not only by physicians, who must be prepared to perform an emergency surgical abortion if methotrexate fails, but also by other clinic personnel. Thirty-nine percent of providers thought that medical abortion

recognition, and management of complications."[276] Additionally, ACOG recommends that "[c]linicians other than obstetrician-gynecologists who wish to provide medical abortion services should work in conjunction with an obstetrician-gynecologist or be trained in surgical abortion in order to offer medical abortion treatment."[277] The necessity for training in surgical abortion as well as mifepristone abortion stems primarily from the high failure rate of the Mifeprex Regimen. In the U.S. Clinical Trial, the Mifeprex Regimen failed for 8 percent of women with pregnancies of less than or equal to 49 days' gestational age.[278]

Excessive bleeding, which is much more common following a Mifeprex abortion than a surgical abortion, is particularly likely to necessitate urgent surgical intervention. Based on an international study comparing surgical and medical abortion, FDA's Medical Officer noted that "[o]n the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients" and characterized this as a "serious potential disadvantage of the medical method."[279] In the U.S. Clinical Trial among patients whose pregnancies were of no more than 49 days' gestation, excessive bleeding resulted in one blood transfusion, two hospitalizations, two emergency room treatments, and thirteen surgical interventions.[280] In

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required more training; specifically, learning to do a vaginal ultrasound and to handle the unpredictable outcomes of methotrexate abortion required lengthy training.").

[276] National Abortion Federation, "National Abortion Federation Clinical Policy Guidelines, 1998," Appendix, in Maureen Paul et al., eds., *A Clinician's Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999): at 256 ("*A Clinician's Guide*").

[277] ACOG Practice Bulletin, *infra* Appendix A, at 6.

[278] *See* Medical Officer's Review, *infra* Appendix A, at Table 1. Seventeen percent of women with pregnancies of between 50 and 56 days' gestational age and 23 percent of women with pregnancies between 56 and 63 days were failures. *See id.* In an international study reviewed by the Medical Officer, failure rates for mifepristone abortion were 5.2 percent, 8.6 percent and 16 percent in India, China and Cuba respectively, while comparable failure rates for surgical abortion were 0, 0.4 percent, and 4.0 percent. *See* Medical Officer's Review, *infra* Appendix A, at 19.

[279] Medical Officer's Review, *infra* Appendix A, at 19 (no citation by FDA Medical Officer).

[280] Medical Officer's Review, *infra* Appendix A, at 17.

addition, 5 percent of the patients in this group received uterotonic agents to stem bleeding.[281] A delay in intervention may be life-threatening,[282] as was illustrated by the experience of one of the participants in the U.S. Clinical Trial. The treating physician described the incident to the FDA Advisory Committee:

> In November of 1994, I was called to the [emergency room] for a woman who was bleeding due to a miscarriage, and was in obvious shock. A blood test showed that she had lost between one-half to two thirds of her blood volume . . . .
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> I had thought she was having an incomplete miscarriage, but her husband . . . told me that she had taken RU486 approximately 2 weeks before. It was my clinical opinion that she would die soon if she did not have an immediate [dilation and curettage].
>
> Without even doing the routine preparation we normally do for surgery, I realized that I had to take her immediately to surgery to save her life. I took her to the operating room and removed the contents of her uterus surgically. I gave her two units of packed red blood cells intraoperatively.
>
> Even later that evening, . . . [s]he required two more units of blood because she was still orthostatic and symptomatic.[283]

The Mifeprex Regimen is contraindicated for "any patient who does not have adequate access to medical facilities equipped to provide emergency treatment."[284] FDA's approved regimen, however, does not require prescribing physicians to have *admitting* privileges to emergency facilities. The approved regimen requires only that a physician who is not able "to provide surgical intervention in cases of incomplete abortion or severe bleeding . . . ma[k]e plans to provide such care through others, and [be] able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary."[285] Plans for back-up care

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[281] Medical Officer's Review, *infra* Appendix A, at 17.

[282] When surgery is indicated because of acute bleeding, significant, or even life threatening blood loss, has already taken place. The preoperative preparation of the patient is often compromised in the rush to complete the surgery, which results in higher infection rates and more anesthetic complications, such as aspiration during intubation.

[283] FDA Hearings Transcript, *infra* Appendix A, at 223-25 (testimony of Dr. Mark Louviere).

[284] *See* Mifeprex Label ("Contraindications").

[285] Mifeprex Prescriber's Agreement. FDA, however, took two steps that suggested that it has lingering concerns about the absence of a surgical intervention qualification for Mifeprex prescribers. First, the Mifeprex Label includes a "black box" warning governing surgical back-up. Second, FDA required the Population Council to perform a post-approval study "[t]o ensure that the quality of care is not different for patients who are treated by

may be nothing more than "having the ability and responsibility to direct patients to hospitals, if needed."[286] Moreover, the approved regimen does not include an objective geographical limitation to ensure that the patient has easy access to the designated emergency care facility.[287]

3. The Sponsor's Recent "Dear Doctor Letter" and FDA's Explanatory Webpage Announcing Serious Adverse Events Validate the Petitioners' Concerns

On April 17, 2002,[288] Danco, with FDA's assistance, issued a letter to health care providers to alert them to "New Safety Information," to remind them that Mifeprex was approved for use in a prescribed regimen, and to encourage them to provide patient counseling and report adverse events.[289] The "New Safety Information" consisted of a number of reports of serious adverse events that had been experienced by women who were undergoing or had

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physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention . . . ." Mifeprex Approval Memo, *infra* Appendix A, at 5.

[286] Mifeprex Approval Memo, *infra* Appendix A, at 5. FDA's decision not to include a requirement that the prescribing physician have admitting privileges at a hospital could delay the patient's admission for emergency care. Another likely consequence of not requiring the prescribing physician to have admitting privileges is underreporting of serious adverse events related to the Mifeprex Regimen. The treating physician, not privy to the Prescriber's Agreement, may not file a serious adverse event report or notify the abortion provider of the complications that arose from the Mifeprex Regimen.

[287] The Chinese experience with mifepristone suggests that mifepristone should not be administered in facilities unable to provide potentially necessary emergency services. Thus, recently, the Chinese State Drug Administration responded to concerns that women were suffering as a result of lax controls on mifepristone by reiterating its policy that the drug "can only be administered at a hospital under a doctor's supervision and cannot be sold at pharmacies even with a prescription." *See* Kaiser Family Foundation, "China Reaffirms Restrictions on Unsupervised Mifepristone Use," *Kaiser Daily Reproductive Health Report* (Oct. 15, 2001) (available at: <http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=2&DR_ID=7453>) (reporting also that, "[t]hree years ago, the Shanghai Health Bureau restricted the use of mifepristone to certain hospitals in the area because of fears of complications").

[288] The letter bears the date, April 19, 2002, but was disseminated to the public on April 17, 2002.

[289] Danco Laboratories, Open Letter to Health Care Providers (Apr. 19, 2002) ("Dear Doctor Letter") (available at: <http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf>). Coincidentally, on the same day FDA and Danco publicized these serious adverse events, the agency also announced major changes to the Cytotec (misoprostol) label. *See* FDA, "Major Changes to Cytotec Labeling" (April 17, 2002). Pursuant to these labeling changes, pregnancy was removed from the list of contraindications on the Cytotec label and the black box warning cautioning pregnant women not to take the drug was also removed.

recently completed the Mifeprex Regimen.[290] A number of patients had suffered from ruptured ectopic pregnancies and one of these women died from hemorrhage.[291] The letter also reported "[t]wo cases of serious systemic bacterial infection (one fatal)."[292] The fatality apparently precipitated a halt in the Population Council's Canadian clinical trials of mifepristone.[293] Finally, a 21 year old woman suffered a heart attack three days after she completed the Mifeprex Regimen.[294] These and other adverse events had been reported to FDA through its Adverse Event Reporting System (AERS).[295] Two of the patients who were reported to have suffered life-threatening adverse events were 15 years old.[296] These incidents bear out the concerns about the safety of the regimen detailed above, and the relatively high rate of serious adverse events among adolescents is of particular concern.

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[290] The letter did not specify the number of adverse events about which Danco had been informed, but five individual cases were discussed.

[291] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[292] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[293] It appears that the woman reported to have died from a systemic bacterial infection was a Canadian trial subject. *See* Marnie Ko, "A Volunteer Dies While Testing a Controversial New Drug, Bringing the Trial to a Halt," The Report (Oct. 8, 2001) (available at: <http://report.ca/archive/report/20011008/p48ai011008f.html>). *See* also Henry P. Kaiser Family Foundation, "Population Council Announces Death of Woman Involved in Canadian Mifepristone/Misoprostol Trial," Daily Reproductive Health Report (Sept. 11, 2001) (available at: <http://www.kaisernetwork.org/Daily_reports/rep_index.cfm?DR_ID=6877>). A *Clostridium sordellii* infection apparently caused the woman to suffer septic shock. *See generally* G.L. Mandell, J.E. Bennett, and R. Dolin, *Principles and Practice of Infectious Diseases* (5th ed. 2000): at 2551 (explaining that a disease process in which "clostridia clearly play a major pathogenic role i[s] uterine gas gangrene, now a rare complication that was previously seen in the setting of septic abortion." "*C. sordellii* has been reported as a cause of uterine gas gangrene . . . ."). *See also* FDA Q & A's, *infra* Appendix A, at Question 3 ("Serious systemic bacterial infection is a severe life-threatening infection that spreads throughout the body and can cause death.").

[294] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[295] *See, e.g.,* Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3819498-2 (Nov. 2, 2001) (intervention to prevent permanent impairment or damage); 3806144-7 (Oct. 9, 2001) (death of a patient with an ectopic pregnancy); 3769840-6 (July 30, 2001) (hospitalization of patient with an ectopic pregnancy); 3769842-X (July 30, 2001) (intervention to prevent permanent impairment or damage); 3719885-7 (May 8, 2001) (death in conjunction with the use of misoprostol and Mifegyne, which is the trade name of mifepristone distributed in France); 3713452-7 (Apr. 27, 2001) (intervention to prevent permanent impairment or damage); and, 3769838-8 (July 30, 2001) (intervention to prevent permanent impairment or damage). The AERS depends on voluntary reporting and the accuracy of these reported adverse events cannot be verified, nor can the cause of these events be identified with certainty. There may have been other adverse events that were not reported.

Simultaneously with Danco's distribution of the *Dear Doctor Letter*, FDA published a webpage with 14 questions and answers related to mifepristone in an attempt to answer some of the questions likely to be prompted by the letter and to urge health care providers to adhere to the approved regimen.[297] FDA's answers, however, leave much to be desired from a medical and scientific standpoint.

First, FDA has understated the possibility that the Mifeprex Regimen caused the serious adverse events reported in the letter.[298] FDA did not adequately explain why women who were apparently healthy prior to undergoing the Mifeprex Regimen experienced life-threatening or fatal complications such as ruptured ectopic pregnancies, heart attacks, and systemic bacterial infections.

Second, FDA inappropriately attempted to link these adverse events to the unapproved vaginal administration of misoprostol.[299] It was reckless for FDA to suggest that the vaginal administration of misoprostol caused these adverse events while overlooking critical flaws in the

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[296] *See* Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3803789-5 (Oct. 3, 2001) and 3815629-9 (Oct. 26, 2001).

[297] FDA, "Mifepristone Questions and Answers 4/17/2002" ("FDA Q & As") (available at: <http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm).

[298] *See* Dear Doctor Letter, *infra* Appendix A, at 1 ("No causal relationship between any of these events and use of Mifeprex and misoprostol has been established."). An FDA official interviewed (without attribution) downplayed the connection between the Mifeprex Regimen and the adverse events. *See* Susan Okie, "Physicians Sent Abortion Pill Alert: Six Women Using RU-486 Taken Ill, and Two Died, Letter Says," *Washington Post* (Apr. 18, 2002): at A2 ("These are, in fact, a very small number of events. Some of them were clearly not caused by the drug regimen.").

[299] The repeated references to the unapproved vaginal use of misoprostol in the FDA Q & As give rise to the inference that the reported adverse events are attributable to this single departure from the Mifeprex Regimen. *See, e.g.,* FDA Q & As, *infra* Appendix A, at Question 1 ("In all of these cases, misoprostol was given vaginally, not orally, which is the approved regimen. FDA has not reviewed data on the safety and effectiveness of vaginal administration of misoprostol."); *id*. at Question 4 ("We do not know what role, if any, Mifeprex and 'off-label' use of vaginal misoprostol may have in developing serious infections."); *id* at Question 9 ("Why are physicians using misoprostol 'off-label,' in other words, using misoprostol vaginally at different doses? There are published studies of the use of mifepristone with vaginal administration of misoprostol for abortion. The misoprostol doses used in these studies are higher than those described in the Mifeprex labeling . . . ."); *id*. at Question 10 ("Are there risks with vaginal use of misoprostol?").

approved regimen for Mifeprex use in the United States. FDA should have first assessed essential aspects of this regimen.

It is clear, for example, that absent ultrasonographic screening for ectopic pregnancy, there is increased risk that an intact or rupturing ectopic pregnancy will be misdiagnosed as a normally progressing Mifeprex abortion. Additionally, Mifeprex abortions may be performed by practitioners who are not physicians, who cannot perform surgical abortions, or who are unable to diagnose ectopic pregnancies and their complications.

Nor is there reason to believe that systemic bacterial infection is more likely to occur following vaginal, rather than oral, administration of misoprostol. Misoprostol is commonly administered vaginally for the induction of labor without higher reported rates of either intrauterine or systemic infection when compared to orally administered misoprostol or other methods of labor induction. Rather, the occurrence of life-threatening infection in women undergoing a Mifeprex abortion should raise questions about whether prolonged genital tract bleeding in the artificial hormonal milieu created by the Mifeprex Regimen might foster or promote infectious complications. In addition, infection might occur in women who, believing that their abortion is complete and unaware that their uterus actually contains dead tissue, fail to return for follow-up visits.[300] This may be a particular problem when the Mifeprex Regimen is prescribed to adolescents.

The occurrence of a heart attack in a 21 year old woman is always cause for significant concern. A French woman undergoing a mifepristone abortion suffered a fatal heart attack in

[300] A. Karen Kreutner, M.D., "Postabortion Infections," *Contemporary Ob/Gyn* 1 (2001): at 37-42 (". . . because medical termination may be incomplete in between 3% and 23% of patients, retained tissue and subsequent infection may go unrecognized in those lost to follow up. . . . Some experts fear there will be compliance problems with the third visit, especially when the patient terminates early. In these cases, retained tissue, thought by the patient to be normal bleeding, could lead to endometritis.").

1991. A different prostaglandin (Sulprostone) administered by injection was used in that case.[301] This new case highlights the need for further investigation into a possible causal link between mifepristone-prostaglandin abortions and myocardial infarction.[302]

The ratio of serious adverse events to total uses of the Mifeprex Regimen cannot be ascertained because serious adverse event reporting is likely incomplete and because it is not publicly known how many times the Mifeprex Regimen has been used. Regardless of the relative number of serious adverse events, the nature of these events demands immediate FDA action to prevent future patient injuries and deaths.[303] The Joint Commission on the Accreditation of Healthcare Organizations[304] ("JCAHO" or "Joint Commission") has developed an approach for investigating adverse events similar in gravity to those that prompted the issuance of the Dear Doctor Letter. The JCAHO looks for "sentinel events" which are "unexpected occurrence[s] involving death or serious physical or psychological injury, or the risk thereof."[305] "Sentinel events" *signal* the need for the commencement of a "root cause

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[301] *See* "Noticeboard: A Death Associated with Mifepristone/Sulprostone," *Lancet* 337 (April 20, 1991): at 969-70 ("A spokeswoman for Roussel-Uclaf SA, the company that manufactures mifepristone, said 'the death was clearly from cardiovascular shock following 'Nalador' (Schering) injection.'").

[302] The Mifeprex Regimen should be contraindicated for women with cardiovascular risk factors until further clinical experience indicates that such contraindication is unnecessary.

[303] Even FDA acknowledged the rarity of the events referenced in the Dear Doctor Letter. With respect to bacterial infection, for example, FDA observed that "the rate of serious infection as a complication of pregnancy is 3.5 per 1000 pregnancies. Uterine infection occurs in 0.1-4.7% of first trimester surgical abortions and in 0.0-6.1% of medical abortions. In the past, it was most often associated with illegal abortions. It rarely occurs with pelvic surgery or even with otherwise normal childbirth." FDA Q & A's, *infra* Appendix A, at Question 3. FDA similarly noted the unusual nature of a heart attack in a young woman: "The single heart attack occurred in a 21 year old. A heart attack in very young women is extremely rare. . . . In 1997, the rate among US women aged 20-24 years was 0.19 per 100,000 women." *See id.* at Question 4.

[304] The Joint Commission "evaluates and accredits nearly 18,000 health care organizations and programs in the United States. An independent, not-for-profit organization, JCAHO is the nation's predominant standards-setting and accrediting body in health care. Since 1951, JCAHO has developed state-of-the-art, professionally based standards and evaluated the compliance of health care organizations against these benchmarks." Joint Commission webpage at: <http://www.jcaho.org/whatwedo_frm.html>.

[305] Joint Commission webpage at: <http://www.jcaho.org/sentinel/se_pp.html#I. Sentinel Events>.

analysis" of the event(s),[306] with the goal of developing an appropriate administrative response from the health care organization that will prevent the occurrence of future serious adverse events. A root cause analysis of sentinel events is performed before a statistically significant number of injuries or deaths occurs. It seeks to discern the facts surrounding each occurrence, distinguish factors peculiar to individuals from those pointing to procedural or administrative deficiencies, and recommend corrective measures to such systemic failures in the delivery of a particular therapy.

It is particularly important that FDA react to these sentinel events because the clinical trials underlying the approval of the Mifeprex Regimen did not adhere to FDA's endorsed scientific methodology for such trials. The substandard trial design of the U.S. and French Clinical Trials precluded an accurate estimation of the safety of the Mifeprex Regimen compared to the existing available alternatives. Moreover, FDA did not require the sponsor to conduct rigorous Phase IV studies, which could have compensated for some of these deficiencies by generating additional safety data. The agency has not performed a root cause analysis, but has instead hastily postulated that the vaginal administration of misoprostol is the underlying cause of the adverse events.[307] The Petitioners believe that there are probably more scientifically sound explanations for these adverse events and that the supposed safety of the Mifeprex Regimen has been called into question. The occurrence of the adverse events related to ectopic pregnancies and life-threatening systemic bacterial infections adds significant weight to the concerns of those

[306] The Joint Commission defines "root cause analysis" as "a process for identifying the basic or causal factors that underlie variation in performance, including the occurrence or possible occurrence of a sentinel event. A root cause analysis focuses primarily on systems and processes, not individual performance. It progresses from special causes in clinical processes to common causes in organizational processes and identifies potential improvements in processes or systems that would tend to decrease the likelihood of such events in the future, or determines, after analysis, that no such improvement opportunities exist." Joint Commission webpage at: <http://www.jcaho.org/sentinel/se_pp.html#Root cause analysis>.

who have long warned that mifepristone-misoprostol abortions are dangerous. FDA has previously dismissed such concerns but now must respond to the accumulating evidence and act accordingly. Withdrawal of the approval is warranted.[308]

H. FDA'S APPROVAL OF MIFEPREX SHOULD BE WITHDRAWN BECAUSE THE SPONSOR IS NOT ENFORCING THE LIMITED RESTRICTIONS ON THE USE OF MIFEPREX

Mifeprex abortion providers openly flout the restrictions included in the approved regimen without any reaction from FDA, Danco, or the Population Council.[309] Shortly after approval, FDA asserted that "[i]f restrictions are not adhered to, FDA may withdraw approval."[310] Subpart H authorizes FDA to withdraw approval of a drug approved under Section 314.520 if "[t]he applicant fails to adhere to the postmarketing restrictions agreed upon."[311] When it adopted Subpart H, FDA explained that "[t]he burden is on the applicant to ensure that

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[307] *See* FDA Q & As, *infra* Appendix A, at Nos. 1, 4, 9, 10, and 11.

[308] The Secretary of HHS is authorized by 21 C.F.R. § 314.530(a) to withdraw approval of a Subpart H drug, subject to the applicant's right to a hearing, if, among other things, "(3) [u]se after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug; (4) [t]he applicant fails to adhere to the postmarketing restrictions agreed upon; (5) [t]he promotional materials are false or misleading; or (6) [o]ther evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use."

[309] The absence of a reaction from Danco may not be surprising in light of the cavalier attitude towards the FDA approval process exhibited by Dr. Richard Hausknecht, who is Danco's medical director. As early as July 1994, Dr. Hausknecht, had used methotrexate and misoprostol in clinical tests in the U.S. that Dr. Mitchell Creinin, a prominent abortion researcher, described as "downright unethical" and which Sandra Waldman of the Population Council described as being "very risky." Dr. Hausknecht stopped these experiments in September 1994 when the FDA told him to "stop performing the abortions unless he gets the backing of a medical institution and submits his data and procedures to the FDA for review." Carol Jouzaitis, "Doctor's Abortion-Drug Technique Draws Fire," *Chicago Tribune* (Sept. 12, 1994): at 1 & 14. Dr. Hausknecht admitted, " 'This is a little bit uncharted.' . . . . But he declared: 'Damn it. I'm not going to wait. This is a step forward. This is important. I want to see this available to women where it's not available now.' " *Id*. In addition, Dr. Hausknecht's website explains step two of the Mifeprex procedure that he employs: "At the conclusion of the [first] visit, the patient receives a packet containing tablets of misoprostol which are to be taken orally or placed in the vagina depending on the regimen you and Dr. Hausknecht choose." Available at: <http://www.safeabortion.com/procedure.htm> (visited July 7, 2002). Both the home use and the vaginal administration of misoprostol contravene FDA's approved regimen.

[310] *See* Letter, Melinda K. Plaisier, Associate Commissioner for Legislation (FDA) to Senator Tim Hutchinson (Oct. 20, 2000): at 2 [FDA FOIA Release: MIF 002648-52].

[311] 21 C.F.R. § 314.530(a)(4).

the conditions of use under which the applicant's product was approved are being followed."[312] FDA should exercise its authority to withdraw its approval for Mifeprex.

Among the common departures from the approved regimen is the practice of offering the Regimen to women with pregnancies beyond seven weeks.[313] The "Mifepristone Medication Guide" directs women not to take Mifeprex if "[i]t has been more than 49 days (7 weeks) since your last menstrual period began." Moreover, women who use the Mifeprex Regimen sign a Patient Agreement, which includes a representation by the patient that "I believe I am no more than 49 days (7 weeks) pregnant.").[314] Thus, the practice of offering Mifeprex to women beyond seven weeks not only contravenes the approved regimen, but it also effectively requires patients to make an untruthful representation in the Patient Agreement. The *Los Angeles Times* explained that, "[B]y offering mifepristone up to the ninth week of pregnancy," Family Planning Associates, "the nation's largest for-profit abortion chain," "obtains a competitive edge over Planned Parenthood, which stays within the seven-week guideline."[315]

In another common deviation from the approved regimen, some abortion providers have eliminated the second of the three prescribed visits. During the initial visit, these providers give

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[312] *Subpart H Final Rule*, 57 Fed. Reg. at 58952.

[313] Liberty Women's Health Care of Queens, NY, openly acknowledges its use of Mifeprex beyond seven weeks: "While the FDA has approved mifepristone for non-surgical abortions only up to 7 weeks, we use a modified method to extend this period of eligibility in selected patients an additional 14 days up to 9 weeks." Available at: <http://www.abortbypill.com/2.html> (visited Dec. 31, 2001). Likewise, Preterm, an abortion clinic in Cleveland, Ohio, states that abortion using Mifeprex "is effective in terminating pregnancies up to 63 days (9 weeks) from the last normal menstrual period." Available at: <http://www.preterm.org/nonsurg.htm> (visited July 7, 2002).

[314] *See* Item 4 of the Patient Agreement for Mifeprex (mifepristone) Tablets ("Patient Agreement").

[315] Denise Gellene, "RU-486 Abortion Pill Hasn't Caught on in U.S.," *Los Angeles Times* (May 31, 2000): at A1 (quoting Family Planning Associates' official as saying, "You can catch a lot of women in those two [extra] weeks"). Family Planning Associates' website confirmed that the abortion provider offers Mifeprex to women with pregnancies up to nine weeks' gestational age. Available at: <http://www.webworldinc.com/fpamg/abortion_pill.htm> (visited July 7, 2002) ("Medical abortion is limited to patients less than nine weeks pregnant as verified by ultrasound.").

the patient misoprostol, typically with instructions to administer it to herself vaginally[316] at home two days later.[317] Yet home administration of misoprostol runs counter to what patients agree to in the Patient Agreement, which states that "I will . . . return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant."[318] The Population Council argued in favor of and FDA considered the benefits of self-administration at home, chief among which is the reduced burden on abortion providers and their facilities, but the agency concluded that these benefits are outweighed by the significant risks to women.[319] The second visit affords the physician the opportunity to monitor the status of

[316] The likely reason that FDA's approved regimen calls for oral administration is that it is the only mode of administering misoprostol that is currently approved by the FDA. As discussed above, however, the use of misoprostol in conjunction with mifepristone to effect abortions is itself an unapproved indication.

[317] Presidential Women's Center in West Palm Beach, Florida, for example, gives women "four Misoprostol 200 mcg tablets to take home. Forty eight hours after the Mifepristone tablets have been administered the woman moistens four Misoprostol tablets with tap water and inserts them high into her vagina with her fingers." Available at: <http://www.presidentialcenter.com/medical.html> (visited July 7, 2002). *See also*: <http://www.heritageclinic.com/abortion/medical_abortion_pill.htm> (visited July 4, 2002) (Two days after the patient takes mifepristone, she "inserts Cytotec vaginally, which causes the uterus to contract and expel the embryo. This is very similar to the procedure that was FDA approved in 2000 and is approximately 98% effective. **Note:** The FDA approved protocol calls for 3 Mifeprex pills taken orally the first day and 2 Cytotec pills taken orally two days later. However, subsequent studies have show[n] 1 oral Mifeprex and 4 vaginal Cytotec to be as effective with less gastro-intestinal upset."); *see also*: <http://www.fwhc.org/concord/pages/mifepristone.html> (visited July 7, 2002) (Concord Feminist Health Center's web site describes the second phase of the procedure: "In a few days she inserts misoprostol tablets into her vagina. The pregnancy usually ends at home within four hours."); *see also*: <http://www.gynemed.org/ru.html> (visited July 7, 2002) (Gynemed Surgi-Center's web site states: "You will be given two doses of Misoprostol tablets and instructions on how to insert them into your vagina, which you wil[l] do 48 hours after taking RU486."); *see also*: <http://www.hopeclinic.com/medab.htm> (visited July 7, 2002) (Hope Clinic for Women, Ltd. Explains: "You will receive pills, misoprostol ("miss o pross tul") to take home with you. You will be instructed when to use them; they are placed vaginally."). Even the National Abortion Federation, which initiated a nationwide advertising campaign for Mifeprex, sanctions home administration of misoprostol in its "Medical Abortion Start-Up Packet." *See* National Abortion Federation, "Protocol Recommendations for Use of Mifepristone and Misoprostol in Early Abortion," *Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations* (Washington, D.C.: National Abortion Federation, 2001) at 36 ("Home administration of vaginal misoprostol has been found to be safe and effective up to 63 days' gestation and is highly acceptable to patients.").

[318] *See* Patient Agreement, Item 14. *See also* Mifeprex Medication Guide, which explains that on "Day 3 at your provider's office," "your provider will check to see if you are still pregnant," and "[i]f you are still pregnant, take 2 misoprostol tablets."

[319] FDA, which in its 2000 Mifepristone Approvable Letter, agreed to the Population Council's proposal to allow home administration of misoprostol, rejected that option after reconsideration of the issue. *See* Mifeprex Approval Memo, *infra* Appendix A, at 2-3 ("The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council's statement that women could have the option of taking misoprostol on Day 3 either at home or at the

the termination[320] and assess the need for misoprostol – tasks which cannot be delegated to the patient.[321] In addition, the second visit enables patients whose abortions are complete to avoid having to take misoprostol.[322]

Danco and the Population Council have not effectively constrained providers of Mifeprex to adhere to the approved regimen. It appears instead that Danco and the Population Council have ignored well-publicized departures from that regimen. Deviations from the approved regimen are particularly troubling because the patient is told to disregard the regimen that she reads about in the Medication Guide and pledges to follow in the Patient Agreement. When a drug is approved under Subpart H, the drug's sponsor is responsible for ensuring compliance

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prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. . . . Returning to the health care provider on Day 3 for misoprostol, as in the U.S. clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.").

[320] Because of the complications that can arise, periodic monitoring during the termination process is important. For the significant percentage of patients that fail to return for the third visit, the second visit may be the last opportunity for a health care provider to monitor the termination. In the U.S. Clinical Trial, five percent of patients failed to return for the third visit. *See* Medical Officer's Review, *infra* Appendix A, at 10. In other studies, the "loss to follow-up has ranged from three to eleven percent." *See* Spitz Article, *infra* Appendix A, at 1246 (citations omitted). The rate of patients who do not complete the entire regimen in routine clinical practice is likely to be even higher as they will not necessarily be subject to the U.S. Clinical Trial's exclusion criteria, which, among other things, excluded women who were "unlikely to understand and comply with the requirements of the study." Medical Officer's Review, *infra* Appendix A, at 9.

[321] *See* ACOG Practice Bulletin, *infra* Appendix A, at 6 (*citing* Mitchell Creinin, *et al.*, "Methotrexate and Misoprostol for Early Abortion: A Multicenter Trial," *Contraception* 53 (1996): at 321-27) ("Women as well as their practitioners are often unable to judge correctly if the women have aborted by evaluating symptomatology. In clinical trials with methotrexate and misoprostol, only about half of women who thought they had aborted actually had done so."); Beth Kruse *et al.,* "Management of Side Effects and Complications in Medical Abortion," *American Journal of Obstetrics and Gynecology* 183 (2000): S65-375, S73 ("Studies demonstrate that women may be unable to judge correctly on the basis of symptoms whether abortion has occurred.").

[322] For those patients whose abortions are not complete, the benefits of in-clinic misoprostol use would be enhanced if patients were required to spend several hours afterward in the abortion facility, where they would have ready access to pain medication and other medical help even if the abortion does not occur during the observation period. The Population Council persuaded FDA not to include this requirement, which was included in the protocol for the U.S. Clinical Trial. Forty-nine percent of the participants expelled their pregnancies during the four-hour observation period after the administration of misoprostol. *See* Spitz Article, *infra* Appendix A, at 1243. Nevertheless, a post-misoprostol waiting period was likely disfavored because the protracted presence of large numbers of bleeding and cramping women could place a strain on abortion facilities.

with the restrictions included in the approved regimen for use of the drug.[323] The Population Council and Danco have shirked this responsibility. FDA, therefore, should withdraw its approval of Mifeprex.

I. THE U.S. CLINICAL TRIAL FOR MIFEPRISTONE DID NOT MIRROR THE ANTICIPATED CONDITIONS FOR THE ULTIMATE USE OF THE DRUG

As a general rule, "Phase 3 trials are usually [conducted] in settings similar to those anticipated for the ultimate use of the drug."[324] FDA, however, approved a regimen that does not contain important safeguards that were employed in the U.S. Clinical Trial.[325] In the U.S. Clinical Trial, for example, the investigators relied on transvaginal ultrasonography (along with menstrual history and pelvic examination) to confirm the gestational age of each pregnancy.[326] The use of ultrasonography also excluded women with ectopic pregnancies. Moreover, physicians participating in the U.S. Clinical Trial had experience in performing surgical abortions, were trained in the administration of the mifepristone-misoprostol procedure, and had admitting privileges at medical facilities that could provide emergency care and hospitalization.[327] In addition, "[a]ll patients were within one hour of emergency facilities or the

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[323] *See Subpart H Final Rule*, 57 Fed. Reg. at 58953 ("The limitations on distribution or use required under this rule are imposed on the applicant. Therefore, the burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed.").

[324] Bertram G. Katzung, M.D., Ph.D., and Barry A. Berkowitz, Ph.D., "Basic & Clinical Evaluation of New Drugs" in Bertram G. Katzung, ed., *Basic and Clinical Pharmacology*, 4th ed. (Norwalk: Appleton & Lange, 1989): at 56.

[325] The French Clinical Trials, which were not performed by the Population Council, are not discussed here because they were not conducted for the purpose of supporting the mifepristone NDA and, therefore, were not designed to reflect American conditions of use.

[326] *See* Spitz Article, *infra* Appendix A, at 1242.

[327] "The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and /or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists." Mifeprex Approval Memo, *infra* Appendix A, at 5. Medical Officer's Review,

facilities of the principle [*sic*] investigator."[328] In the U.S. Clinical Trial, after taking misoprostol, "women were monitored for four hours for adverse events."[329] FDA has not retained these requirements governing physician training, ultrasound, the post-misoprostol waiting period, or physician privileges at facilities that provide emergency care.[330] FDA should not have extrapolated conclusions about the safety and efficacy of FDA's approved regimen from data generated under trial conditions not mirroring the approved regimen. Effectively, therefore, the agency approved a drug regimen that it had not tested.

J. BY WAIVING THE PEDIATRIC STUDY REQUIREMENT, FDA MAY HAVE ENDANGERED THE HEALTH OF ADOLESCENT GIRLS

FDA's approval of Mifeprex violated FDA's regulations, effective April 1, 1999, requiring that new drugs be tested for safety and effectiveness in the pediatric population (collectively, the "*Pediatric Rule*").[331] Requiring data on girls age 18 and under also would have been consistent with the guidelines for trials in the pediatric population that FDA accepted at the

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infra Appendix A, at 6 (The U.S. Clinical Trial was "conducted at centers that could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures.").

[328] Mifeprex Approval Memo, *infra* Appendix A, at 5. The "one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services." *Id.* FDA contends that concerns arising from the elimination of the geographical proximity rule have "been dealt with through labeling, which makes it clear that if there isn't adequate access to emergency services, the medication is contraindicated." Mifeprex Approval Memo at 5.

[329] *See* Spitz Study, *infra* Appendix A, at 1242.

[330] The Prescriber's Agreement requires only that the supervising physician be "able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary." By contrast, the protocol for the U.S. Clinical Trial required that the physician have "privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc." Mifeprex Approval Memo, *infra* Appendix A, at 5. The shift in focus from access by the provider of the abortion to access by the woman who has the abortion, attenuated the link between the abortion provider and the emergency care provider, a link that is critical to ensuring that women receive timely emergency care.

[331] *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Final Rule*, 63 Fed. Reg. 66632 (Dec. 2, 1998) (*Pediatric Adopting Release*). The notice of proposed rulemaking was released as: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Proposed Rule*, 62 Fed. Reg. 43900 (Aug. 15, 1997).

International Conference on Harmonization.[332] Nevertheless, in the Mifeprex Approval Letter, FDA stated, "We are waiving the pediatric study requirement for this action on this application."[333] Thus, FDA approved Mifeprex for use without requiring safety and effectiveness testing for the pediatric population.[334]

As FDA noted when it adopted the *Pediatric Rule*, "many of the drugs and biological products that are widely used in pediatric patients carry disclaimers stating that safety and effectiveness in pediatric patients have not been established."[335] FDA observed that "the absence of pediatric labeling information poses significant risks for children."[336] The ICH has noted that adolescence "is a period of sexual maturation; medicinal products may interfere with the actions of sex hormones and impede development."[337] Such hormonal changes may "influence the results of clinical studies."[338] These concerns for the health of infants, children, and adolescents

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[332] *FDA Guidance: E11 Clinical Testing for Pediatric Uses* at 9 and 11 (Heading for Section 2.5.5). FDA, cognizant of the need for such studies, obtained a commitment from the sponsor in 1996 to conduct Phase IV studies to examine the safety and efficacy of the regimen in girls under 18 years of age. FDA subsequently curtailed this Phase IV study requirement when it approved the Mifeprex NDA.

[333] Mifeprex Approval Letter at 3.

[334] The Mifeprex Label accordingly included the standard disclaimer employed in drug labeling when the drug sponsor has not provided sufficient information to support a pediatric use for the drug: "Safety and effectiveness in pediatric patients have not been established."

[335] *Pediatric Adopting Release*, 63 Fed. Reg. at 66632.

[336] *Pediatric Adopting Release*, 63 Fed. Reg. at 66632.

[337] FDA, "Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population" (Rockville, Md.: Dec. 2000): at 11 (§ 2.5.5) ("*FDA Guidance: E11 Clinical Testing for Pediatric Uses*"). Section 2.5.5 states that the adolescent subgroup should extend from "12 to 16-18 years (dependent on region)." *Id.* at 11-12 (§ 2.5.5).

[338] *See FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses* at 12 (§ 2.5.5). These ICH concerns, quoted below, pertaining to the difficulty of testing drugs in the adolescent population amplify the need for FDA to have required clinical study of the difficulties that might arise when teenage girls undergo the Mifeprex Regimen:

> Many diseases are also influenced by the hormonal changes around puberty (e.g., increases in insulin resistance in diabetes mellitus, recurrence of seizures around menarche, changes in the frequency and severity of migraine attacks and asthma exacerbations). Hormonal changes may thus influence the results of clinical studies.
>
> Within this age group, adolescents are assuming responsibility for their own health and medication. Noncompliance is a special problem, particularly when medicinal products (for example, steroids) affect

prompted FDA to begin the rulemaking that culminated with the issuance of the *Pediatric Rule*, establishing "a presumption that all new drugs and biologics will be studied in pediatric patients" unless the requirement is waived.[339] More specifically, the *Pediatric Rule* requires that applicants seeking approval for new chemical entities, new biological products, new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration contain safety and effectiveness information on relevant pediatric age groups.[340]

FDA made clear that the Mifeprex NDA was covered by the *Pediatric Rule*.[341] Nevertheless, FDA fully waived the rule for Mifeprex without explanation. Full or partial

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appearance. In clinical studies compliance checks are important. Recreational use of unprescribed drugs, alcohol, and tobacco should be specifically considered.

The upper age limit varies among regions. It may be possible to include older adolescents in adult studies, although issues of compliance may present problems. Given some of the unique challenges of adolescence, it may be appropriate to consider studying adolescent patients (whether they are to be included in adult or separate protocols) in centers knowledgeable and skilled in the care of this special population.").

Id. at 12 (§ 2.5.5).

[339] *Pediatric Adopting Release*, 63 Fed. Reg. at 66634 (introduction to "II. Highlights of the Final Rule"). The importance of testing drugs in children was highlighted during the recent controversy surrounding FDA's attempt to suspend the *Pediatric Rule*. FDA's planned two-year suspension came in response to the passage of the Best Pharmaceuticals for Children Act, which offers incentives for manufacturers to test drugs in children. Public Law No. 107-109, 115 Stat. 1408 ("BPCA"). *See also* Association of American Physicians and Surgeons, Inc. v. FDA, Defendants' Motion for Stay of Proceedings, Civil Action No. 00-2898 (HHK) (Mar. 18, 2002). FDA later reversed its position in response to criticism from physicians and members of Congress. FDA's attempt to suspend the *Pediatric Rule* prompted the introduction of identical legislation in the House of Representatives and the Senate to codify the *Pediatric Rule*. *See* S. 2394, 107th Congress, 2nd Session (2002) (co-sponsors: Senators Hillary Rodham Clinton (D-NY), Mike DeWine (R-OH), and Chris Dodd (D-CT)); and H.R. 4730, 107th Congress, 2nd Session (2002) (co-sponsors: Representatives John D. Dingell (D-MI), Henry A. Waxman (D-CA), Rosa DeLauro (D-CT), Anna Eshoo (D-CA) and Sherrod Brown (D-OH)). As Senator Hillary Rodham Clinton, a co-sponsor of the Senate bill explained, "if we want to protect our children over the long term, then we in Congress need to step in and make the Pediatric Rule the law of the land. Short of taking that action, we risk denying children the protection that we require for adults." Press Release, "Senators Will Introduce Legislation to Codify Pediatric Rule" (Apr. 17, 2002) (available at: <http://clinton.senate.gov/~clinton/news/2002/04/2002417811.html>). *See also* Marc Kaufman and Ceci Connolly, "U.S. Backs Pediatric Tests In Reversal on Drug Safety," *Washington Post* (April 20, 2002): at A3.

[340] *Pediatric Adopting Release*, 63 Fed. Reg. at 66634 ("A. Scope of the Rule"), and as required pursuant to 21 C.F.R. § 314.55(a).

[341] The Mifeprex Approval Letter stated: "Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application." Mifeprex Approval Letter at 3. Because the Mifeprex NDA was filed before the Pediatric Rule went

waivers of the pediatric study requirement may be granted either upon request of the applicant or by FDA on its own motion.[342] Both FDA-initiated and sponsor-requested waivers must satisfy certain criteria. FDA is required to grant a full or partial waiver "if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver … have been met."[343]

Section 314.55 provides three procedural tracks by which an applicant may obtain a waiver of the study requirement. The first requires that two conditions being met: [344] (1)"[t]he drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients," *and* (2) the drug product "is not likely to be used in a substantial number of pediatric patients." With respect to this basis for waiver, FDA has "emphasize[d] that the study requirement applies to a product that offers a meaningful therapeutic benefit even if it is not used in a substantial number of pediatric patients, and vice versa."[345] As noted above, FDA, in connection with its determination to approve Mifeprex under Subpart H, concluded that the Mifeprex Regimen provides a therapeutic benefit over the existing treatment – surgical

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into effect, if a waiver had not been granted, the Population Council would have had until December 2, 2000 to submit "an assessment of pediatric safety and effectiveness." *See Pediatric Adopting Release*, 63 Fed. Reg. at 66658-59 ("V. Implementation Plan").

[342] Although it appears that FDA waived the rule *sua sponte*, FDA should have required the manufacturer to provide certain information to support the waiver. The agency has not released such documents to the public in response to FOIA requests. When it adopted the *Pediatric Rule*, the agency noted: "FDA agrees that the burden is on the manufacturer to justify waivers, but believes that the rule already adequately imposes that burden. The rule requires both a certification from the manufacturer that the grounds for waiver have been met and an adequate justification for the waiver request." *Pediatric Adopting Release*, 63 Fed. Reg. at 66648 (§ 29).

[343] 21 C.F.R. § 314.55(c)(4)("FDA action on waiver.").

[344] 21 C.F.R. § 314.55(c)(2)(i).

[345] *Pediatric Adopting Release*, 63 Fed. Reg at 66635 ("II.D.2. Waiver of the Study Requirement," *see* first paragraph).

abortion.[346] This conclusion by itself precludes FDA from using the first method for granting waiver of the *Pediatric Rule*.[347]

Even if FDA had not judged the Mifeprex Regimen to offer a "meaningful therapeutic benefit," the second requirement for waiver in this first track is not met because Mifeprex can be expected to be used in a "substantial number of pediatric patients," which FDA defines as "50,000 pediatric patients with the disease for which the drug or biological product is indicated."[348] In the *Pediatric Adopting Release*, FDA stated that the "relevant age groups will . . . be defined flexibly."[349] With respect to Mifeprex, it would have been appropriate to classify girls under the age of 18 as pediatric patients because safety and effectiveness in this population had not been studied.[350] If the pediatric population comprises all girls age 17 and under, then we estimate that there were 357,200 pediatric pregnancies per year from 1995 to 1997 in the United States.[351] If the pediatric population comprises all girls age 16 and under, then we estimate that there were a total of 196,520 pregnancies per year from 1995 to 1997.[352] Even if the pediatric population encompasses only girls age 15 and under, we estimate that there were

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[346] *See* Mifeprex Approval Memo at 6.

[347] FDA noted that, for purposes of the *Pediatric Rule*, it would rely "in part, on CDER's current administrative definition of a 'Priority' drug, applied to pediatric populations" to define "meaningful therapeutic benefit." The phrase, "meaningful therapeutic benefit," appears identical in the Subpart H and Priority review contexts. As noted above, Mifeprex was accorded priority review. The modifications to "meaningful therapeutic benefit" for purposes of the *Pediatric Rule* appear to have broadened the scope of the phrase. *See Pediatric Rule*, 63 Fed. Reg. at 66646.

[348] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647.

[349] *Pediatric Rule*, 63 Fed. Reg. at 66634 ("C. Age Groups"). After noting comments to the proposed rule that argued for flexibility in setting age definitions (including a comment arguing for "pediatric patient" to include those "from 0 to 21 years"), FDA stated that "the age ranges identified in the proposal may be inappropriate in some instances" and that it had "deleted the references in the rule to specific age ranges." *Id*. at 66651.

[350] Although FDA acknowledged that the safety and effectiveness of Mifeprex were not studied in girls under age 18 and required a statement to that effect in the labeling, the agency anticipated and even encouraged use in this population when it stated that: "there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients." Mifeprex Approval Memo at 7.

[351] *See infra* Appendix B at B-3.

[352] *See infra* Appendix B at B-4.

85,960 pregnancies per year from 1995 to 1997 in this age range.[353] Thus, under any definition of the pediatric population, the 50,000 patient cut-off set forth in the *Pediatric Adopting Release* is exceeded. In sum, *neither* of the requisite conditions for a waiver of the *Pediatric Rule* under the first waiver track provided in Section 314.55 is satisfied.[354]

Second, FDA may also waive the pediatric study requirements if the "necessary studies are impossible or highly impractical because, *e.g.*, the number of such patients is so small or geographically dispersed."[355] FDA explained that "that this ground for waiver [must] be interpreted narrowly":[356]

> Although the number of patients necessary to permit a study must be decided on a case-by-case basis, FDA agrees that there are methods available to conduct adequate studies in very small populations. . . . Because of the speed and efficiency of modern communications tools, geographic dispersion will justify a waiver only in extraordinary circumstances and will generally have to be coupled with very small population size. FDA is not persuaded that inability to recruit patients because of parental fears associated with administration of the drug is an adequate basis to conclude that studies are impractical where there is also evidence that similar products are regularly prescribed to pediatric patients outside of clinical trials.[357]

Pediatric Mifeprex studies would not have been either "impossible or highly impractical." As described above and in Appendix B, the population of pediatric females that becomes pregnant each year is large and the female population is evenly distributed throughout the United States. Thus, this second waiver track available under Section 314.55 could not have been satisfied (and FDA apparently has not taken a position to the contrary).

FDA may waive the pediatric study requirement under Section 314.55's third waiver track when "[t]here is evidence strongly suggesting that the drug product would be ineffective or

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[353] *See infra* Appendix B at B-4.

[354] *See* 21 C.F.R. § 314.55(c)(2)(i).

[355] *See* 21 C.F.R. § 314.55(c)(2)(ii).

[356] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647 (§ 26, final paragraph).

unsafe in all pediatric age groups."[358] As noted above, FDA endorsed the proposition that "there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen."[359] Thus, by suggesting that Mifeprex could be used appropriately in the pediatric population, FDA eliminated this third track as a possible basis for waiver.

Absent a waiver or deferral, the *Pediatric Rule* requires any drug application to "contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indication in all relevant pediatric subpopulations . . . ."[360] FDA is authorized instead to extrapolate such data from adult studies "[w]here the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients."[361] The underlying adult studies, however, must be "adequate and well-controlled."[362] As noted above, the Population Council did not provide evidence from adequate and well-controlled studies as to the safety and effectiveness of Mifeprex in the *adult* population. Reliance on these flawed adult studies for a determination of the safety and effectiveness of Mifeprex in the pediatric population was inappropriate. Furthermore, to assume that the effects of a potent antiprogesterone, mifepristone, and a

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[357] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647 (§ 26, final paragraph).

[358] 21 C.F.R. § 314.55(c)(2)(iii).

[359] Mifeprex Approval Memo at 7.

[360] 21 C.F.R. § 314.55(a). FDA stated that it was waiving the *Pediatric Rule*. Mifeprex Approval Letter at 3. The agency did not assert that it had made a determination that pediatric studies were not required because the adult trials were sufficient to support extrapolation of conclusions as to safety and effectiveness in the pediatric population. However, because FDA failed to provide any justification for its waiver, it is difficult to determine whether the agency was, in fact, relying on this provision to eliminate the pediatric study requirement for Mifeprex.

[361] *See* 21 C.F.R. § 314.55(a).

[362] *See* 21 C.F.R. § 314.55(a).

powerful prostaglandin analogue, misoprostol, in pregnant adults can be extrapolated to pregnant adolescents, who are still developing physiologically and anatomically, is medically unsound.[363]

FDA violated its own rules when it waived the Pediatric Rule in the face of explicit criteria that necessitated compliance with the rule.[364] Furthermore, FDA offered no explanation for its determination to waive the rule. As FDA's treatment of other drugs illustrates, a waiver would have been appropriate only if Mifeprex had already been tested in children and labeled accordingly, or if the *Pediatric Rule's* criteria for waiver were satisfied.[365] Because FDA waived the study requirement in the face of explicit criteria that appear to prohibit such action in this instance, the agency violated its rule. In addition to violating Section 314.55, FDA's unexplained waiver of the *Pediatric Rule* for the Mifeprex NDA constitutes agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.[366]

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[363] The Mifeprex Regimen acts upon the reproductive system, which changes dramatically during adolescence. Adolescents, for example, could face disruptions in ovulatory function as a result of concentrations of mifepristone in developing ovarian follicles, or other health problems. Moreover, teenagers may face heightened risks arising from decreased compliance with the full regimen, poor recall of their last menstrual period, and their reluctance to tell others about their pregnancies.

[364] Of course, a partial waiver of the study requirement is appropriate for the non-adolescent pediatric sub-groups. *See* 21 C.F.R. § 314.55(c)(3). According to *FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses*, the pediatric sub-populations other than "adolescents" are: 1) preterm newborn infants; 2) term newborn infants (0 to 27 days); 3) infants and toddlers (28 days to 23 months); 4) children (2 to 11 years). *FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses* at 9 (§ 2.5).

[365] In April 2000, FDA approved a suitability petition for Pamidronate Disodium Injection, 3 mg/mL, 10 mL vials, and 9 mg/mL, 10 mL vials, the listed drug products for which are Aredia (Pamidronate Disodium for Injection), 30 mg/vial and 90 mg/vial, and determined that the "proposed change in dosage form is subject to the Pediatric Rule but that a full waiver of the pediatric study requirement . . . is appropriate." *See* Letter, FDA to Mitchall G. Clark (April 18, 2000): at 1 (Docket No. 00P-0091/CPI) (concluding "that investigations are not necessary to demonstrate the safety and effectiveness of your proposed product in the pediatric population since the necessary studies are impossible or highly impractical because the number of patients is small and geographically dispersed"). *See also* Letter, FDA to The Weinberg Group, Inc. (June 13, 2000): at 1-2 (Docket No. 99P-5447/CPI) (approving a generic manufacturer's petition to file an Abbreviated New Drug Application for Cefaclor Chewable Tablets, 125 mg, 187 mg, 250 mg, and 375 mg, the listed drug products for which are Ceclor (Cefaclor) for Oral Suspension, 125 mg/5mL, 187 mg/5mL, 250 mg/5mL, and 375 mg/5mL because FDA determined that the "proposed change in dosage form is subject to the Pediatric Rule" but "that investigations are not necessary to demonstrate the safety and effectiveness of your proposed products in the pediatric population, because the specific drug products that you reference are adequately labeled for pediatric use").

[366] FDA has required numerous drug sponsors to comply with the *Pediatric Rule*, but it approved Mifeprex without stating its basis for waiving the requirement. *See, e.g.*, Letter, FDA to King & Spalding (June 13, 2000): at 1

K. FDA'S UNEXPLAINED REDUCTION OF THE SPONSOR'S PHASE IV REQUIREMENTS WAS ARBITARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

Not only did FDA improperly and without explanation waive its own pediatric testing requirements, but it also inexplicably narrowed the scope of the Population Council's commitments to conduct post-approval Phase IV studies. As a general rule, the clinical trials required by FDA to support an NDA are adequate to establish short-term drug safety and effectiveness. The standard pre-approval clinical trials, however, are typically incapable of providing either the amount or type of data necessary to assess a drug's long-term effects.[367] Phase IV, which occurs after a drug is approved, provides the opportunity to "monitor[ ] the safety of the new drug under actual conditions of use in large numbers of patients."[368] Not only

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(Docket No. 99P-2776/CPI) (denying a generic manufacturer's petition to file an Abbreviated New Drug Application for Oxycodone Hydrochloride and Acetaminophen Oral Solution, 7.5 mg/500 mg per 15 mL, the listed drug product for which is Oxycodone and Acetaminophen Tablets 7.5 mg/500 mg, based on the fact that FDA "has determined that your proposed change in dosage form is subject to the Pediatric Rule and has concluded that investigations are necessary to demonstrate the safety and effectiveness in the pediatric population . . . . Therefore, the Agency concludes that the proposed product should be evaluated for safety and efficacy in the pediatric population."); Letter, FDA to Abbott Laboratories (Sept. 29, 1999): at 1-2 (Docket No. 98P-0821/CPI) (denying a generic manufacturer's petition to file an Abbreviated New Drug Application for Hydromorphone Hydrochloride Injection, 0.2 mg/mL, 30 mL vials, the listed drug product for which is Dilaudid-HP Injection, 10 mg/mL, 5 mL ampoules and 50 mL vials, because the "proposed change in route of administration is subject to the Pediatric Rule," "clinical trials are required for this specific drug product," and "investigations are necessary to demonstrate the safety and effectiveness in the pediatric population").

[367] A.G. Gilman, T.W. Rall, A.S. Nies, P. Taylor, eds., *The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990): at 77 ("Although assessment of risk is a major objective of [clinical trials], this is far more difficult than is the determination of whether a drug is efficacious for a selected condition. Usually about 500 to 300 carefully selected patients receive a new drug during phase-3 clinical trials . . . . Thus, the most profound and overt risks that occur almost immediately after the drug is given can be detected in a phase-3 study, if these occur more often than once per 100 administrations. Risks that are medically important but delayed or less frequent than 1 in 1000 administrations may not be revealed prior to marketing. It is thus obvious that a number of unanticipated adverse and beneficial effects of drugs are only detectable after the drug is used broadly.").

[368] Bertram G. Katzung, M.D., ed., *Basic and Clinical Pharmacology*, 4th ed. (Norwalk, CT: Appleton & Lange, 1989): at 56. "Final release of a drug for general prescription use should be accompanied by a vigilant postmarketing surveillance program. The importance of careful and complete reporting of toxicity after marketing approval by the FDA can be appreciated by noting that many drug-induced effects have an incidence of 1:10,000 or less. . . . Because of the small numbers of subjects in phases 1-3, such low-incidence drug effects will not generally be detected before Phase 4, no matter how carefully the studies are executed. Phase 4 has no fixed duration." *Id*. at 56-7.

did FDA approve the NDA on the basis of clinical trials so defective with respect to their design and execution as to render them insufficient to establish short-term safety and effectiveness, but FDA also permitted the Population Council to substantially pare down the Phase IV trials that it would perform.

In response to an FDA request, on September 16, 1996, the Population Council agreed to conduct a set of Phase IV studies.[369] FDA "reminded" the Population Council of these commitments in both the 1996 and 2000 Approvable Letters.[370] The Population Council agreed to perform studies with the following objectives:

1. To monitor the adequacy of the distribution and credentialing system.
2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.
3. To assess the long-term effects of multiple use of the regimen.
4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.
6. To ascertain the effect on children born after treatment failure.[371]

These studies would have addressed some of the health issues that were not evaluated during pre-approval testing.

The Mifeprex Approval Letter released on September 28, 2000, however, contains only two Phase 4 study obligations, a radical curtailment of the earlier commitments.[372] The letter

[369] FDA made its request on August 22, 1996, after it had received Phase IV study recommendations from the FDA Advisory Committee. *See* Medical Officer's Review, *infra* Appendix A, at 20-24.

[370] *See* 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 7-8 and 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5.

[371] 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 7-8 and 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5.

[372] *See* Mifeprex Approval Letter, *infra* Appendix A, at 2-3.

stated that "the following Phase 4 commitments, specified in [the Population Council's] submission dated September 15, 2000 . . . *replace all previous commitments* . . . ."[373]

(1) "A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention."[374]
(2) "A surveillance study on outcomes of ongoing pregnancies."[375]

FDA stated that "[p]revious study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms."[376] The agency, thus, compounded its failure to require the Population Council and Danco to comply with the strictures of the Pediatric Rule when it permitted them to consider the effect of the Mifeprex Regimen on patients under 18 as part of another study rather than as a separate Phase IV study.[377] The Approval Letter explained that

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[373] Mifeprex Approval Letter, *infra* Appendix A, at 2.

[374] Mifeprex Approval Letter, *infra* Appendix A, at 3. The Population Council acknowledged three weaknesses of this study. First, the sample size would be limited so that the sponsor "will only be able to determine whether the combined safety rates of hospitalizations, medically necessary surgical interventions, and IV fluids in each of the two cohorts are within plus or minus 5 percentage points of the expected 2% rate. We will not be able to detect differences of individual safety outcomes such as blood transfusions and deaths." *See* Amendment 062 to the NDA, Revised Materials (Sept. 19, 2000): at 3. [FDA FOIA Release: MIF 007896-7903]. Second, the Population Council predicted that it might have difficulty finding women who were referred to another provider for care. *Id*. at 3-4. Third, it might be difficult to find women who did not return for their follow-up visit. *Id*. at 4. These three study weaknesses appear, at least in part, to stem from faulty selection criteria for study subjects. Patients should not be enrolled in a study unless they are willing to comply with follow-up visits and telephone inquiries. Additionally, informed consent forms authorize investigators to request medical records from other health care providers.

[375] Mifeprex Approval Letter, *infra* Appendix A, at 3.

[376] Mifeprex Approval Letter, *infra* Appendix A, at 3. These issues were characterized by the sponsor as "Secondary Study Objectives." *See* Amendment 062 to the NDA (Sept. 19, 2000): at 1. The failure to consider each issue in a separate study is likely to compromise the quality of the data generated. Because the study is primarily focused on a provider-level variable (ability to provide surgical intervention), the study will not necessarily yield a meaningful sample size for each of the relevant patient-level variables (age and smoking status). Patients will be enrolled "consecutively from each provider until the provider's quota is met." *See id.* at 2.

[377] The Population Council submitted data from the Spitz Study on 106 women age 35 and older and 51 patients under age 20. *See* Mifeprex Approval Letter, *infra* Appendix A, at 7. However, the effects and potential age-specific risks of the Mifeprex Regimen on women outside the tested age range deserve separate consideration in studies with far more subjects. Approximately 279,000 girls nineteen and younger and more than 84,000 women over the age of 35 obtain abortions in the United States annually. *See* Appendix B, *infra*, at B-4 (§§ 5 and 6). The Mifeprex Regimen, which directly interacts with the reproductive system, could conceivably interfere with pubertal development, as discussed above, and might pose unique risks to women who are nearing the end of their reproductive years.

"the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996."[378]

It appears, however, that the modifications came largely in response to the Population Council's unwillingness to explore the ramifications of the Mifeprex Regimen. On August 18, 1999, the Population Council acknowledged its Phase IV commitments, but stated that "[w]e plan to discuss in more detail and develop a consensus with the FDA post-NDA approval."[379] The Population Council complained, for example, that "[a] prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome, might result in an invasion of women's privacy and would not likely produce a meaningful scientific result for decades."[380] Similarly, the Population Council informed FDA that it was "not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing

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[378] Mifeprex Approval Memo, *infra* Appendix A, at 7. FDA's conclusion that the reduction to only two Phase IV studies "reflect[s] current postmarketing questions" ignores a number of issues about Mifeprex that remain unexplored. Because mifepristone interferes with pregnancy by binding to the progesterone receptor in the placenta, there is concern that the drug may affect not only the uterus, but the brain, breasts, adrenal glands, ovaries, and immune cells, all of which also have progesterone receptors. Concerns that mifepristone may have a carcinogenic effect on breast tissue have also been expressed. S*ee, e.g.,* Testimony of Dr. Joel Brind, FDA Hearings Transcript, *infra* Appendix A, at 172-175. Mifepristone also could affect the pituitary gland, the adrenal glands, and immune cells, all of which have glucocorticoid receptors. In addition, it is unclear whether a woman who undergoes multiple mifepristone-misoprostol abortions could suffer adverse effects. *See* ACOG Practice Bulletin, *infra* Appendix A, at 9 ("No well-designed prospective studies address the issue of repeat medical abortion."). Questions also remain about possible effects on the children born to women who have terminated a previous pregnancy with the Mifeprex Regimen. *See, e.g.,* P. Van der Schoot and R. Baumgarten, "Effects of Treatment of Male and Female Rats in Infancy with Mifepristone on Reproductive Function in Adulthood," *Journal of Reproduction and Fertility* 90 (1990): 255-66 (finding that rats exposed to mifepristone in their infancy suffered infertility in adulthood)[FDA FOIA Release: MIF 007165- 007176].

[379] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999).

[380] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999); s*ee also* Mifeprex Approval Memo at 7 (agreeing with the Population Council's reasoning).

this, as it could violate women's privacy."[381] The Population Council's concerns about privacy lack merit. Patients who participate in clinical trials give their consent to participate and to be monitored, thus eliminating concerns about privacy. Similarly, FDA should not have accorded undue weight to the Population Council's protestations about the potential expense of the trials; drug sponsors, who stand to profit from a drug's sales, are responsible for bearing the expenses incurred in establishing the safety and efficacy of a drug.[382]

FDA's acquiescence in the Population Council's reduction in its Phase IV commitments compounded the Agency's earlier failure to require the sponsor to conduct clinical trials in accordance with the requirements of Section 314.126 of FDA's rules. FDA's inadequately justified curtailment of the sponsor's Phase IV study commitments was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.

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[381] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999). The necessity of long-term monitoring is particularly critical to compensate for the unusually short tracking periods employed in the U.S. Clinical Trial, in which investigators generally did not track patients after their third visit. *See* Spitz Article, *infra* Appendix A, at 1242. "Follow-up was extended beyond visit 3 if there was uncertainty about the completeness of the abortion or if bleeding persisted." *Id*. Five percent of the participants in the U.S. Clinical Trial were not tracked through the third visit (which would have occurred on Day 15) because they failed to return for it, suggesting that each of these women was last seen on Day 3, only 2 days after the initial administration of mifepristone. *See* Medical Officer's Review, *infra* Appendix A, at 10. Abbreviated follow-up periods run counter to ICH standards, which state that in clinical trials of drugs intended for use during pregnancy, "followup of the pregnancy, fetus, and child is very important." *FDA Guidance (ICH: E8): General Considerations*, *infra* Appendix A, 62 Fed. Reg. at 66117 (§ 3.1.4.3) ("Special populations").

[382] In fact, the sponsors of Mifeprex received substantial outside funding to support their efforts. *See* "Mifepristone: FDA Approval Imminent, Advocates Predict," *Kaiser Daily Reproductive Health Report* (Sept. 28, 2000) (available at: <http://www.kaisernetwork.org/reports/2000/09/kr000928.3.htm>) ("Danco Laboratories, LLC, a small New York-based company, will market the drug with funding from billionaire financier Warren Buffet and hedge-fund czar George Soros and a $10 million loan from the David and Lucile Packard Foundation."); Sharon Bernstein, "Persistence Brought Abortion Pill to U.S.," *Los Angeles Times* (Nov. 5, 2000): at A1 ("The Population Council raised $16 million from like-minded foundations, including the Open Society Institute of New York, which is the philanthropic arm of billionaire George Soros, and the California-based Kaiser Family Foundation.").

IV. PETITIONERS SEEK LEAVE TO AMEND

The Petitioners respectfully inform FDA that they may file amendments to this Petition as information becomes available from Freedom of Information Act requests made before the filing date of this document.[383]

V. CONCLUSION

For the foregoing reasons, the Petitioners respectfully request that the Commissioner immediately enter an administrative stay to halt any further distribution and marketing of Mifeprex until final agency action is taken on this Petition. The Petitioners also respectfully request that the Commissioner revoke approval of Mifeprex for the medical termination of pregnancies less than 49 days' gestation. On the basis of the evidence presented above, the Petitioners respectfully request a full FDA audit of the French and U.S. Clinical Trials.[384]

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[383] The Petitioners have filed numerous Freedom of Information Act ("FOIA") requests with FDA that remain unanswered, including: 1) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Aug. 31, 2001) (seeking "an entire copy of FDA's letter to the Population Council dated, or mailed, on or about June 1, 2000, along with any attachments, appendices, and other accompanying materials"); 2) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Aug. 31, 2001) (seeking "an entire copy of the new drug application . . . filed . . . on or about March 18, 1996 (NDA 20-687)"); 3) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Sept. 14, 2001) (seeking a copy of data submitted by the sponsor "related to the use of mifepristone by women over the age of thirty-five, females under the age of eighteen, and women who smoke" and of the Phase IV study protocols submitted by the Sponsor and any Phase IV trial data); and, 4) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Feb. 6, 2002) (seeking a correct listing of all drug applications approved pursuant to 21 C.F.R. § 314.520 and documents detailing FDA's reasoning for approving drugs under this section of its rules).

[384] An audit of the U.S. Clinical Trial is additionally warranted because of an unusual data management decision made by the Population Council with the apparent approval of the FDA:

> Thank you for speaking with me the other day about our data dilemma. In response to our conversation, we have decided to create two versions of our electronic database from the mifepristone study. The first will reflect exactly the physical copies of the patient record forms, and will be used as the basis for our regulatory submissions to you. The second version will closely match the first, particularly on safety and efficacy indicators, but certain variables will be modified to create an internally consistent database that we can use easily for our planned scholarly publications on the topic. We will keep careful track of the changes we make and we will be able to explain them to an FDA auditor should the need arise. One result

VI. ENVIRONMENTAL IMPACT

This Petition for withdrawal of approval of an NDA is categorically excluded under 21 C.F.R. § 25.31(d). An environmental impact statement is, thus, not required.

VII. ECONOMIC IMPACT

The Economic Impact information shall be submitted only when and if requested by the Commissioner following review of the Petition, in accordance with 21 C.F.R. § 10.30.

CERTIFICATIONS AND SIGNATURES

On behalf of the petitioner organizations listed below, we the undersigned hereby certify that, to the best of petitioners' knowledge, this Citizen Petition is true and accurate. It includes all available information relevant to this Petition, including information both favorable and unfavorable to Petitioners' position in this matter.

So executed this ____ day of August 2002.

Donna Harrison, M.D.
Chairperson, Subcommittee on Mifeprex
American Association of Pro-Life
Obstetricians and Gynecologists
P.O. Box 414
Eau Claire, MI 49111
Phone: (616) 921-2513

of this approach to handling the data is that certain aspects of our future publications may differ from tabulations that appear in our regulatory submissions.

Letter, Charlotte Ellertson, Population Council, to [Redacted], FDA/CDER (July 28, 1997): at 1 [FDA FOIA Release: MIF 006489].

So executed this ____ day of August 2002.

/S/_____
Gene Rudd, M.D.
Associate Executive Director
Christian Medical Association
P.O. Box 7500
Bristol, TN 37621
Phone: (423) 844-1000

So executed this ____ day of August 2002.

/S/_____

Sandy Rios, President
Concerned Women for America
1015 Fifteenth Street, N.W.
Suite 1100
Washington, D.C. 20005
Phone: (202) 488-7000

EXHIBIT 21

Robert O'Harrow Jr.,
Drug's U.S. Marketer Remains Elusive,
Wash. Post (Oct. 11, 2000)

Democracy Dies in Darkness

Drug's U.S. Marketer Remains Elusive

Fearing Abortion Foes, Danco Keeps Location, Phone Number Secret

October 11, 2000 More than **24 years ago**

By Robert O'Harrow Jr.

NEW YORK -- When many pharmaceutical companies win federal approval to market a new drug, they rush out predictions of potential riches for investors. Not so with Danco Laboratories LLC.

"A lot of what we're about is not driven by the profit motive," explained Richard Hausknecht, medical director of the firm, which just received permission to market the abortion pill known as RU-486.

"I'm not in this to get rich, because it's not going to make me any money," said Hausknecht, who said he is paid by the hour for his part-time work at Danco. "Here's a chance to offer to American women a real new option, something that has been denied to them for political reasons for 15 years."

Secretive and obscure, Danco is one of the most enigmatic companies in the pharmaceutical industry. It has worked for years and spent millions of dollars to bring to market a drug that investors knew would immediately face intense resistance--and they feared possibly violent intervention--from people opposed to abortion.

Danco has only a handful of employees. For security reasons, company officials say, Danco's telephone number is unlisted and the details of its whereabouts are carefully guarded. Company officials will say only that Danco is housed in an ordinary suite of offices somewhere in midtown Manhattan.

They say Danco intends to make a profit eventually. Its immediate plan is to make RU-486 available in the United States within a month as an early alternative to surgical abortion. The cost of the procedure, which includes two drugs and three office visits, is expected to be about $300, around the same as a surgical abortion.

The company also intends to research the possibility that the drug could also be a treatment for ovarian cancer and other life-threatening ailments.

Food and Drug Administration officials agree that Danco is not the usual pharmaceutical company. The agency "followed all normal" procedures in approving the drug, including inspecting the manufacturing facilities, officials said. But regulators determined that information about the manufacturer was confidential under statutes governing trade secrets and freedom of information.

FDA Commissioner Jane E. Henney said the agency broke with precedent by not publishing the names of the experts who reviewed RU-486 for the agency. In another first, it did not publish the name or location of the company that will manufacture the drug.

Some antiabortion activists fear that because of Danco's secretive approach, it will not be held accountable the way other drug companies have.

"This company seems rather clandestine and, I believe, suspicious," said Judie Brown, president of the American Life League, an antiabortion group based in Stafford, Va. "Women should be able to know immediately who the provider of a particular product is."

Danco has a close relationship with the Population Council, a nonprofit reproductive-rights group that sponsored the drug for approval. In 1994, the Population Council was given the rights to sell RU-486 by French drugmaker Roussel-Uclaf SA, which was put off by the controversy surrounding the drug in the United States.

The council, supported by the Buffett Foundation and others intent on making abortion more accessible, in turn gave Danco the rights to manufacture and distribute the drug.

According to records filed in Delaware on Feb. 7, Danco was formed in the Cayman Islands on July 25, 1995. On those papers, Hausknecht was listed as vice president--a formality, he said, that lasted only a week.

Apart from some basic facts, company officials are chary with details about Danco's structure, its investors and its plans.

The chief executive is Roy Karnovsky, a former marketing executive for the Merck Human Health Division of Merck & Co. Through a spokesman, he declined to discuss the company.

Medical director Hausknecht is an associate professor of obstetrics and gynecology at Mount Sinai School of Medicine in New York. He also serves on an advisory board for Planned Parenthood and was the medical director for Planned Parenthood of New York City.

Danco's director of public affairs is Heather M. O'Neill, who has helped prepare materials for FDA hearings about the drug. O'Neill, a graduate of Harvard University's John F. Kennedy School of Government, previously worked as a consultant at the Population Council.

O'Neill, who joined Danco in 1997, declined to provide the names of individual investors. But she acknowledged that supporters generally share the company's desire to make RU-486 available.

Instead of talking about company profits, she refers to its "project."

"Everyone here is committed to this project, to making Mifeprex [the trade name for RU-486] available to all women," she said. "We've been singleminded in our determination in making Mifeprex an option American woman can have."

"It's extremely unusual," Kevin Schulman, director of the Center for Clinical and Genetic Economics at the Duke Clinical Research Institute. "Only people who are truly dedicated to 'the cause' would have stuck with it. The unique thing here is how everybody [involved] has a shared vision."

O'Neill said the company may eventually try to market RU-486 abroad but has no plans to do so now. "We, I think, would be interested in looking at certain other countries around the world," she said.

She said the company will soon have a higher profile at medical conferences and will begin providing educational material on how to use the drug safely and effectively.

The fact the manufacturer is not named would not prevent someone from filing an RU-486-related lawsuit. The target would be Danco, O'Neill said. "Danco is responsible for all aspects of the drug's introduction into the United States, from FDA compliance to manufacturing, marketing and distribution," she said.

O'Neill acknowledged that crucial financial support over the past decade came from several foundations.

The Buffett Foundation, which was begun by investor Warren E. Buffett and places a strong emphasis on reproductive issues, made at least $2 million in interest-free loans to the Population Council, according to tax documents filed in 1995. That money was in turn used to conduct clinical trials of RU-486.

One of Danco's main backers has been the David and Lucile Packard Foundation, which lent Danco $10 million in 1998 to support approval and marketing of RU-486.

Sarah Clark, director of the Packard Foundation's Population Program, said her group and other Danco backers share an array of motivations for taking on responsibility for such a controversial drug.

"We're trying to make sure this choice is available and is not kept out for the wrong reasons," she said. If it were up to more profit-oriented drug companies alone, she added, RU-486 would probably not be on the market: "We wouldn't have to make loans to Danco if the commercial market were there."

EXHIBIT 22

Hannah Levintova,
The Abortion Pill's Secret Money Men,
Mother Jones (March–April 2023)

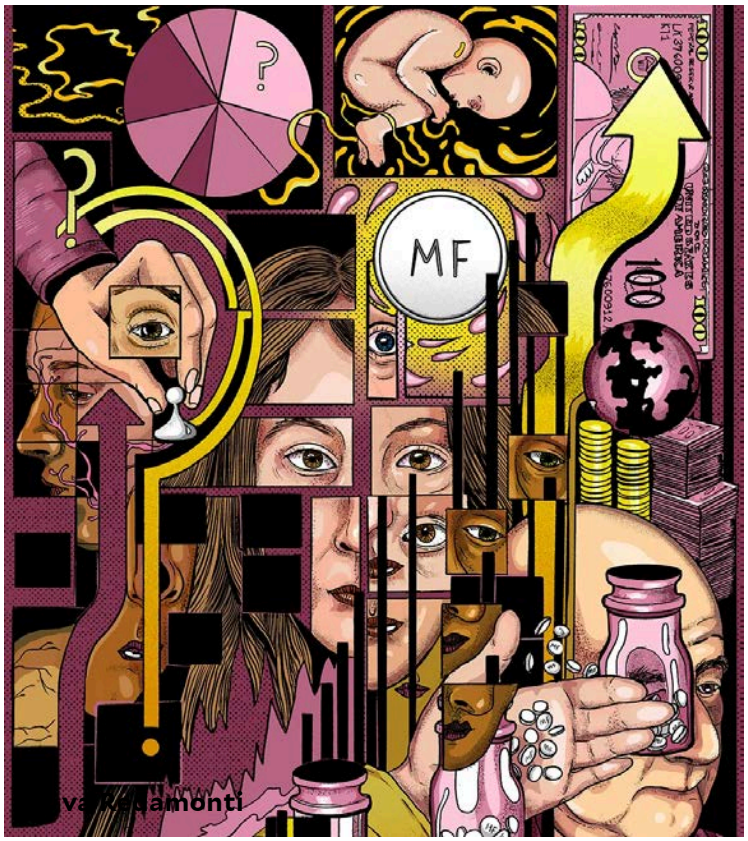
REPRODUCTIVE RIGHTS

The Abortion Pill's Secret Money Men

The untold story of the private equity investors behind Mifeprex—and their escalating legal battle to cash in post-Dobbs.

HANNAH LEVINTOVA

MARCH+APRIL 2023



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In 1993, a group of activists rented a warehouse in suburban Westchester County, New York. It was smaller than they'd hoped and had limited ventilation, but the two other locations they'd tried to rent belonged to universities and required jumping through too many bureaucratic hoops the exact sort of paper trail this group was trying to avoid.

Led by renowned pro-choice activist Lawrence Lader, their goal was to replicate RU-486, the revolutionary abortion pill developed in the 1980s by French manufacturer Roussel-Uclaf—which was unwilling to navigate American abortion politics to bring the pill stateside. Lader's group, code named ARM Research Council, set up shop just months after Dr. David Gunn was shot and killed outside his Florida clinic, the first US physician to be murdered by an anti abortion activist. Perhaps unsurprisingly, no US manufacturer wanted to wade into the increasingly fraught abortion debate to bring the medication to American women, either. So with the help of lawyers and activists, Lader had smuggled RU-486 into the United States, and his group was going to try to reproduce it.

In their warehouse, they got to work building an underground drug laboratory, complete with a huge, customized ventilation hood, fire prevention devices, and specially designed sinks. The whole project "had the trappings of a CIA operation," Lader would later write. They figured out a system for replenishing their near constant need for dry ice from a supplier 15 miles away, and crafted a strategy to avoid detection by anti-abortion groups, the garbage collector, and their landlord. If anyone asked what they were up to, the group—which included a doctor who lived 1,000 miles away and asked to go by Dr. X; a Columbia University chemist working for free; and two assistants agreed on a cover story: They were working on a new treatment for cancer.

Meanwhile, Roussel Uclaf and its parent company were in a drawn out negotiation with a Manhattan based reproductive health nonprofit, called the Population Council, over the official patent for RU-486. The same month

that the French company finally agreed to give the Council the patent, Lader's secret lab announced that it had successfully developed its own copy of the drug, whose scientific name is mifepristone. The two groups knew of each other's work, and Lader had even reached out to the Population Council about collaborating, but the Council had demurred.

The tale of who funded this effort to legally bring mifepristone to women across the country, and what benefits those funders might reap, has been mostly kept quiet.

Lader's group knew American women could not wait the many years it would take for the Council to arrange an official manufacturing operation with full approval from the Food and Drug Administration. So, it got its own permission from the FDA to conduct limited testing, which would allow it to start distributing small batches of the drug to a network of 10 clinics. There, patients could get both mifepristone and misoprostol, a common ulcer drug, which, when taken in tandem, can cause a medication abortion. For the few who were able to try it, it was an emotional and physical relief: It meant they could have an abortion privately and without a vacuum aspiration machine, whose suction "feels like you're getting the life sucked out of you," as one early mifepristone recipient described it to the *Boston Globe*.

All the while, the Council was working to find a manufacturer willing to make the drug, win full FDA authorization, and sell it across America.

When the FDA finally approved mifepristone seven years later, the Council's distribution venture, which came to be called Danco Labs, was ready to go. Within two months, the drug was shipped out to doctors. At the clinics brave enough to be early adopters, women began showing up from farther and farther away; in some places the medicine was double the cost of a surgical abortion, but that hardly seemed to matter. By 2020, the pill had become the most popular way to get an abortion in the United States.

How Private Equity Looted America

Read more from our May+June 2022 issue on vulture capitalists, their political enablers, and the working people fighting back:

- The Smash and Grab Economy
- Real Estate Predators Tried to Cash In on the Pandemic. Then Tenants Fought Back.
- Everything Everywhere All at Once: How Private Equity Rules Your World
- Biden and Trump Both Trashed Private Equity's Favorite Tax Dodge. Surprise! It's Still Here.
- These Are Congress' Biggest Private Equity Investors

- The Fight to Keep Their "Poor People's Paradise" out of Private Equity's Hands
- My Newspaper Was Gutted by Journalism's Biggest Bogeyman

Over the last two decades, mifepristone's dramatic origin story has made its way into books and the pages of the *New York Times*. But the tale of who funded this effort to legally bring it to women across the country, and what benefits the funders might reap from their investments, has been mostly kept quiet. This was in part because the 1990s were the apex of anti abortion violence, so investors required secrecy. It was also because the funding sources seemed like a minor plot point in a project that had the potential to transform reproductive health care for millions.

"I don't think anybody thinks they're going to make a lot of money," Peg Yorkin, one of the activists crucial to the US mifepristone campaign, told the *Los Angeles Times* when the pill became available. "We're just happy that it's going to be happening."

But the small group of investors who backed the Population Council's drive to manufacture and distribute the drug since its earliest days have made a lot of money on the mifepristone business—tens of millions of dollars, according to court filings. Their windfall has come through a byzantine corporate structure set up in the 1990s by a private equity fund, now called MedApproach Holdings, to allow investors to pour money into Danco Labs until 2019 the only US retailer of mifepristone—without disclosing their identities. As states have imposed ever-stricter limits on abortion access, their investments have generated hefty returns.

On the heels of the Supreme Court's ruling in *Dobbs v. Jackson Women's Health Organization* last June, undoing the federal right to abortion and the FDA's announcement, in January, that retail pharmacies can now sell abortion pills these investors are likely to earn even more, as medication abortion becomes the only option for millions of women living in the 26 states where abortion is now illegal or severely restricted. The potential is so promising that two of the primary investors have engaged in a bitter court battle to take control of the investment, and Danco itself.

Their story has a dizzying plot that involves Cayman Islands shell companies, LLCs named after racehorses, a shadowy priest, a disbarred attorney, and a finance whiz behind an infamous Wall Street hedge fund collapse. The legal battle, which has been fought in three states and cost millions in attorneys' fees, shows how investors have come to view the desperation of pregnant women as an important problem to solve—but also a golden ticket.

In 1986, a North Carolina lawyer named Joseph Pike purchased one of the earliest manufacturers of intrauterine devices for $1.1 million. The company, Finishing Enterprises Inc., was making IUDs for another business called GynoPharma. At the time, GynoPharma wasn't selling IUDs in the United States American women shunned them after the Dalkon Shield, a different IUD, was found to cause severe injuries in the '80s. Its copper IUDs were primarily being purchased by governments and NGOs for distribution in developing nations, but Pike spent the next five years helping to bring this IUD, the Paragard, to the United States. After it hit the market, he sold FEI for a reported $65 million—an astounding return of more than 5,800 percent. "It was a good play for me," he says.

A multimillionaire at just 41, Pike ditched his lawyer job and moved to La Jolla, one of San Diego's most exclusive neighborhoods, to "enjoy life." He took up golf and played as often as he felt like it. But soon Pike heard from the Population Council about a business proposition: It wanted to develop and market medication abortion in the United States. At that time, advocates were flying lobbyists to Europe and picketing outside the New Jersey office of the French pill's parent company to get them to sell the drug in America. As Pike saw it, it was another opportunity to make some real money and do some good along the way.

Pike was the Council's go to because they'd worked together on the copper IUD. The Council had developed it and then granted GynoPharma the license, and it collected royalties as Pike successfully built up the IUD business and sold it. Pike had proved himself to be a businessman who could breathe life, and dollars, into a controversial women's health product. The Council gave him the exclusive right to sell mifepristone in the US and tasked him with drumming up investors.

The controversy surrounding mifepristone meant that neither the government nor mainstream companies would go anywhere near it.

Typically, drugs in the United States are not funded by private individuals. Instead, the federal government finances initial research, while later stages of development are paid for by pharmaceutical companies. Venture capitalists and private equity investors usually only get involved in drugs developed to treat rare diseases—those that affect fewer than 200,000 people per year because pharma companies are unlikely to invest in these typically less profitable treatments. But mifepristone was far from a "rare disease" drug—in the 1990s, about 1.5 million American women were having abortions annually. (That number has since come down to just under a million, thanks to the growing availability of contraceptives.) Yet the controversy surrounding mifepristone meant that neither the government nor mainstream companies would go anywhere near it.

In 1994, Pike got to work, traveling the country with Susan Allen, a doctor and abortion provider he'd brought on to be the face of the abortion pill effort. Pike recalls that they spent their time pitching wealthy liberals, including Susan Buffett, Gloria Vanderbilt, a George Soros representative, and a handful of other celebrities. His fundraising overlapped with the O.J. Simpson murder trial, and Pike says he even met with one of Simpson's defense lawyers, Bob Shapiro. Pike won't say which, if any, of these people invested in the project, but he estimates that altogether there were about 50 pitch meetings.

One of the investors who did sign on was Greg Hawkins, a veteran of the major investment bank Salomon Brothers, who was then helping run the hedge fund Long Term Capital Management. (Hawkins did not comment for this story.) Pike met Hawkins in New York City in 1995 and told him what he'd told everyone else: To protect investors' privacy, he would craft a corporate structure that would be based offshore and involve a slew of sub entities in essence, a Russian nesting doll of holding companies that would quietly fund the mifepristone effort. The project did not have FDA authorization yet, which meant there was no immediate way to bring in revenue. But eventually, they would pay back their investors, and then some. Hawkins decided he wanted in.



Pike set about creating a dizzying chain of intermediate companies registered around the world. First, he filed paperwork to create Danco Laboratories Inc. as a Cayman Islands company, also registered in Delaware. (Danco was named after Pike's son.) Then he listed an intermediate company in California, Danco LP. He also registered another intermediate company, ND Management, in the Cayman Islands.

Each entity controlled the next one: ND Management oversaw Danco LP, which owned Danco Labs, the company that would actually sell the abortion drug whose backers this tangle of entities was set up to obscure. The secrecy was para mount, given the threat of reputational or financial consequences—or worse—for anyone publicly tied to the project; anti abortion violence was continuing to escalate. Extremists murdered abortion providers in Florida and Massachusetts, and anti abortion groups threatened a boycott of more than 70 medications made by affiliates of RU 486's manufacturer, Roussel. Pike, who'd been identified in news stories, got death threats himself.

Pike had already found someone to help build this financial vehicle: an experienced health care financier from Nashville named Brad Daniel. Daniel had started two biotech hedge funds, as well as a private equity fund, called Bio-Pharm Investments, that specialized in providing seed money to pharmaceutical ventures. Like Pike, Daniel would later recall that his motivations were twofold: He believed in the social benefits of mifepristone, and in the enormous financial potential. (Daniel did not comment for this story.)

Daniel created a fund, MedApproach, where investors would plunk their money in Danco's mifepristone business. His private equity fund, Bio-Pharm, would oversee MedApproach, receiving a 1 percent management fee and 20 percent of all profit distributions that MedApproach's investors got from their stakes in Danco's business.

All this was happening when private equity investing was becoming in vogue. It began in the 1980s, when a generation of shrewd financiers popularized a type of business takeover, called a leveraged buyout, that secured private equity's status as a new place for wealthy investors to grow their money. They had also kicked off a broader philosophical shift —one where the main value of a business lies less in the benefit a product offered customers and other stakeholders, and more in the financial returns extracted for its shareholders.

By the 1990s, when the mifepristone venture was getting off the ground, this new attitude had propelled private equity investment into new sectors, like health care, technology, and pharmaceuticals. The pill presented an obvious financial opportunity: the rare sort of drug that they'd never have trouble selling, for a condition that would never cease to exist.

The pill presented an obvious financial opportunity: the rare sort of drug that they'd never have trouble selling, for a condition that would never cease to exist.

Within two years, Pike and Daniel found a handful of willing investors who together put more than $13 million into MedApproach. Hawkins was the largest investor funding the Russian nesting doll of financial entities, pitching in $1.5 million, so that, by 1996, he owned three quarters of MedApproach. Over the next two years, he loaned the Danco project an additional $4 million, according to his declarations in court.

But then the project hit a roadblock. The Population Council discovered in 1997 that Pike had an unsavory history that they worried could tank the abortion pill project just as it was in the middle of clinical trials and its campaign for FDA approval. The prior year, as he'd been ramping up the mifepristone investments, Pike had pleaded guilty to a misdemeanor forgery charge in North Carolina, tied to a 1985 real estate deal. He'd gotten a suspended two year sentence, 18 months of probation, and a fine. He had also been stripped of his law license.

(Pike explains that the charge came from a disgruntled former client he'd once helped buy land. When the client wanted to get rid of it years later, Pike couldn't help because he had retired from practicing law. The client claimed Pike had misrepresented facts; Pike says he pleaded guilty to make the case go away.)

The Population Council wanted the mifepristone project to be squeaky clean. If Pike stayed on, they felt that years of work, the $13.3 million in investments he'd secured, and FDA approval could all be in danger. Keeping him involved in the project, they said, would mean that "another weapon with which to attack [the abortion pill] will be furnished to its ideological opponents."

It took a lawsuit to get Pike off the project. As part of his exit, the Population Council insisted that the investors Pike had found have the chance to leave, since the Council could no longer guarantee the promises Pike had made to them. Spooked by the disarray and the fact that Danco still did not have government approval to sell its only product, many investors opted to pull their funds. But Hawkins stayed in and paid $3.5 million to buy out most of Pike's investment. Daniel also stayed involved, securing more control over the company and further compensation that would amount to hundreds of thousands annually. (Pike, meanwhile, fought to keep a 25 percent stake, $1.5 million in consulting fees, and a portion of the future profits on the shares he'd given up, capped at $21 million.) Hawkins also pledged up to $13.7 million to buy up shares ditched by other investors, potentially giving him a majority of the entire investment.

Three months later, in July 1998, Hawkins invited Daniel to visit him at his home in Saratoga, New York. Over lunch at the Saratoga Race Course's private club, he told Daniel that something was "terribly wrong." His hedge fund was having liquidity issues and would have little or no additional funds to invest in MedApproach meaning he would not be able to cover the nearly $14 million commitment he'd made to buy out investors.

Hawkins asked to transfer his existing stake to his wife, Sharon—to protect himself, his family, and that investment from whatever might come next at his hedge fund. Daniel agreed. Later, Hawkins told Daniel that he would solicit other investors to cover the millions he'd committed to MedApproach but now could not come up with.

Over the next two months, Hawkins' hedge fund, Long Term Capital Management, collapsed. Famed on Wall Street for sophisticated math that delivered huge returns, it lost billions in a matter of weeks, thanks to a mix of events that included Russia's default on a chunk of its Treasury debt, which LTCM had heavily invested in. At its peak, LTCM had controlled 5 percent of assets on the global market, so its downfall roiled the worldwide financial system. Soon, the Federal Reserve stepped in to organize a $3.5 billion bailout financed by the leading Wall Street banks.

Amid all that, Daniel and Hawkins began having weekly talks to figure out how to move forward with the mifepristone investment. The buyout of the original investors would wrap up in the summer of 1999, and Hawkins was scouting new funders.

According to Daniel, Hawkins said that he had heard from a Catholic priest who wanted to invest in medication abortion but required absolute anonymity.

In these calls, Hawkins told Daniel about an idea: He'd created five different LLCs, several named after his racehorses, where new investors could put money for the abortion pill project while staying unidentified. One LLC in particular, Shiroyama, he said, required extra care. According to Daniel, Hawkins said that he had heard from a Catholic priest who wanted to invest in medication abortion but required absolute anonymity. So sensitive was this investment that Hawkins needed to entice the priest with a $320,000 sweetener. He asked Daniel to move that sum from his wife's stake into the Shiroyama LLC forfeiting some of the Hawkinses' own investment in the deal and passing it to the priest to entice the clergyman to invest further. By approving the transfer, Daniel said he was also losing out financially: Less of the money invested this way would end up in his pocket, because the LLC would not have to pay his private equity fund's 1 percent management fee (or 20 percent of any profits it accrued). But it seemed that both Daniel and Hawkins were giving something up to help the project get on its feet, in hopes of reaping the rewards later.

After the sweetener, the priest seemed to come through according to Daniel, Shiroyama LLC invested just shy of $950,000 over the next year. Later on, Hawkins asked Daniel to move another $1.7 million of his wife's interest into three of the LLCs, as additional enticements for more investors he was drumming up. Yet another LLC plowed $700,000 into the project.

The LLC investments came just in time: On September 28, 2000, the FDA officially approved Mifeprex, the commercial name for Danco's mifepristone pill. These investors' financial bet was finally on track to pay dividends.

Within three years, the Danco project had earned enough on Mifeprex to start repaying investors. Several Supreme Court cases soon made it easier for states to enact abortion restrictions, an opportunity that conservative states took up with gusto sending ever more women looking for the discreet pill they could take at home. By 2010, about a quarter of early abortions were done with mifepristone, and Danco had paid everyone back. Now that everyone had been made whole, it was time to finally start making a profit, which was great news for both investors and Daniel's

private equity fund, now named MedApproach Holdings, which would get somewhere between 10 and 20 percent of profits made by investors, as well as the management fees it had deferred while the project got off the ground.

Daniel contacted Hawkins to get clearer information on all of the investors so he could pay them their portions of the profits. He says he sent multiple emails, heard nothing for five months, and eventually mailed him a letter. That's when Hawkins called Daniel, who recalls Hawkins angrily reiterating that Shiroyama's investor was a priest who required absolute confidentiality. "You are never going to find out who he is," he said, "and it is none of your business!" In a second call, Daniel says Hawkins offered to pay him money instead of providing any documentation revealing the identities of the investors he'd brought in. (A source with knowledge of the proceedings says that Hawkins never made this offer.)

That started a snowball of suspicion, and within a matter of months, Daniel filed a lawsuit against Hawkins in federal court. The proceedings led to a stunning revelation: There never was a priest. The money that had passed through the Shiroyama LLC had been from the purportedly broke Hawkinses. (In federal court documents, Hawkins maintained that he never called the investor a priest; rather, he had merely said he was a religious friend. This friend had planned to invest but backed out due to his faith and fear of anti-abortion reprisals, forcing Hawkins to use his own money to cover the investment. The friend filed a declaration in court supporting much of Hawkins' account, though he contests that he'd ever committed to an investment in the first place.) The whole thing looked like a scheme by the Hawkinses to expand their investment in medication abortion and reap its returns—while paying less in management fees and sharing fewer profits. Daniel claimed that the demise of LTCM had been a hit on the Hawkinses' wealth, and the tale of the secret, abortion-supporting priest was a way to make some of it back. The Hawkinses disagreed, saying they'd never misled Daniel, and that their investment in the Shiroyama LLC was aboveboard and never intended as a profitable runaround. Eventually, Daniel and the Hawkinses opted to settle for an undisclosed amount.

Documents filed by Daniel as part of a lawsuit say that the Hawkinses' investment in MedApproach has made a return on investment of 228.79 percent.

Both parties have made a fortune on Mifeprex. Documents filed by Daniel as part of a different lawsuit say that the Hawkinses' investment in MedApproach has made a return on investment of 228.79 percent. The actual dollar amount has been fastidiously redacted in all the case's legal filings, but based on the Hawkinses' disclosures of their total investment in the mifepristone project—between $9 million and $11 million—their earnings would come to between $20.5 million and $25.1 million. (A source familiar with the suit disputes this return on investment, arguing it is far lower.)

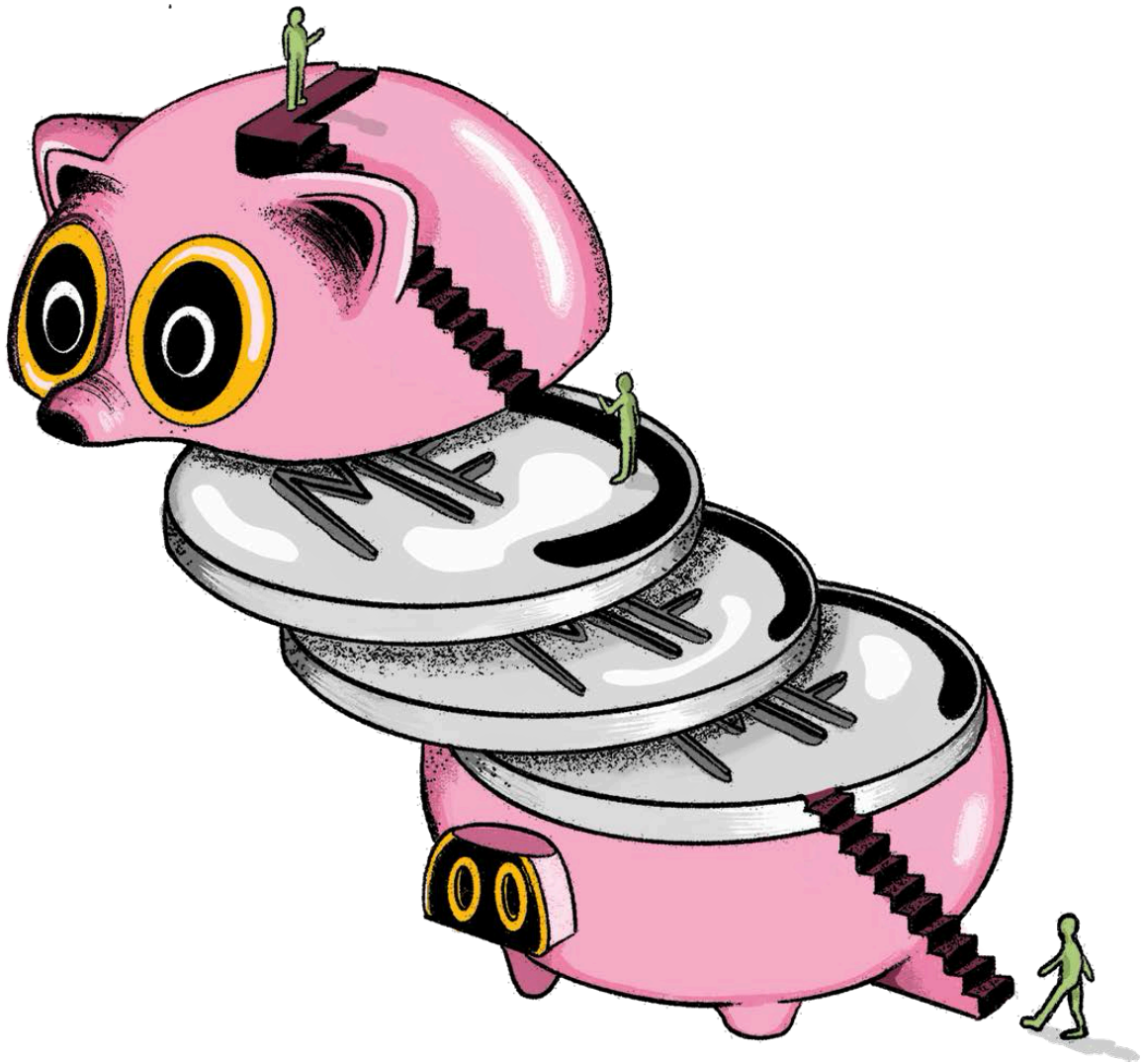
Those same filings say that the average return on investment for everyone who invested in Danco was about 452 percent over 23 years. Even in the high flying world of private equity where the average annual return over the last 20 years has been about 10.5 percent—that's nothing to sneeze at. In a 2022 deposition, the CFO of Danco confirmed that "the Project has ultimately become quite successful," and investments have "been extremely profitable."

Since the Supreme Court gutted *Roe*, demand for medication abortion has skyrocketed. One study analyzed nearly 43,000 medication requests from 30 states and found the average number of daily requests nearly tripled, driven primarily by increases in the 12 states where lawmakers have banned abortion completely. Meanwhile, two of the main digital health startups offering medication abortion by mail—Hey Jane and Choix—reported enormous jumps in interest from potential customers. Choix raised $1 million in venture capital funding in the weeks following the leak of the Supreme Court decision. In October, Hey Jane raised $6.1 million from venture capital investors, after seeing a

fivefold increase in new telehealth patients per day. During the fundraising round, venture capitalists wanted to invest more in the company than Hey Jane had asked for.

All of that suggests that Danco's business is set to remain profitable, even as a cheaper generic version of mifepristone has cut into Mifeprex's business over the past few years. Just how profitable is anyone's guess but valuable enough that Daniel and the Hawkinses have kept fighting about it. In May 2021, the Hawkinses filed a lawsuit in Delaware to wrest control of Danco from Daniel. Their goal was to put an end to what they see as Daniel's extractive, autocratic management of the company by installing a proper board to oversee him. The lawsuit also had the potential to secure more profits for the Hawkinses.

When the Danco project was restructured in the '90s and the Hawkinses' shares got moved around, a restriction was appended to their stake: Daniel, whose private equity fund controlled the investment, would hold votes attached to the shares. In other words, the Hawkinses' investment gave them the right to partake in Danco's profits, but they could not have a say in the operations of the company. That right stayed with Daniel, in the form of a proxy vote. The Hawkinses' lawsuit sought to win back their votes, ostensibly to sell their stake at a better price. (Shares that don't have votes attached are worth a lot less.)



For Daniel, the stakes are enormous. His proxy vote affords him control over company operations and, combined with his role as executive chair of Danco's board of directors which gives him final approval of the company's budget

earns him about $455,000 in annual fees and compensation. He earns an extra $75,000 each year for work related to particular entities that are part of Danco's complex financing structure, as well as tens of thousands more for other Danco related business. All told, Daniel has earned about $10.3 million in fees alone.

This past January, the Delaware Supreme Court sided with the Hawkinses. The consequences of the decision are still unfolding. But now that the Hawkinses have regained their shares' voting power, they have additional authority to push for changes at Danco. "This has been an incredibly challenging ordeal for Mrs. Hawkins," her spokesperson said in a statement. "Her focus has always been on preserving women's right to safe, reproductive health care. The battle over corporate governance has threatened women's ability to receive the full benefit of this impactful medicine. We are deeply grateful that the courts in Delaware have cleared the way for that to happen."

For both sides, each of these lawsuits have been a fight to preserve the wealth they've built through the mifepristone project, and to pave the way for earning even more while keeping the other party from wresting away money and control. A source close to the Hawkinses, for example, called Daniel a "control freak" who hoards money from Danco for himself. Meanwhile, one of Danco's other major investors accused the Hawkinses of trying to steal the business.

Pike told me something similar. "Greg, this is basically his only asset," he said. "His billion dollars he thought he had [through LTCM], he doesn't have, and he's obsessed with not being able to control his destiny."

That destiny could not be more promising. The end of *Roe v. Wade*, mixed with the FDA's new approval of retail sales for mifepristone, could unlock immense profit. Their product's mission may be a social good, but creating value for investors themselves seems to have become a driving motivation: one where women faced with impossible circumstances are reduced to the impersonal language of customer capture.

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EXHIBIT 23

Letter from Center for Drug Evaluation and Research to Ann Robbins, Ph.D.
(Sept. 18, 1996)

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20-687

Trade Name: Mifeprex

Generic Name: mifepristone

Sponsor: Population Council

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-687

APPROVABLE LETTER

NDA 20-687

SEP 18 1996

The Population Council
Attention: Ann Robbins, Ph.D.
Scientist
1230 York Avenue
New York, NY 10021

Dear Dr. Robbins:

Please refer to your new drug application dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mifepristone Tablets, 200 mg.

We acknowledge receipt of your amendments dated April 19, June 20, July 25, August 15, and September 16 (telefacsimile), 1996.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following information:

Clinical

Please submit a comprehensive description of the proposed distribution system.

Chemistry, Manufacturing, and Controls

Drug Substance:

Drug Product:

Biopharmaceutics

To support the rationale for using the stated dissolution medium and volume plus the selected for the proposed dissolution method, please provide the following information:

1. pH solubility data for mifepristone;

2. condition information at for various media;

3. Tablet dissolution profiles (including raw data and mean data) in various media (i.e., simulated gastric fluid and simulated intestinal fluid, at a range of pH's representative of physiological conditions) that provide adequate conditions with appropriate sampling times to characterize the profile; and

4. Raw data and profiles at different in the dissolution media cited above.

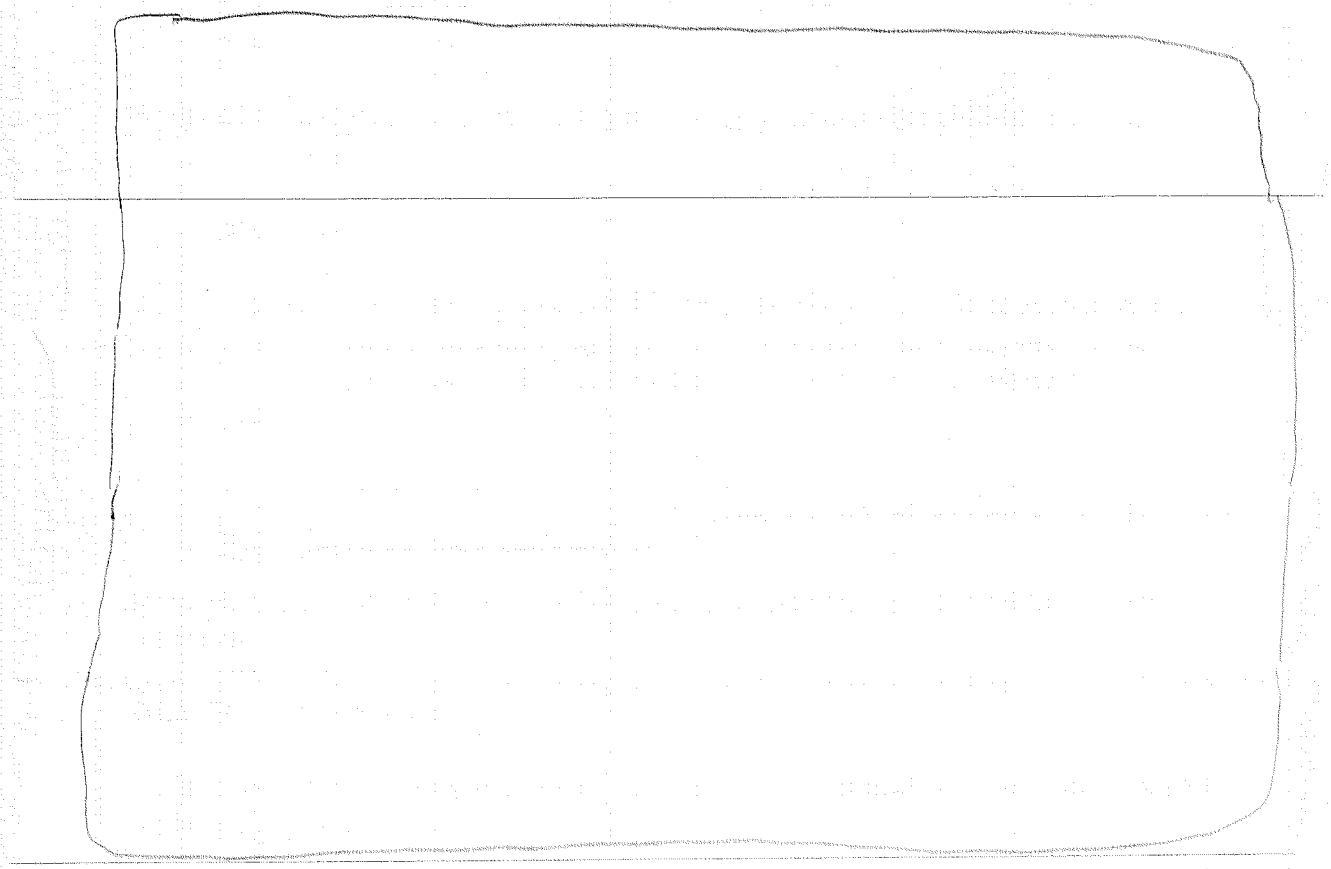
Physician Labeling

General Comments

1. Please excerpt and incorporate sections from the approved labeling for misoprostol that are relevant for single-dose use of misoprostol as provided for in this labeling.

2. Since mifepristone is not an established name as described under section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act, you should apply to the USAN Council for adoption of a name that will comply with that section of the act. They can be reached at the following address:

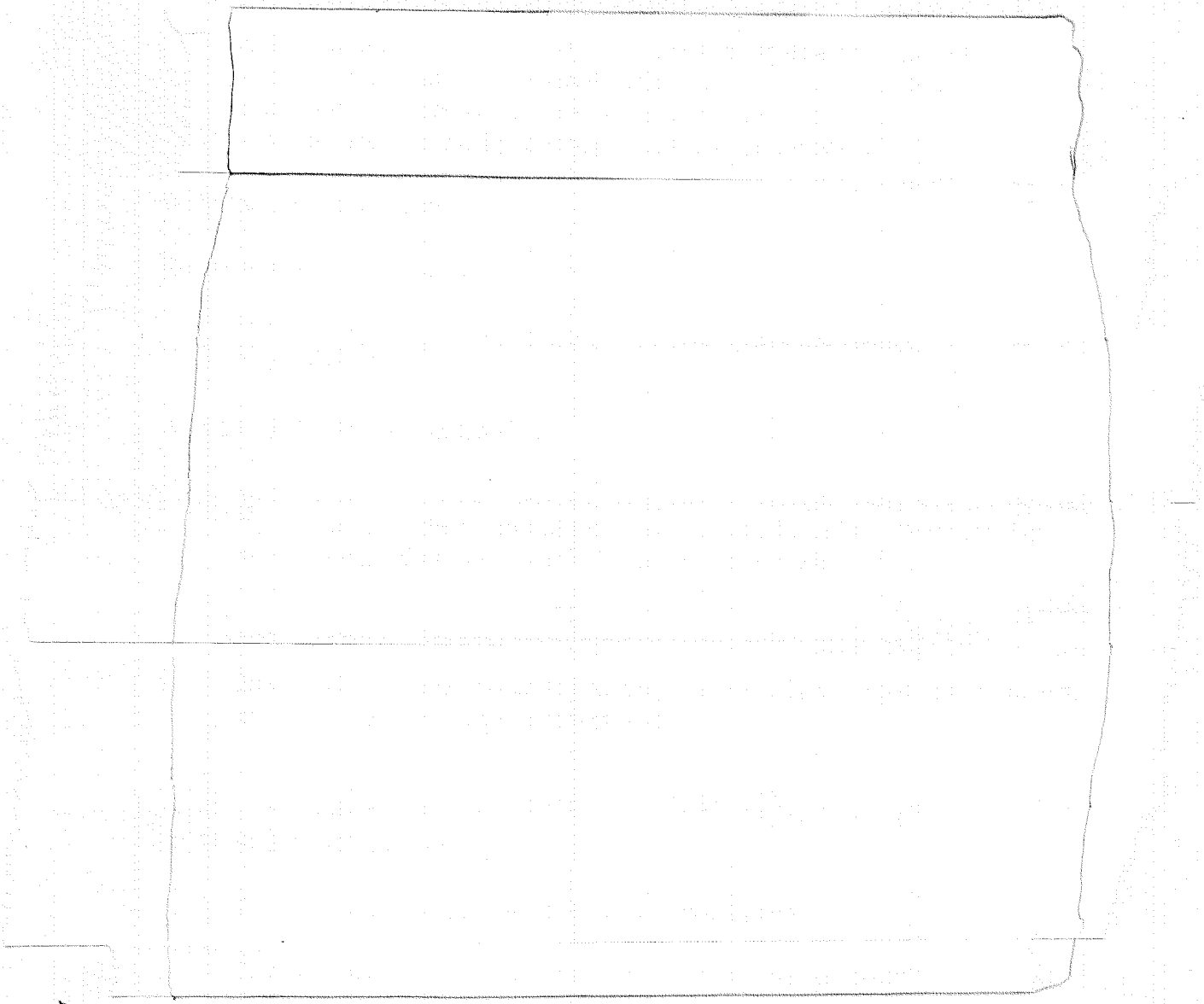
United States Adopted Names (USAN) Council
American Medical Association
535 North Dearborn Street
Chicago, IL 60610



3 Page(s) Redacted

Draft

Labeling



Phase 4 Commitments

We remind you of your commitments dated September 16, 1996, to perform the following Phase 4 studies:

1. To monitor the adequacy of the distribution and credentialing system.

2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

3. To assess the long-term effects of multiple use of the regimen.

4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.

6. To ascertain the effect of the regimen on children born after treatment failure.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug product.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug, and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, (3) other dose levels, etc.

In addition, we have the following requests for information that should be addressed:

Clinical:

We remind you of your commitment to submit full study reports of the U.S. trials promptly after their completion. We anticipate that you will revise your labeling to incorporate U.S. data at that time.

Drug Substance:

Drug Product:

[redacted]

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Reproductive and Urologic Drug Products, and two copies of both the promotional material and the package inserts directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

[redacted]

Sincerely yours,

/S/

9/18/96

[redacted]

EXHIBIT 24

2000 FDA Approval Letter for Mifeprex (mifepristone) Tablets (Sept. 28, 2000)

Sep 28 2000

NDA 20-687

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIFEPREX™ (mifepristone) Tablets, 200 mg.

We acknowledge receipt of your submissions dated April 19, June 20, July 25, August 15 and September 16 and 26, 1996; January 30, March 31, July 28, August 5, September 24, November 26, 1997; January 30 (2), February 19, Aril 27, June 25, October 26, December 8, 1998; February 8 and 22, March 31, April 28, May 10 and 20, June 3 (2), 15, 23, 25, and 30, July 14 (2) and 22, August 3, 13, 18 and 30, September 3, 8, 13 and 30, October 5, 26 and 28, November 16 and 29 (2), December 6, 7 and 23, 1999; and January 11, 21 and 28 (2), February 16 and 24, March 3, 6, 9, 10, 30 and 31 (2), April 20, May 3, 11 and 17, June 22 and 23, July 11, 13, 25 and 27, August 18, 21 and 24, September 8, 12, 15 (2), 19 (2), 20, 21, 22, 26 (2), and 27 (2), 2000. Your submission of March 30, 2000 constituted a complete response to our February 18, 2000 action letter.

This new drug application provides for the use of Mifeprex™ for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Mifeprex™ (mifepristone) Tablets, 200 mg, for use as recommended in the agreed upon labeling text. The application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced regulations.

The final printed labeling (FPL) [including the professional labeling (Package Insert), the Medication Guide required for this product under 21 CFR Part 208, the Patient Agreement Form, and the Prescriber's Agreement Form] must be identical to the submitted draft labeling (Package Insert, Medication Guide, Patient Agreement Form, and the Prescriber's Agreement Form submitted September 27, 2000; and the immediate container and carton labels submitted July 25, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-687." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.520, distribution of the drug is restricted as follows:

> Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.

- Ability to diagnose ectopic pregnancies.

- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

- Has read and understood the prescribing information of Mifeprex™.

- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.

- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.

- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.

- Must record the Mifeprex™ package serial number in each patient's record.

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission.

> This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns, and other matters.

We also note the following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments replace all previous commitments cited in the September 18, 1996 and the February 18, 2000 approvable letters. These Phase 4 commitments are:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.
2. A surveillance study on outcomes of ongoing pregnancies.

You have agreed to provide the final Phase 4 protocols for these studies within six months.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call **[Redacted] .**

Sincerely,

[Redacted]

Center for Drug
Evaluation and Research

EXHIBIT 25

2019 FDA ANDA Approval Letter to
GenBioPro, Inc.
(Apr. 11, 2019)

ANDA 091178

ANDA APPROVAL

(b) (6), (b) (4)
GenBioPro, Inc.
(b) (6), (b) (4)
Attention: (b) (6), (b) (4)

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on February 3, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mifepristone Tablets, 200 mg.

Reference is also made to the complete response letter issued by this office on February 23, 2018, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The (b) (6) has determined your Mifepristone Tablets, 200 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Mifeprex Tablets, 200 mg, of Danco Laboratories, LLC.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our letter dated June 15, 2011. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your REMS, known as the Mifepristone REMS Program, submitted on May 30, 2017; is approved, and will be posted on the FDA REMS website: http://www.fda.gov/rems

The REMS consists of ETASU and an implementation system.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Your REMS must be fully operational before you introduce Mifepristone Tablets, 200 mg, into interstate commerce.

The Mifepristone REMS uses a single, shared system for the ETASU. This single, shared system REMS Program currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 091178 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 091178/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES
SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR ANDA 091178

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS submission.

For more information on submitting REMS in SPL format, please email REMSWebsite@fda.hhs.gov

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

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[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

(b) (6)

Digitally signed by (b) (6)
Date: 4/11/2019 02:22:21PM
GUID: 54078879000a1b9e15dd31ed6f0343ca

EXHIBIT 26

FDA Center for Drug Evaluation & Research
Letter to Population Council re: NDA
(Feb. 18, 2000)

/S/

NDA 20-687

FEB 18 2000

Population Council
Attention: Sandra P. Arnold
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for mifepristone 200 mg tablets.

We acknowledge receipt of your submissions dated September 18 and 26, 1996; January 30, March 6 and 31, July 28, August 5, September 3 and 24, November 26, 1997; January 30, February 19, April 27, June 25, October 26, December 7 and 8, 1998; February 8, 22, March 31, April 28, May 10, 20, June 3 (2), 15, 25, 30, July 14, 22, August 3, 13, 18, 30, September 3, 8, 13, 30, October 5, 26, 28, November 16, 29 (2), December 6, 7, 23, 1999; January 21, 28 (2), and February 16, 2000. Your submission of August 18, 1999 constituted a complete response to our September 18, 1996 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Chemistry

Drug Substance

Drug Product

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Labeling

Address the recommendations in the enclosed draft labeling for the Physician Insert and Patient Package Insert.

It will be necessary for you to submit revised draft labeling for the drug. We recommend that the

labeling be identical in content to the enclosed draft labeling (text for the Physician Package Insert and Patient Package Insert).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Phase 4 Commitments

We remind you of your commitments dated September 16, 1996, to perform the following Phase 4 studies:

1. To monitor the adequacy of the distribution and credentialing system,

2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of the method failure,

3. To assess the long-term effects of multiple use of the regimen,

4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not,

5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke,

6. To ascertain the effect of the regimen on children born after treatment failure.

Distribution Plan

We have completed our review of this application, including the restrictions on the distribution and use of this product proposed in your January 21, 2000 submission, entitled "Distribution Plan". We have concluded that adequate information has not been presented to demonstrate that the drug, when marketed in accordance with the terms of distribution proposed, is safe and effective for use as recommended. The restrictions on distribution will need to be amended.

We have thus considered this application under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) and have concluded that restrictions as per CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product.

Promotional Activities

Please note that promotional activities for this NDA are subject to 21 CFR 314.550. As such, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the [redacted] and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you have regarding your new drug. Please provide updated information as

listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call [redacted]

Sincerely,

[redacted]

/S/

Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT 27

2000 FDA Approval Memo. to Population Council re: NDA 20-687 Mifeprex (mifepristone) (Sept. 28, 2000)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 28, 2000

FROM: /S/

SUBJECT:

TO: NDA 20-687 MIFEPREX (mifepristone) Population Council

This memo documents the approval action concerning the Population Council's NDA for mifepristone for the medical termination of intrauterine pregnancy through 49 days' pregnancy. The application was initially submitted to the Food and Drug Administration (FDA) on March 14, 1996. The Reproductive Health Drugs Advisory Committee met on July 19, 1996 and voted that benefits exceeded risk for this drug product with 6-yes, 0-no, and 2 abstentions. An approvable action letter was issued September 18, 1996 citing deficiencies in areas of Clinical (distribution system), Chemistry/Manufacturing and Controls, Biopharmaceutics, and Labeling. A complete response was received August 18, 1999. The last action by the Office was on February 18, 2000. That approvable action letter listed application deficiencies consisting of Chemistry/Manufacturing and Controls, Labeling, and the Distribution System issues. The Population Council submitted a complete response on March 30, 2000. After a brief summary of effectiveness and safety, this memo addresses those outstanding issues listed in the last action letter, Phase 4 commitments, and other issues.

Summary of Effectiveness and Safety

Effectiveness and safety data were derived from one U.S. clinical trial and two French trials. Effectiveness was defined as the complete expulsion of products of conception without the need for surgical intervention.

The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period. Demographic data showed racial composition of the U.S. trial was similar to the overall U.S. general population. Medical abortion was complete in 92.1% of 827 subjects. Surgical intervention was performed in 7.9% of subjects: 1.6% had medically indicated interventions (1.2% for heavy bleeding), 4.7% had incomplete abortions, 1.0% had ongoing pregnancies, and 0.6% had intervention at the patient's request. One of the 859 patients received a blood transfusion.

The two French trials enrolled a total of 1,681 women providing effectiveness outcomes and 1,800 women providing safety information. Medical abortion was complete in 95.5% of the 1681 subjects. Surgical intervention was performed in 4.5% of subjects: 0.3% for bleeding, 2.9% for incomplete abortions, and 1.3% for ongoing pregnancies. Of the 1,800 women, 2 patients received blood transfusions.

The Advisory Committee reviewed the French data in 1996 and voted 6-yes and 2-no for data supporting efficacy, 7-yes and 1-abstention for data supporting safety. As stated above, the overall vote for benefits exceeding risk was 6-yes, 0-no, and 2-abstentions. During the second review cycle in 1999, the committee received a copy of the U.S. study report, as they requested, to provide FDA with comments. None were received. The U.S. trial data confirms the effectiveness and safety of the product.

Chemistry/Manufacturing

In May, 2000 the Population Council informed the Division of Reproductive and Urologic Drug Products that the bulk drug substance maker had changed manufacturing processes last summer. New analytic, physical, and stability data were received and reviewed and found to be adequate to ensure the quality of the drug manufacturing was preserved.

An inspection of the bulk drug substance maker was performed on July 24-28, 2000. Deficiencies were cited and the manufacturer corrected these. These corrections were found acceptable.

Because the drug is being distributed directly to qualified physicians, there is minimal chance for drug name confusion and I agree with the name, Mifeprex.

Labeling

Labeling is important to educate prescribers and patients about the safe and effective use of the drug and to inform health professionals about adverse event risks. The 1996 Advisory Committee strongly supported education of users of mifepristone. By coupling professional labeling with other educational interventions such as the Medication Guide, Patient Agreement, and Prescriber's Agreement, along with having physician qualification requirements of abilities to date pregnancies accurately and diagnose ectopic pregancies (and other requirements), goals of safe and appropriate use may be achieved. The drug's labeling is now part of a total risk management program that will be summarized below. The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement will together constitute the approved product labeling to ensure any future generic drug manufacturers will have the same risk management program.

The labeling for mifepristone has been revised to provide information about how to report adverse events. FDA and the Population Council agree that a black box will highlight special items related to the drug. In addition, FDA has determined that a Medication Guide for this drug will help ensure dispensers provide important information to patients to enhance compliance with the regimen for safety and efficacy. Furthermore, a patient agreement fosters active patient education and participation in this regimen. The Population Council will provide these educational materials (the professional labeling, the Medication Guide, the patient agreement form, and the Prescriber's Agreement form). The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement must be read, understood, and attested to by physicians who meet prescribing qualifications (discussed below).

Black Box

21 CFR 201.57(e) permits FDA to require a black box warning for special problems, particularly those that may lead to death or serious injury. The Population Council agreed in its July 5, 2000 submission to a black box warning. It was agreed that the box would contain the following:

> "If Mifeprex results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions of whom to call and what to do in the event of an emergency following administration of Mifeprex.
>
> Prescribers should make sure the patients receive and have an opportunity to discuss the Medication Guide and Patient Agreement."

Misoprostol Administration

The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council's statement that women could have the option of taking misoprostol on Day 3 either at home or at the prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. The data were anecdotal off-label experience with

a vaginal misoprostol regimen, an observational study about home use in Guadeloupe, and a U.S. clinical study of home use of a different regimen with different drug doses. The only study that commented on whether home use led to correct use was the Guadeloupe study reporting that 4% of patients who took misoprostol at home did it incorrectly. Returning to the health care provider on Day 3 for misoprostol, as in the U.S. clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.

Early in drug development, a mandatory observation period of 3-4 hours was instituted in clinical trials worldwide when a prostaglandin analogue, sulprostone, was used with mifepristone and felt to have some cardiovascular risk. This drug is no longer being used with mifepristone and is not a marketed drug in the U.S.; therefore, the rationale for an observation period is moot. There is no more likelihood of an adverse event occurring in the few hours after misoprostol administration than during the entire study period.

Therefore, as a consequence of this re-evaluation, the labeling currently reads that the patient returns on Day 3 for misoprostol and is given instructions about adverse events and whom to contact for questions and emergencies.

Access to Health Care and Emergency Services

FDA agreed with the Population Council that access to health care and emergency services is critical for the safe and effective use of the drug. The clinical trials ensured access to services. The labeling has a black box highlighting the possible need for surgical intervention and either the provision of access to these services by the prescriber or through referral. The labeling has a contraindication if there is no access to medical facilities for emergency services. The Patient Agreement emphasizes the need to know what to do in the case of an emergency.

Patient Agreement Form

Patients should be informed about the indication of the drug and how it is given. They must understand the type of regimen they are about to commit to and its risks and benefits. The signed agreement form will be given to the patient for her reference and another kept in the medical record. The Population Council has committed to auditing prescribers to ascertain whether they have obtained signed copies of the Patient Agreement forms.

Biopharmaceutics

This review cycle, the clinical biopharmaceutical reviewers evaluated new data in the published literature regarding the metabolism of mifepristone by the P450 3A4 system. Mifepristone is a substrate and this may inhibit drug metabolism of certain drugs and induce metabolism of others. This information was placed in the professional labeling and patients are instructed in the Medication Guide that use of other drugs may interfere with actions of mifepristone and misoprostol.

Pharmacology-Toxicology

Current literature on the effects of human fetal exposure to mifepristone and misoprostol or mifepristone alone was reviewed to ensure risk information was current. Many of the case reports of malformation concern the unsuccessful use of misoprostol for abortion, resulting in limb, facial, cranial, and other abnormalities. Many reports were retrospective in nature, subject to reporting and recall bias. Nevertheless, the risk of malformation is very important to address. This drug's indication is for pregnancy termination. The labeling, Medication Guide, process of obtaining patient agreement on medical abortion, and the commitment of the physicians through their signed Prescriber's Agreement are all meant to ensure women are completely informed about the process and make a commitment to follow through.

The labeling for Mifeprex states that it is used with misoprostol for termination of pregnancy of 49 days or less. Human data on mifepristone and misoprostol used in this timeframe is available. Safety Update Report #3 submitted on March 31, 2000 contains [redacted] Periodic Safety Update Report #9 for the period of September 1, 1998 to November 30, 1999. It lists 38 on-going pregnancies with mifepristone plus misoprostol. The Lancet published a letter in July 1998 from [redacted] in which they mention that they had reviewed 71 cases of continuing pregnancies after failed early termination of pregnancy occurring from 1987 to 1998 and found no reported cases of malformation associated with use of mifepristone and misoprostol. There was one report of sirenomelia and cleft palate in a patient who had a therapeutic termination at week 7 gestation associated with mifepristone use alone. On July 6, 1999 the European Summary of Product Characteristics contains a statement for mifepristone that in humans, the reported cases do not allow a causality assessment for mifepristone alone or used with a prostaglandin. On August 21, 2000 the sponsor provided [redacted] 12/1/99 to 5/31/00 Periodic Safety Update on pregnancy outcomes following early pregnancy exposure. The current labeling has these new data on 82 pregnancies exposed to mifepristone only (40) and mifepristone used with misoprostol (42). FDA agrees that no conclusion can be made from the data at this time. Information on the possibility of a risk of malformation, including the above information as well as the anecdotal reports, is nevertheless included in the professional labeling, Medication Guide, and Patient Agreement. The Population Council has committed to continuing ongoing surveillance of human malformation risk.

Medication Guide

This product will be approved with a Medication Guide which dispensers must provide with the drug. It is important for patients to be fully informed about the drug, as well as the need for follow up, especially on Day 14 to confirm expulsion. A Medication Guide was determined to be necessary to patients' safe and effective use of the drug. The drug product is important to the health of women and the Medication Guide will encourage patient adherence to directions for use. Patient adherence to directions for use and visits is critical to the drug's effectiveness and safety.

Distribution System

Since 1996, FDA and the Population Council have agreed, as publicly discussed with the Reproductive Drug Products Advisory Committee, that once approved, the drug will be distributed directly to physicians. It will not be available from pharmacies. There were also discussions about the qualifications of the physicians receiving mifepristone for dispensing. The Committee also stated it was important that women have access to medical abortion as this new therapeutic option may offer women avoidance of a surgical procedure.

In January 2000, the Population Council provided its initial plan for drug distribution. This plan was resubmitted in its complete response of March 30, 2000. This plan had acceptably addressed the issue of physical security of the drug. The distribution system plan stated specific requirements imposed on and by distributors of the drug, including procedures for storage, dosage tracking, damaged product returns, and other matters. See Subpart H of this memo for more details. Other aspects of the distribution system are addressed below.

Physician Qualifications

Physician qualifications were discussed within CDER, the Agency, and with the Population Council. FDA also discussed physician qualifications with a special government employee with expertise in early pregnancy. The Population Council proposed that the drug be directly distributed to qualified physicians, as opposed to other types of health care professionals (midwives, physician's assistants, nurse practitioners, etc.). This restriction was supported by the discussions of the 1996 Advisory Committee. In fact, the clinical trial data was derived from the experience of physicians using this drug. Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician, from

dispensing the drug to patients, provided state laws permit this. Should data be provided to amend the restriction to physicians, FDA will consider them.

The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and/or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists. All patients were within one hour of emergency facilities or the facilities of the principle investigator.

The role of ultrasound was carefully considered. In the clinical trial, ultrasound was performed to ensure proper data collection on gestational age. In practice, dating pregnancies occurs through using other clinical methods, as well as through using ultrasound. Ultrasound information can be provided to the prescribing physicians to guide treatment, but this information can be obtained through consultation referral from an ultrasound provider and does not necessarily need to be obtained by the prescriber him/herself. The labeling recommends ultrasound evaluation as needed, leaving it to the medical judgement of the physician.

The Population Council proposed that any physician who could date pregnancies and diagnose ectopic pregnancies should be able to receive the drug from the distributor. These two qualifications alone limit the number of physicians who will be eligible to receive mifepristone from the Population Council's distributor(s) to those physicians who are very familiar with managing early pregnancies. These two qualifications also are performance-based standards and do not limit providers of mifepristone to specific medical subspecialties. Education about the use of the drug is described above in the Labeling section of this memo. Because qualified physicians will be using this drug, there is no need for special certification programs. The current labeling and distribution system states physician need not have skills for handling surgical interventions, but could provide referral to services for incomplete abortion and emergency care. The Population Council stated that current medical practice is structured on referral of patients who need surgery (for example, women with a spontaneous incomplete abortion or a cardiologist's patient who needs by-pass grafts) to a physician possessing the skills to address the problem. Moreover, within the U.S. clinical trial, 11 patients out of roughly 850 patients needed surgical intervention to handle bleeding, the most important urgent adverse event associated with this drug, and 3 of these patients were handled by non-principal investigators such as the emergency room and non-study gynecologist. This suggests that patients will get the needed surgical intervention by either their physician or another physician with the needed skills. Referral to a hospital for emergency services does not mean having admitting privileges, but having the ability and the responsibility to direct patients to hospitals, if needed. The professional labeling and the Medication Guide highlight that surgery may be needed and patients need to know if the provider of mifepristone will furnish surgical intervention or if the patient will be referred. If the latter, the treating health care provider must give the patient the name, address, and phone number of this referred provider. To ensure that the quality of care is not different for patients who are treated by physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention, FDA has proposed and the Population Council has agreed to structure a Phase 4 monitoring study. This monitoring study incorporates study questions of four of the original six Phase 4 commitments. See Phase 4 Commitments for additional information.

Finally, the one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services. This concern has been dealt with through the labeling, which makes it clear that if there isn't adequate access to emergency services, the medication is contraindicated.

Subpart H

In the February 18, 2000 approvable letter, FDA stated that the eventual approval of this drug would be under Subpart H. (21 CFR 314.500-314.560). This subpart applies to certain new drugs that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. FDA has determined that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H. The meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure. Subpart H applies when FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with special skills or experience. In the case of mifepristone, the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications. Under 21 CFR 314.520, distribution of mifepristone is restricted as described below.

- Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:
  - Ability to assess the duration of pregnancy accurately
  - Ability to diagnose ectopic pregnancies
  - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
  - Has read and understood the prescribing information of Mifeprex
  - Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
  - Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure
  - Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
  - Must record the Mifeprex package serial number in each patient's record

- With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:
  - Secure manufacturing, receiving, and holding areas for the drug
  - Secure shipping procedures, including tamper-proof seals
  - Controlled returns procedures
  - Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
  - Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
  - Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

The Population Council agreed to approval under Subpart H in their letter of September 15, 2000.

Phase 4 Commitments

In 1996, the Population Council committed to 6 post-marketing studies: 1) to monitor the adequacy of the distribution and credentialing system; 2) to follow up on the outcome of a representative sample of mifepristone treated women who have surgical abortion because of method failure; 3) to assess the long term effects of multiple use of the regimen; 4) to ascertain frequency with which women follow the complete treatment regimen and the outcome of those who do not; 5) to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke; 6) to ascertain the effect of the regimen on children born after treatment failure.

During this review cycle, items 1, 2, 4 and 5 were revised and integrated into a monitoring study to ensure providers who did not have surgical intervention skills and referred patients for surgery had similar patient outcomes as those patients under the care of physicians who possessed surgical skills (such as those in the clinical trial). This study specifically addresses adequacy of qualifications (#1). FDA reviewed the protocols from the Population Council submitted on September 7, 2000 and provided a revised protocol on September 13, 2000 in which the investigators collect data on safety outcomes (#2), return for their follow up visits (#4), and include all ages (#5) and collect smoking status (#5). Commitment #2 was defined by the Advisory Committee discussions of 1996 surrounding the question of whether certain physician specialties would have higher rates of problems encountered with medical abortion. This study specifically will investigate the performance of specialties with surgical skills compared to those that refer for surgical interventions with respect to incidence of medical abortion failures.

The Population Council agrees to study ongoing pregnancies and their outcomes through a surveillance, reporting, and tracking system (#6). This protocol summary and a summary for the monitoring system was received on September 19, 2000 and both were found to be adequate.

The Population Council asked that Commitment #3 (to assess the long term effects of multiple use of the regimen) be waived because it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug, especially given privacy issues. In addition, the pharmacology of mifepristone does not suggest any carry over effect after one-time administration. The Agency agrees with this assessment.

As a note, this cycle the Population Council provided new data concerning Commitment #5 (to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke), from Spitz et al. This study had 106 women ages 35 years or older as well as 51 subjects under age 20, all of whom were 49 days or less since their last menstrual period. The data on the older women is informative and of meaningful sample size. FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Sptiz data actually suggests a trend towards increased success of medical abortion with younger patients. However, as these age groups were not part of the NDA indication and the data on safety and effectiveness were only reviewed for the indication's age group (18-35 years of age), the trials excluded patients younger than 18 years old, and the raw data from Sptiz have not been submitted for review, the labeling states the safety and efficacy in these groups have not been studied. The Population Council will collect outcomes in their Phase 4 studies of women of all ages to further study this issue. With respect to smokers, the Population Council will study smokers of various ages to collect safety information. In sum, the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996.

The postmarketing audit of signed Patient Agreement forms was discussed above.

Public Comments Considered

The Food and Drug Administration received over 1,000 letters or emails from the public about mifepristone. Most comments objected to various restrictions of the drug's distribution. For example, many letters opposed press reports of an alleged FDA public registry of doctors who dispense mifepristone. Other letters focused on the research uses of mifepristone for neurologic and oncologic diseases and the concern that restricting distribution after approval would constrain off-label uses. Still other letters expressed misunderstanding that experimental indications that are subject to INDs would be limited by an approval of mifepristone with distribution restrictions. These comments were reviewed and considered.

Risk Management Program

Risk management for a drug has the goal of optimizing the use of a product by maximizing its benefits and minimizing its risks. Interventions to manage risk include education to physicians, patients, and the public, labeling (including warnings, precautions, contraindications, dosage and administration, and Medication Guide), restriction of product use or supply, and packaging changes. This drug is being approved under Subpart H (restrictions on distribution) as part of the risk management program. The Population Council and FDA have identified the areas below, among others, that contribute to drug safety and effectiveness:

1. Proper selection of patients via physicians who are qualified to do so by dating pregnancies and diagnosing ectopics,
2. Qualified physicians to administer or supervise the administration of the medication
3. Compliance with the regimen by physicians and patients through education and monitoring
4. Safety and effectiveness information that fully informs patients and physicians about the risks and benefits of the treatment
5. Evaluation of physician qualifications through Phase 4 studies has been discussed in above sections.
6. Physical packaging in unit of dosing to ensure proper dose and provision of Medication Guide with each dose
7. Active patient participation in the treatment through the Patient Agreement and Medication Guide with an audit of signed Patient Agreement to ensure compliance
8. Active programs to get physicians to report adverse events and ongoing pregnancies to provide accurate risk information
9. Commitment to review and revise the risk management program for improved public health

All components of this risk management program have been discussed above, including the Medication Guide, the labeling that includes the Prescriber's and Patient Agreement forms, approval under Subpart H, and Phase 4 studies to evaluate risk management interventions and to gather data on risks.

In summary, all approval issues related to the NDA have been addressed adequately.

APPEARS THIS WAY
ON ORIGINAL

EXHIBIT 28

Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007,
73 Fed. Reg. 16313, 16314 (Mar. 27, 2008)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–N–0174]

Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing this notice to notify holders of certain prescription new drug and biological license applications that they will be deemed to have in effect an approved risk evaluation and mitigation strategy (REMS) under the Food and Drug Administration Amendments Act of 2007 (FDAAA). Holders of applications deemed to have in effect an approved REMS are required to submit a proposed REMS to FDA.

DATES: Submit proposed REMSs to FDA by September 21, 2008.

ADDRESSES: Written communications regarding the applicability of this notice to a specific product should be identified with Docket Number FDA–2008–N–0174 and submitted to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic communications to *http://www.regulations.gov*. Information about FDA implementation of FDAAA is available on the Internet at *http://www.fda.gov/oc/initiatives/advance/fdaaa.html*.

FOR FURTHER INFORMATION CONTACT: Mary Dempsey, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 4326, Silver Spring, MD 20993–0002, 301–796–0147.

SUPPLEMENTARY INFORMATION:

I. Introduction

On September 27, 2007, the President signed into law FDAAA (Public Law 110–85). Title IX, subtitle A, section 901 of FDAAA created new section 505–1 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355–1). Section 505–1(a) of the act authorizes FDA to require persons submitting certain applications[1] to submit and implement a REMS if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug and informs the holder of the application for the drug of the determination. Section 909 of FDAAA provides that Title IX, subtitle A takes effect 180 days after its enactment, which is March 25, 2008.

FDAAA also contains REMS requirements for drug and biological products approved before the effective date of Title IX, subtitle A. Section 909(b)(1) of FDAAA specifies that a ''drug that was approved before the effective date of this Act is * * * deemed to have in effect an approved risk evaluation and mitigation strategy under section 505–1 of the Federal Food, Drug, and Cosmetic Act * * * if there are in effect on the effective date of this Act elements to assure safe use—(A) required under section 314.520 or section 601.42 of title 21, Code of Federal Regulations; or (B) otherwise agreed to by the applicant and the Secretary [of Health and Human Services] for such drug.''

Section 909(b)(3) of FDAAA states: ''Not later than 180 days after the effective date of this Act, the holder of an approved application for which a risk evaluation and mitigation strategy is deemed to be in effect * * * shall submit to the Secretary a proposed risk evaluation and mitigation strategy. Such proposed strategy is subject to section 505–1 of the Act as if included in such application at the time of submission of the application to the Secretary.''[2]

Section 909(b)(2) of FDAAA states that a REMS for a drug deemed to have a REMS consists of the timetable required under section 505–1(d) of the act and any additional elements under section 505–1(e) and (f) of the act in effect for the drug on the effective date of FDAAA.

The purpose of this notice is to identify those drugs that FDA has determined will be deemed to have in effect an approved REMS and to notify holders of applications for such drugs that they are required to submit a proposed REMS by September 21, 2008. FDA is developing guidance on the preferred content and format of a proposed REMS required to be submitted under section 909(b) of FDAAA and will issue it as soon as possible.

II. List of Drug and Biological Products Deemed to Have a REMS

Drug and biological products deemed to have in effect an approved REMS are those that on March 25, 2008 (the effective date of Title IX, subtitle A of FDAAA), had in effect ''elements to assure safe use.'' ''Elements to assure safe use'' include the following: (1) Health care providers who prescribe the drug have particular training or experience, or are specially certified; (2) pharmacies, practitioners, or health care settings that dispense the drug are specially certified; (3) the drug is dispensed to patients only in certain health care settings, such as hospitals; (4) the drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results; (5) each patient using the drug is subject to certain monitoring; or (6) each patient using the drug is enrolled in a registry (see section 505–1(f)(3) of the act).

Some applications approved before the effective date of FDAAA Title IX, subtitle A contain these elements to assure safe use.[3] Some of these applications were approved under § 314.520 (21 CFR 314.520) or § 601.42 (21 CFR 601.42). Others were not approved under part 314, subpart H or part 601, subpart E, but still contain elements to assure safe use that were agreed to by the applicant and the Secretary for such drug. Since 2005, these elements typically appeared in approved risk minimization action plans (RiskMAPs) (see the guidance for industry entitled ''Development and Use of Risk Minimization Action Plans'' (70 FR 15866, March 29, 2005)).

FDA has reviewed its records to identify applications that were approved before the effective date of Title IX of FDAAA with elements to assure safe use and has identified the drug and biological products listed in table 1 of this document as those that will be deemed to have in effect an approved REMS.

[1] Section 505(p)(1) of the act (21 U.S.C. 355(p)(1)) states that section 505–1 of the act applies to applications for prescription drugs approved under section 505(b) or (j) of the act and applications approved under section 351 of the Public Health Service Act (42 U.S.C. 262).

[2] Title IX, subtitle A of FDAAA, which includes section 909, takes effect March 25, 2008; 180 days after that date is September 21, 2008.

[3] These plans sometimes contain other elements to minimize risk such as a Medication Guide (21 CFR part 208) or a communication/educational plan for health care providers or patients. A drug will not be deemed to have a REMS if it has only a Medication Guide, patient package insert, and/or communication plan (see section 505–1(e)(2) and (e)(3) of the act).

TABLE 1.—PRODUCTS DEEMED TO HAVE IN EFFECT AN APPROVED REMS

Generic or Proper Name	Brand Name	Application Number[1]	Date of Approval[2]
Abarelix	Plenaxis[3]	NDA 21–320	11/25/2003
Alosetron	Lotronex	NDA 21–107	02/09/2000
Ambrisentan	Letairis	NDA 22–081	06/15/2007
Bosentan	Tracleer	NDA 21–290	11/20/2001
Clozapine	Clozaril	NDA 19–758 ANDA 74–949 ANDA 75–417 ANDA 75–713 ANDA 75–162 ANDA 76–809	09/26/1989 11/26/97 5/27/99 11/15/02 4/26/05 12/16/05
	Fazaclo ODT	NDA 21–590	02/09/2004
Dofetilide	Tikosyn	NDA 20–931	10/01/1999
Eculizumab	Soliris	BLA 125166	03/16/2007
Fentanyl PCA	Ionsys[3]	NDA 21–338	05/22/2006
Fentanyl citrate	Actiq	NDA 20–747	11/04/1998
Isotretinoin	Accutane Amnesteem Claravis	NDA 18–662 ANDA 75–945 ANDA 76–135 ANDA 76–356	05/07/1982 11/2002 04/2003 04/2003
	Sotret	ANDA 76–041 ANDA 76–503	12/2002 06/2003
Lenalidomide	Revlimid	NDA 21–880	12/27/2005
Mifepristone	Mifeprex	NDA 20–687	09/28/2000
Natalizumab	Tysabri	BLA 125104	11/23/2004
Small pox (Vaccinia) Vaccine, Live	ACAM2000	BLA 125158	08/31/2007
Sodium oxybate	Xyrem	NDA 21–196	07/17/2002
Thalidomide	Thalomid	NDA 20–785 NDA 21–430	07/16/1998

[1] New drug application (NDA), abbreviated new drug application (ANDA), biologics license application (BLA).
[2] The original date of approval of the drug. FDA may have required elements to assure safe use at a later date.
[3] Product is not currently marketed in the United States.

FDA is further asking members of the public to please notify the agency if they are aware of applications that have not been identified in this document and that they believe should be deemed to have in effect an approved REMS. Please provide the information to Mary Dempsey, Risk Management Coordinator (see the **FOR FURTHER INFORMATION CONTACT** section of this document).

Any application holder that believes its product identified in this notice should not be on the list of drug or biological products that will be deemed to have in effect an approved REMS should submit a letter identified with Docket Number FDA–2008–N–0174 to the Division of Dockets Management (see **ADDRESSES**) stating why the application holder believes its product was improperly identified in this notice. FDA will notify the application holder within 30 days of receipt of the letter of its determination.

Dated: March 19, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E8–6201 Filed 3–26–08; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committees: Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

EXHIBIT 29

2011 FDA Supplemental Approval Letter to
Danco Laboratories, LLC
(June 8, 2011)
("2011 Approval Letter")

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-014

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated September 16, 2008, received September 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for MIFEPREX® (mifepristone) Tablets. We note that NDA 020687 is approved under the provisions of 21 CFR 314.520 (Subpart H).

This supplemental application provides for a proposed risk evaluation and mitigation strategy (REMS) for MIFEPREX (mifepristone) and was submitted in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified MIFEPREX (mifepristone) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

We acknowledge receipt of your amendments dated December 9, 2008, November 8, 2010, and May 19 and 27, 2011.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for MIFEPREX (mifepristone) to ensure the benefits of the drug outweigh the risks of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX (mifepristone) and are able to assure patient access to appropriate medical facilities to manage any complications.

Your proposed REMS, as amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

The REMS assessment plan will include the information submitted to FDA on May 27, 2011, and should include the following information:

a. Per section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
b. Per section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify future submissions containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020687
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 020687
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

As part of the approval under Subpart H, as required by 21 CFR 314.550, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days

before the intended time of initial distribution of the labeling or initial publication of the advertisement. Send one copy to the (b) (6) and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

ENCLOSURES:
REMS Document
REMS Materials

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

06/08/2011

EXHIBIT 30

2011 REMS for NDA 20-687 Mifeprex
(mifepristone) Tablets, 200mg
(June 8, 2011)
("2011 REMS")

NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg

Danco Laboratories, LLC PO Box 4816
New York, NY 10185

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

A. To provide information to patients about the benefits and risks of MIFEPREX before they make a decision whether to take the drug.

B. To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX and are able to assure patient access to appropriate medical facilities to manage any complications.

II. REMS ELEMENTS

A. Medication Guide

1. A Medication Guide will be dispensed with each MIFEPREX prescription in accordance with 21 CFR 208.24.

2. Please see the appended Medication Guide.

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe MIFEPREX will be specially certified.

   Danco will ensure that healthcare providers who prescribe MIFEPREX are specially certified.

   a. To become specially certified, each prescriber must complete and fax to the MIFEPREX distributor the one-time Prescriber's Agreement, agreeing that they meet the qualifications and will follow the guidelines outlined in the Prescriber's Agreement.

   b. The following materials are part of the REMS and are appended:

      i. Prescriber's Agreement.

      ii. Patient Agreement.

2. MIFEPREX will be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals.

   Danco will ensure that MIFEPREX will only be available to be dispensed in a clinic, medical office, or hospital, by or under the supervision of a specially certified prescriber. MIFEPREX will not be distributed to or dispensed through retail pharmacies.

3. MIFEPREX will only be dispensed to patients with documentation of safe use conditions.

   Danco will ensure that MIFEPREX will only be dispensed to patients with documentation of the following safe use conditions:

   a. The patient has completed and signed the Patient Agreement, and the Patient Agreement has been placed in the patient's medical record.

   b. The patient has been provided copies of the signed Patient Agreement and the Medication Guide.

C. Implementation System

The Implementation System will include the following:

1. Distributors who distribute MIFEPREX will be certified. To become certified, distributors must agree to:

   a. Ship drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements, and maintain secure and confidential records of shipments.

   b. Follow all distribution guidelines, including those for storage, tracking package serial numbers, proof of delivery, and controlled returns.

2. Danco will assess the performance of the certified distributors with regard to the following:

   a. Whether a secure, confidential and controlled distribution system is being maintained with regard to storage, handling, shipping, and return of MIFEPREX.

   b. Whether MIFEPREX is being shipped only to site locations identified by specially certified prescribers in the signed Prescriber's Agreement and only available to be dispensed to patients in a clinic, medical office, or hospital by or under the supervision of a specially certified prescriber.

3. If Danco determines the distributors are not complying with these requirements, Danco will take steps to improve their compliance.

D. Timetable for Submission of Assessments

Danco will submit REMS assessments to the FDA one year from the date of the approval of the REMS and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the assessment reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Danco will submit each assessment so that it will be received by the FDA on or before the due date.

MEDICATION GUIDE

Mifeprex® (MIF-eh-prex)
(mifepristone)

Read this information carefully before taking Mifeprex* and misoprostol. It will help you understand how the treatment works. This MEDICATION GUIDE does not take the place of talking with your health care provider (provider).

What is Mifeprex?

Mifeprex is used to end an early pregnancy. It blocks a hormone needed for your pregnancy to continue. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. When you use Mifeprex (Day 1), you also need to take another medicine misoprostol, 2 days after you take Mifeprex (Day 3), to end your pregnancy. But, about 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Prompt medical attention is needed in these circumstances. Serious infection has resulted in death in a very small number of cases; in most of these cases misoprostol was used in the vagina. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your provider. Your provider's telephone number is _____.

Be sure to contact your provider promptly if you have any of the following:

Heavy Bleeding. Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.

Abdominal Pain or "Feeling Sick". If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

Fever. In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your provider right away. Fever may be a symptom of a serious infection or another problem (including an ectopic pregnancy).

Take this MEDICATION GUIDE with you. When you visit an emergency room or a provider who did not give you your Mifeprex, you should give them your MEDICATION GUIDE so that

they understand that you are having a medical abortion with Mifeprex.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

Talk with your provider. Before you take Mifeprex, you should read this MEDICATION GUIDE and sign a statement (PATIENT AGREEMENT). You and your provider should discuss the benefits and risks of your using Mifeprex.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

How should I take Mifeprex?

- **Day 1 at your provider's office:**
  - Read this MEDICATION GUIDE.
  - Discuss the benefits and risks of using Mifeprex to end your pregnancy.
  - If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
  - After getting a physical exam, swallow 3 tablets of Mifeprex.
- **Day 3 at your provider's office:**
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your provider may send you home with medicines for these symptoms.
- **About Day 14 at your provider's office:**
  - This follow-up visit is very important. You must return to the provider about 14 days after you have taken Mifeprex to be sure you are well and that you are not pregnant.
  - Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them because they may interfere with the treatment. Ask your provider about what medicines you can take for pain.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop breastfeeding for a few days.

What are the possible and reasonably likely side effects of Mifeprex?

Cramping and bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must return to your provider on Day 3 and about Day 14. See "How should I take Mifeprex?" for more information on when to return to your provider. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9–16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

Other common symptoms of treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

* * *

Medicines are sometimes prescribed for purposes other than those listed in a MEDICATION GUIDE. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration.

Rev 3: 4/22/09
*Mifeprex is a registered trademark of Danco Laboratories, LLC.

M I F E P R E X®
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.

- Ability to diagnose ectopic pregnancies.

- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.

- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.

- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.

- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com
*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

ACCOUNT SETUP FORM

MIFEPREX™ (Mifepristone) Tablets, 200 mg; NDC 64875-001-03

To set up your account:

1. Read the Prescriber's Agreement on the back of this Account Setup Form.
2. Complete and sign this form.
3. Fax the completed Account Setup Form to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.
4. The distributor will call to finalize your account setup and take your initial order.
5. Subsequent orders may be phoned in and are usually shipped within 24 hours.
6. Unopened, unused product may be returned for a refund or exchange up to a year after the expiration date.

Billing information

Bill to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Shipping information (❑ Check if same as above)

Ship to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Additional site locations

I will also be prescribing Mifeprex* at these additional locations:

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

(Any additional sites may be listed on an attached sheet of paper.)

Request additional materials

❑ Medication Guides ❑ Patient Agreements

❑ State Abortion Guidelines ❑ Patient Brochures

Establishing your account (required only with first order)

Each facility purchasing Mifeprex must be included on this form (see additional site locations box above) before the distributor can ship the product. Please read the Prescriber's Agreement on the reverse of this form and sign below.

By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.

Print Name _____ Signature _____

Medical License # _____ Date _____

Fax this completed Account Setup Form to the authorized distributor. Fax: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

*Mifeprex is a trademark of Danco Laboratories, LLC.

MIFEPREX™ (Mifepristone) Tablets, 200 mg

Reference ID: 2957855

Mifeprex® (Mifepristone) Tablets, 200 mg

PATIENT AGREEMENT

Mifeprex* (mifepristone) Tablets

1. I have read the attached MEDICATION GUIDE for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:
    - contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
    - contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
    - contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
    - take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
    - return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
    - return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature: _____

Patient Name (print): _____

Date: _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature: _____

Name of Provider (print): _____

Date: _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the MEDICATION GUIDE to the patient.

Rev 2: 7/19/05
*Mifeprex is a registered trademark of Danco Laboratories, LLC.

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

State of Missouri, *et al.*, *Intervenor-Plaintiffs,* and **State of Florida, State of Texas,** *Proposed Intervenor-Plaintiffs,* and **Rosalie Markezich** and **State of Louisiana**, by and through its Attorney General, **Liz Murrill**, *Proposed Intervenor-Plaintiffs*, v. **United States Food and Drug Administration,** *et al.,* *Defendants,* and **Danco Laboratories, LLC,** *Intervenor-Defendant*, and **GenBioPro, Inc.,** *Intervenor-Defendant.*	**Civ. No. 2:22-cv-00223-Z**

APPENDIX IN SUPPORT OF PROPOSED INTERVENOR-PLAINTIFFS ROSALIE MARKEZICH AND THE STATE OF LOUISIANA'S MOTION TO INTERVENE

VOLUME B

INDEX

VOLUME A	
Ex. 1: Society of Family Planning, #WeCount Report April 2022 to June 2024 (Oct. 22, 2024)	App. 1-57
Ex. 2: Society of Family Planning, #WeCount Report April 2022 to December 2024 (Jun. 23, 2025)	App. 58-125
Ex. 3: 2021 FDA Letter to ACOG and SMFM About Mifepristone REMS (Apr. 12, 2021)	App. 126-128
Ex. 4: Dr. Margaret Carpenter indictment	App. 129-131
Ex. 5: Center for Drug Evaluation and Research, Application Number: 20-687 Medical Review(s) (Jan. 27, 2000	App. 132-175
Ex. 6: Blake M. Autry & Roopma Wadhwa, *Mifepristone*, StatPearls (Feb. 28, 2024)	App. 176-184
Ex. 7: *The Facts on Mifepristone,* Planned Parenthood	App. 185-188
Ex. 8: *Medication Abortion: Your Questions Answered*, Yale Med. (Sept. 11, 2023	App. 189-194
Ex. 9: FDA-Approved Label for Mifepristone (Mifeprex) (Jan. 2023) ("Mifeprex 2023 Label")	App. 195-214
Ex. 10: 2021 FDA Letter to AAPLOG and Am. Coll. of Pediatricians denying in part and granting in part 2016 Citizen Petition, Docket No. FDA-2019-P-1534 (Dec. 16, 2021)	App. 215-255
Ex. 11: Center for Drug Evaluation and Research, Application Number: 020687Orig1s020 Summary Review (Mar. 29, 2016) ("FDA 2016 Summary Review")	App. 256-284
Ex. 12: Maarit Niinimaki et al., *Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study*, BMJ (April 20, 2011)	App. 285-292
Ex. 13: Jamie Bryan Hall & Ryan T. Anderson, *The Abortion Pill Harms Women: Insurance Data Reveals One in Ten Patients Experiences a Serious Adverse Event,* Ethics & Pub. Pol'y Ctr. (Apr. 28, 2025)	App. 293-299
Ex. 14: James Studnicki et al., *Comparative Acuity of Emergency Department Visits Following Pregnancy Outcomes Among Medicaid Eligible Women, 2004–2015*, Int'l J. Epidemiology & Pub. Health Rsch., Apr. 2024	App. 300-304
Ex. 15: *Will a doctor be able to tell if you've taken abortion pills?* Women Help Women (Sept. 23, 2019)	App. 305-307
Ex. 16: *How do you know if you have complications and what should you do?* Aid Access	App. 308-310

Ex. 17: *Am. Coll. of Obstetricians and Gynecologists Practice Bulletin No. 181: Prevention of Rh D Alloimmunization*, 130 Obstetrics & Gynecology 481 (Aug. 2017)	App. 311-325
Ex. 18: Katherine A. Rafferty & Tessa Longbons, *#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives*, 36 Health Commc'n 1485 (2021	App. 326-336
Ex. 19: Population Council	App. 337-351
Ex. 20: 2002 Citizen Petition of AAPLOG to FDA (Aug. 8, 2002) ("2002 Citizen Petition")	App. 352-444
Ex. 21: Robert O'Harrow Jr., *Drug's U.S. Marketer Remains Elusive*, Wash. Post (Oct. 11, 2000)	App. 445-448
Ex. 22: Hannah Levintova, *The Abortion Pill's Secret Money Men*, Mother Jones (March–April 2023)	App. 449-459
Ex. 23: Letter from Center for Drug Evaluation and Research to Ann Robbins, Ph.D. (Sept. 18, 1996)	App. 460-470
Ex. 24: 2000 FDA Approval Letter for Mifeprex (mifepristone) Tablets (Sept. 28, 2000)	App. 471-474
Ex. 25: 2019 FDA ANDA Approval Letter to GenBioPro, Inc. (Apr. 11, 2019)	App. 475-481
Ex. 26: FDA Center for Drug Evaluation & Research Letter to Population Council re: NDA (Feb. 18, 2000)	App. 482-489
Ex. 27: 2000 FDA Approval Memo. to Population Council re: NDA 20-687 Mifeprex (mifepristone) (Sept. 28, 2000)	App. 490-498
Ex. 28: Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16313, 16314 (Mar. 27, 2008)	App. 499-501
Ex. 29: 2011 FDA Supplemental Approval Letter to Danco Laboratories, LLC (June 8, 2011) ("2011 Approval Letter")	App. 502-506
Ex. 30: 2011 REMS for NDA 20-687 Mifeprex (mifepristone) Tablets, 200mg (June 8, 2011) ("2011 REMS")	App. 507-517
VOLUME B	
Ex. 31: 2016 FDA Letter to AAPLOG, Christian Medical & Dental Associations, and Concerned Women for America denying 2002 Citizen Petition, Docket No. FDA2002-P-0364 (Mar. 29, 2016) ("2016 Petition Denial")	App. 518-551
Ex. 32: 2020 Letter from ACOG & SMFM to FDA about Mifepristone REMS (Apr. 20, 2020) ("2020 ACOG-SMFM Letter")	App. 552-555
Ex. 33: Students for Life of America, Citizen Petition to FDA (Dec. 13, 2022)	App. 556-623

Ex. 34: 2023 FDA Letter to Students for Life of Am. denying 2022 SFLA Petition, Docket No. FDA-2022-P-3209 (Jan. 3, 2023)	App. 624-626
Ex. 35: 2021 FDA Center for Drug Evaluation & Research Director Patrizia Cavazzoni Letter to Dr. Graham Chelius (Dec. 16, 2021)	App. 627-628
Ex. 36: Oral History Interview with Ruth B. Merkatz (Oct. 16, 2019)	App. 629-727
Ex. 37: White House, Readout of White House Roundtable Meeting with Women's Rights and Reproductive Health Leaders (Sept. 3, 2021)	App. 728-731
Ex. 38: White House, Press Briefing by Press Secretary Jen Psaki and Deputy National Security Advisor for Cyber and Emerging Technologies Anne Neuberger, September 2, 2021 (Sept. 2, 2021)	App. 732-769
Ex. 39: Ian Millhiser, *It sure sounds like Roe v. Wade is doomed*, Vox (Dec. 1, 2021)	App. 770-778
Ex. 40: White House, Remarks by President Biden Before Meeting with His Task Force on Reproductive Healthcare Access (Jan. 22, 2024)	App. 779-786
Ex. 41: White House, Remarks by President Biden on the Supreme Court's Decision on Affirmative Action (June 29, 2023)	App. 787-794
Ex. 42: White House, FACT SHEET: President Biden to Sign Executive Order Protecting Access to Reproductive Health Care Services (July 8, 2022)	App. 795-802
Ex. 43: White House, Remarks by President Biden on the Supreme Court Decision to Overturn *Roe v. Wade* (June 24, 2022)	App. 803-809
Ex. 44: Exec. Order No. 14076, Protecting Access to Reproductive Healthcare Services, 87 Fed. Reg. 42053 (July 8, 2022)	App. 810-813
Ex. 45: Exec. Order No. 14079, Securing Access to Reproductive and Other Healthcare Services, 87 Fed. Reg. 49505 (Aug. 3, 2022)	App. 814-817
Ex. 46: Presidential Memorandum, Further Efforts To Protect Access to Reproductive Healthcare Services, 88 Fed. Reg. 4895 (Jan. 22, 2023)	App. 818-821
Ex. 47: White House, FACT SHEET: President Biden Announces Actions In Light of Today's Supreme Court Decision on *Dobbs v. Jackson Women's Health Organization* (June 24, 2022)	App. 822-824
Ex. 48: Press Release, HHS, HHS Secretary Becerra's Statement on Supreme Court Ruling in *Dobbs v. Jackson Women's Health Organization* (June 24, 2022)	App. 825-826
Ex. 49: Press Release, HHS, Remarks by Secretary Xavier Becerra at the Press Conference in Response to President Biden's Directive following Overturning of Roe v. Wade (June 28, 2022)	App. 827-830
Ex. 50: Center for Drug Evaluation and Research, Application Number: 020687Orig1s025 Summary Review (Jan. 3, 2023) ("FDA 2023 Summary Review")	App. 831-920

Ex. 51: Center for Drug Evaluation and Research, Application Numbers: 020687 and 91178 Rationale Review (Dec. 16, 2021) ("FDA 2021 Rationale Review")	App. 921-971
Ex. 52: FDA Adverse Events Reporting System (FAERS) Public Dashboard	App. 972-989
Ex. 53: Kathi A. Aultman et al., *Deaths and Severe Adverse Events After the Use of Mifepristone as an Abortifacient from September 2000 to February 2019,* 26 Issues in L. & Med., no. 1, Nov. 1, 2021	App. 990-1015
Ex. 54: *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* (Apr. 2021)	App. 1016-1064
VOLUME C	
Ex. 55: Christiana A. Cirucci et al., *Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act*, 8 Health Servs. Rsch & Managerial Epidemiology 1, 1 (2021)	App. 1065-1070
Ex. 56: Pam Belluck, *CVS and Walgreens Will Begin Selling Abortion Pills this Month*, N.Y. Times (Mar. 1, 2024)	App. 1071-1076
Ex. 57: 2019 REMS Single Shared System for Mifepristone 200MG (Apr. 2019)	App. 1077-1085
Ex. 58: HHS, Marking the 50th Anniversary of Roe: Biden-Harris Administration Efforts to Protect Reproductive Health Care (Jan. 19, 2023)	App. 1086-1092
Ex. 59: Press Release, HHS, HHS Releases Report Detailing Biden-Harris Administration Efforts to Protect Reproductive Health Care Since Dobbs (Jan. 19, 2023)	App. 1093-1096
Ex. 60: White House, FACT SHEET: The Biden-Harris Administration's Record on Protecting Access to Medication Abortion (Apr. 12, 2023)	App. 1097-1099
Ex. 61: HHS, Secretary's Report, Health Care Under Attack: An Action Plan to Protect and Strengthen Reproductive Care (Aug. 2022)	App. 1100-1123
Ex. 62: Abuzz, *Abortion Pill Access in Louisiana*	App. 1124-1126
Ex. 63: Abuzz, *Need abortion care at home?*	App. 1127-1133
Ex. 64: A Safe Choice, *Home*	App. 1134-1140
Ex. 65: A Safe Choice, *Online Consultation Form*	App. 1141-1143
Ex. 66: Choices Rising, *Abortion Pill*	App. 1144-1148

Ex. 67: MAP, *Frequently asked questions*	App. 1149-1152
Ex. 68: Scott Calvert, *The Parties Where Volunteers Pack Abortion Pills for Red-State Women*, Wall St. J. (Aug. 12, 2024)	App. 1153-1160
Ex. 69: Rachel Roubein, *'Shield' Laws Make it Easier to Send Abortion Pills to Banned States*, Wash. Post. (July 20, 2023)	App. 1161-1166
Ex. 70: Rebecca Grant, *Group Using 'Shield Laws' to Provide Abortion Care in States That Ban It*, The Guardian (July 23, 2023)	App. 1167-1170
Ex. 71: Aid Access, *Get Abortion Pill Online in Louisiana*	App. 1171-1175
Ex. 72: Elissa Nadworny, I*nside a medical practice sending abortion pills to states where they're banned,* NPR (Aug. 7, 2024)	App. 1176-1183
Ex. 73: Abigail Brooks & Dasha Burns, *How a network of abortion pill providers works together in the wake of new threats*, NBC News (April 7, 2024)	App. 1184-1191
Ex. 74: Pam Belluck, *Abortion Shield Laws: A New War Between the States*, N.Y. Times (Feb. 22, 2024)	App. 1192-1209
Ex. 75: Caroline Kitchener, *Alone in a bathroom: The fear and uncertainty of a post-Roe medication abortion*, Wash. Post (April 11, 2024)	App. 1210-1244
Ex. 76: Her Safe Harbor, *Abortion Pills Online*	App. 1245-1250
Ex. 77: Pam Belluck, *A day with one abortion pill prescriber*, N.Y. Times (Jun. 9, 2025)	App. 1251-1264
VOLUME D	
Ex. 78: Abuzz, *FAQs*	App. 1265-1278
Ex. 79: ACT, *Who We Are*	App. 1279-1283
Ex. 80: ACT, *What We Do*	App. 1284-1288
Ex. 81: ACT, *FAQs*	App. 1289-1293
Ex. 82: ACT, *Resources*	App. 1294-1297
Ex. 83: Alaa Elassar, *New York Doctor Indicted in Louisiana Abortion Case Recognized as a Leader in Women's Reproductive Health*, CNN (Feb. 23, 2025)	App. 1298-1311
Ex. 84: Rosemary Westwood, *After Historic Indictment, Doctors Will Keep Mailing Abortion Pills Over State Lines*, NPR (Mar. 19, 2025)	App. 1312-1322

Ex. 85: Katherine Donlevy, *Louisiana DA warns there's trove of evidence against NY doctor who allegedly mailed abortion pills to teen – who was planning gender reveal party: report*, New York Post (Feb. 15, 2025)	App. 1323-1328
Ex. 86: Lorena O'Neil, *Louisiana Mother Pleads Not Guilty Following Abortion Pill Indictment*, La. Illuminator (Mar. 11, 2025)	App. 1329-1332
Ex. 87: Press Release, ACT, Statement on Governor Hochul's Response to Louisiana Extradition Order (Feb. 13, 2025)	App. 1333-1334
Ex. 88: Press Release, Protecting Reproductive Freedom: Governor Hochul Signs Legislation Affirming New York's Status as a Safe Haven for Reproductive Health Care (Feb. 3, 2025)	App. 1335-1345
Ex. 89: Rosemary Westwood, *Louisiana Investigates Second Case Against New York Doctor Over Mailing Abortion Pills*, La. Illuminator (May 13, 2025)	App. 1346-1348
Ex. 90: Governor Kathy Hochul (GovKathyHochul), X (May 13, 2025, 4:28 PM)	App. 1349-1350
Ex. 91: Society of Family Planning, #WeCount Report April 2022 to December 2024 (Jun. 23, 2025)	App. 1351-1368
Ex. 92: Rosalie Markezich Declaration	App. 1369-1374
Ex. 93: *Exhibit 5: Medicaid as a Share of States' Total Budgets and State-Funded Budgets, SFY 2021,* Medicaid and CHIP Payment and Access Commission (MACPAC) (2023)	App. 1375-1378
Ex. 94: Julie O'Donoghue, *Louisiana Medicaid Set to Grow Under Landry, Even as D.C. May Force Cuts,* La. Illuminator, (Mar. 26, 2025)	App. 1379-1384
Ex. 95: Louisiana Department of Health, Medicaid Annual Report 2022/2023	App. 1385-1510
Ex. 96: Marc Roemer, HHS, Agency for Healthcare Research and Quality, *Costs of Treat-and-Release Emergency Department Visits in the United States, 2021* (September 2024)	App. 1511-1524
Ex. 97: Hospital Services Provider Manual: Chapter Twenty-Five of the Medicaid Services Manual, State of Louisiana Bureau of Health Services Financing, § 25.2 (July 1, 2011)	App. 1525-1623
Ex. 98: Louisiana Medicaid Hospital Ambulatory Surgery Fee Schedule: State Hospitals (Effective Jan. 1, 2025)	App.1624-1692
Ex. 99: Louisiana Medicaid Hospital Ambulatory Surgery Fee Schedule: Rural Hospitals (Effective Jan. 1, 2025)	App. 1693-1760
Ex. 100: Louisiana Medicaid Hospital Ambulatory Surgery Fee Schedule: Non-Rural and Non-State Hospitals (Effective Jan. 1, 2025)	App. 1761-1829

Ex. 101: Medicaid Services, Louisiana Department of Health	App. 1830-1839
Ex. 102: State Hospitals Outpatient Services Fee Schedule (Effective Jan. 1, 2025)	App. 1840-1935
Ex. 103: Small Rural Hospital Outpatient Services Fee Schedule (Effective Jan. 1, 2025)	App. 1936-2031
Ex. 104: Louisiana Medicaid Hospital Provider Inpatient Per Diem Rates (Effective 7/1/2024)	App. 2032-2038
Ex. 105: Pam Belluck, *California Passes Bill Allowing Omission of Patients' Names from Abortion Pill Bottles*, N.Y. Times (Sept. 11, 2025)	App. 2039-2043
Ex. 106: The Associated Press, *Texas Has a New Abortion Pill Law. But At Least One Provider Plans to Keep Shipping Them There,* Newsday (Sept. 18, 2025)	App. 2044-2047
Ex. 107: Caroline Kitchener, *Blue-state doctors launch abortion pill pipeline into states with bans*, Wash. Post (July 19, 2023)	App. 2048-2061

EXHIBIT 31

2016 FDA Letter to AAPLOG, Christian Medical & Dental Associations, and Concerned Women for America denying 2002 Citizen Petition, Docket No. FDA2002-P-0364 (Mar. 29, 2016) ("2016 Petition Denial")

DEPARTMENT OF HEALTH & HUMAN SERVICES

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Re: Docket No. FDA-2002-P-0364

Dear Drs. Harrison and Rudd and Ms. Nance:

This letter responds to your citizen petition submitted on August 20, 2002, to the Food and Drug Administration (FDA or Agency) on behalf of the American Association of Pro Life Obstetricians and Gynecologists (AAPLOG), the Christian Medical Association (CMA) (n/k/a the Christian Medical and Dental Associations), and Concerned Women for America (CWA) (Petition).[1] Your Petition requests that the Agency stay FDA's approval of Mifeprex (mifepristone, also known as RU-486), thereby halting the distribution and marketing of the drug pending final action on the Petition. The Petition also requests that the Agency revoke FDA's approval of Mifeprex and requests a full audit of the French and U.S. clinical trials submitted in support of the new drug application (NDA) for Mifeprex.

We have carefully considered the information submitted in your Petition, comments on your Petition submitted to the docket, other submissions to the docket, and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, your Petition is denied.

[1] The citizen petition was originally assigned docket number 2002P-0377/CP1. The number was changed to FDA-2002-P-0364 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. This citizen petition was submitted by AAPLOG, CMA, and Sandy Rios, the then-President of CWA. We have addressed this response to CWA's current CEO and President, Penny Young Nance.

I. BACKGROUND

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (NDA 20-687). The application was approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the approval letter, including a requirement that Mifeprex be provided by or under the supervision of a physician who meets eight qualifications specified in the letter.

The September 28, 2000, approval letter also listed two Phase 4 commitments[2] that the then-applicant of the Mifeprex NDA (i.e., the Population Council)[3] agreed to meet. In addition, the letter stated that FDA was waiving the pediatric study requirement in 21 CFR 314.55.

II. DISCUSSION OF ISSUES RAISED

You maintain that good cause exists for granting an immediate stay of the Mifeprex approval and for the subsequent revocation of that approval under 21 CFR 314.530 (Petition at 3). You contend that:

- The approval of Mifeprex in 2000 violated the Administrative Procedure Act's (APA's) prohibition against agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (5 U.S.C. 706(2)(A));
- The 2000 approval violated section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355) because Mifeprex does not satisfy the safety and labeling requirements of that section; and
- FDA approved Mifeprex in 2000 despite the presence of substantial risks to women's health, including fatal hemorrhage and serious bacterial infections.

You make eight arguments for the stay and revocation of the 2000 Mifeprex approval, as follows (Petition at 4-7):

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[2] For purposes of this petition response, the term 'Phase 4 commitments' refers to the postmarketing studies that the Mifeprex sponsor agreed to perform as a condition of approval.

[3] Effective October 31, 2002, the Population Council transferred ownership of the Mifeprex NDA to Danco Laboratories, LLC (Danco), which had been licensed to manufacture and market Mifeprex.

- That the approval of Mifeprex in 2000 violated the legal requirements of the accelerated approval regulations under 21 CFR Subpart H.
- That Mifeprex was not proven safe and effective in 2000 as required by law.
- That the Mifeprex regimen requires that Mifeprex be used in conjunction with another drug, misoprostol, which has not been separately approved as an abortifacient.
- That the Mifeprex regimen was approved in 2000 without adequate safety restrictions.
- That the drug's sponsor, following the approval in 2000, neglected to require Mifeprex providers to adhere to the restrictions contained in the regimen approved at that time.
- That the safeguards employed in one of the clinical trials that supported the 2000 approval were not mirrored in the regimen that FDA approved.
- That FDA improperly waived a requirement for pediatric studies in connection with the 2000 Mifeprex approval.
- That FDA did not require the sponsor of Mifeprex to honor its commitments for Phase 4 studies.

We respond to each of these arguments below.

We note your petition challenges the original approval of Mifeprex in 2000, and therefore this response is addressed to the 2000 approval and to the labeling that was approved at that time. Today, the Agency is approving a supplemental NDA submitted by Danco Laboratories, LLC (Danco), the holder of the Mifeprex NDA. This supplemental NDA proposed modified labeling for Mifeprex, including an updated dosing regimen, and included data to support the new labeling. After reviewing Danco's supplemental NDA, FDA determined that it met the statutory standard for approval. The fact that the previously approved regimen is no longer included in the labeling does not reflect a decision that there were safety or effectiveness concerns with the previously approved regimen.

A. Approval of Mifeprex Was Consistent With Subpart H

You maintain that FDA's 2000 approval of Mifeprex under the subpart H regulations was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law, and thus violated the APA (Petition at 18-23). You state that pregnancy, without major complications, is not a serious or life-threatening illness; instead, you claim it is a normal physiological state experienced by most females one or more times and is rarely accompanied by life-threatening complications (Petition at 19). You contend that Mifeprex does not provide meaningful therapeutic benefit to patients over existing treatments because surgical abortion is a less dangerous, more effective alternative for the termination of pregnancy, and that Mifeprex does not treat any subset of the female population that is unresponsive to or intolerant of surgical abortion

(Petition at 21-23). Thus, you assert that the approval of Mifeprex did not meet the requirements for product approval under subpart H (Petition at 23).

We disagree with your conclusion that we inappropriately approved Mifeprex under subpart H. As stated in section I above, the accelerated approval regulations apply to new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (§ 314.500). As FDA made clear in the preamble to the final rule for subpart H, the subpart H regulations are intended to apply to serious or life-threatening conditions, as well as to illnesses or diseases.[4] The Agency also made clear that a condition need not be serious or life-threatening in all populations or in all phases to fall within the scope of these regulations.[5] Unwanted pregnancy falls within the scope of subpart H under § 314.500 because unwanted pregnancy, like a number of illnesses or conditions, can be serious for certain populations or under certain circumstances.

Pregnancy can be a serious medical condition in some women.[6] Pregnancy is the only condition associated with preeclampsia and eclampsia and causes an increased risk of thromboembolic complications, including deep vein thrombophlebitis and pulmonary embolus. Additionally, there is a significant risk of a major surgical procedure and anesthesia if a pregnancy is continued; for 2013 (the most recent data available), the Centers for Disease Control and Prevention reported an overall 32.7 percent rate of cesarean sections in the United States.[7] Other medical concerns associated with pregnancy include the following: disseminated intravascular coagulopathy (a rare but serious complication); amniotic fluid embolism; life-threatening hemorrhage associated with placenta previa, placenta accreta, placental abruption, labor and delivery, or surgical delivery; postpartum depression; and exacerbation or more difficult management of preexisting medical conditions (e.g., diabetes, lupus, cardiac disease, hypertension). In addition, approximately 50 percent of all pregnancies in the United States each year are unintended.[8] According to the

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[4] See, e.g., 57 FR 58942, 58946 (Dec. 11, 1992).

[5] Id.

[6] According to data from the Centers for Disease Control and Prevention (CDC), for 2012 (the most recent year for which data are available), the pregnancy-related mortality ratio in the United States was 15.9 maternal pregnancy-related deaths per 100,000 live births. See CDC, Pregnancy Mortality Surveillance System, available on the CDC Web page at http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html. A 2012 study by Raymond and Grimes provides a comparison for the mortality rate associated with legal abortion to live birth in the United States for the earlier period from 1998 through 2005. Investigators reported that over the study period, the pregnancy related mortality rate among women who delivered live neonates was 8.8 deaths per 100,000 live births. This lower rate excludes deaths from ectopic pregnancies, stillbirths, gestational trophoblastic disease, etc. During the same period, the rate of abortion related mortality was 0.6 per 100,000 abortions. The risk of childbirth related death was therefore approximately 14 times higher than the rate associated with legal abortion. Raymond, EG and DA Grimes, Feb. 2012, The Comparative Safety of Legal Induced Abortion and Childbirth in the United States, Obstet Gynecol, 119 (2, Part 1):215-219.

[7] See CDC, Nov. 5, 2014, Trends in Low-risk Cesarean Delivery in the United States, 1990-2013, National Vital Statistics Report, 63(6), available at http://www.cdc.gov/nchs/data/nvsr/nvsr63/nvsr63_06.pdf .

[8] Guttmacher Institute, Feb. 2015, Unintended Pregnancy in the United States, at 1, available at http://www.guttmacher.org/pubs/FB-Unintended-Pregnancy-US.pdf. See also Institute of Medicine, 2011,

Institute of Medicine, women experiencing an unintended pregnancy may experience depression, anxiety, or other conditions.[9]

Furthermore, consistent with § 314.500, medical abortion through the use of Mifeprex provides a meaningful therapeutic benefit to some patients over surgical abortion.[10] Although FDA provided several examples in the preamble to the final rule to illustrate how the term "meaningful therapeutic benefit" might be interpreted, the Agency did not suggest that the meaning of the term was limited to the examples provided.[11] In the Phase 3 clinical trial of Mifeprex conducted in the United States, medical termination of pregnancy avoided an invasive surgical procedure and anesthesia in 92 percent of the 827 women with an estimated gestational age (EGA) of 49 days or less.[12] Complications of general or local anesthesia, or of intravenous sedation ("twilight" anesthesia), can include a severe allergic reaction, a sudden drop in blood pressure with cardiorespiratory arrest, death, and a longer recovery time following the procedure. Medical (non-surgical) termination of pregnancy provides an alternative to surgical abortion; it is up to the patient and her provider to decide whether a medical or surgical abortion is preferable and safer in her particular situation.[13]

Clinical Preventive Services for Women: Closing the Gaps (Closing the Gaps), at 102-110, available at http://books.nap.edu/openbook.php?record_id=13181 (stating that "[u]nintended pregnancy is highly prevalent in the United States").

[9] See Closing the Gaps, supra note 8, at 103.

[10] For a discussion of how FDA interprets the phrase "meaningful therapeutic benefit to patients over existing treatments" in 21 CFR 314.500, see FDA guidance for industry, *Expedited Programs for Serious Conditions—Drugs and Biologics*, at 3-4, 16-17, available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[11] 57 FR 58942, 58947 (Dec. 11, 1992).

[12] FDA, 1999, Medical Officer's Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion Up to 63 Day Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments (Medical Officer's Review), at 11 (Table 1) and 16, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf and http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P2.pdf. Spitz, IM, et al., 1998, Early Pregnancy Termination With Mifepristone and Misoprostol in the US, NEJM, 338:1241-1243.

[13] CDC data indicate that for the 730,322 abortions reported in 2011, there were 2 deaths. The CDC's calculated case fatality rate over the period from 2008 to 2011 (the most recent year for which data are available), the case fatality rate was 0.73 legal induced abortion-related deaths per 100,000 reported legal abortions. http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6410a1.htm?s_cid=ss6410a1_e. Mortality rates identified by type of abortion (medical or surgical) were not available. However, the evidence suggests that the risk of mortality associated with medical abortion is quite low. Confirmation of the low risk of medical abortion is provided in a study by Trussell, et al., which recorded no deaths for 711,556 medical abortions performed by Planned Parenthood clinics under the buccal misoprostol administration protocol (Trussell J, D Nucatola, et al., Mar. 2014, Reduction in Infection-Related Mortality Since Modifications in the Regimen of Medical Abortion, Contraception, 89(3):193-6). We note that one study reported a comparatively high occurance of fatality (1 death in a study of 11,155 early medical abortions); however, this apparent high occurence of fatality is likely due to instability in the estimate as a result of the small sample size (Goldstone P, J Michelson, et al., Sept. 3, 2012, Early Medical Abortion Using Low-Dose Mifepristone Followed by

You cite a study by Jensen, et al., as support for your claim that surgical abortion is less dangerous and more effective than Mifeprex (Petition at 21-22 (citing Jensen, JT, et al., 1999, Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study, Contraception, 59:153-159 (Jensen study)). This study was a prospective, nonconcurrent cohort analysis comparing the patients from one site in the U.S. phase 3 trial and a separate group of patients (who were not part of the U.S. phase 3 trial) who underwent surgical abortion at the same facility. The populations that were compared were not randomized to treatment (i.e., medical or surgical abortion) and the treatment periods did not overlap.[14] In addition, the data on medical abortion cited in the Jensen study are based on the 178 subjects at a single site in the phase 3 U.S. Mifeprex trial that enrolled 2,121 women. This small subset of the U.S. trial included patients with pregnancies of up to 63 days' gestation. Although you cite a surgical intervention rate of 18.3 percent in the Mifeprex patients, the surgical intervention rate for Mifeprex patients with an EGA ≤ 49 days was 12.7 percent (9 of 71), which, because of the small number of patients in the two groups, is not statistically significantly different from the 3.9 percent rate for re-intervention in the comparative surgical group (3 of 77).[15] Furthermore, the 3.9 percent who first had a surgical abortion and then required surgical re-intervention ultimately required *two* surgical interventions, not one, thereby exposing them twice to the risks inherent in invasive surgical procedures and anesthesia. Finally, although you state that the medical abortion patients in the Jensen study reported significantly longer bleeding than did surgical patients, there was not a greater amount of bleeding in the medical abortion group, nor was there a significant difference between the two treatment groups in the incidence of anemia as determined by the overall change in hemoglobin concentrations.

You state that FDA "viewed [s]ubpart H as the only available regulatory vehicle that had the potential to make Mifeprex safe" (Petition at 23 (footnote omitted)). The question of whether subpart H was "the only available regulatory vehicle" is not relevant here. As described above, Mifeprex met the criteria for approval under subpart H. Additionally, as stated in the September 28, 2000, memorandum to NDA 20-687 (Mifeprex Approval Memorandum), "the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications" that were set out in the approval letter and the Prescriber's Agreement.[16]

Buccal Misoprostol: A Large Australian Observational Study, Med J Aust, 197(5):282-6). Much more accurate and meaningful data are provided by Trussell's study covering >700,000 medical abortions.

[14] We are not suggesting that in order to be adequate and well-controlled a trial must be concurrently controlled. As discussed below in section II.B.1, FDA's regulations in § 314.126 recognize a number of different types of controls.

[15] In addition, the mean surgical intervention rate for all Mifeprex patients with gestational ages ≤ 49 days in the Phase 3 U.S. trial was 7.9 percent (65 of 827 evaluable patients).

[16] FDA, Sept. 28, 2000, Memorandum to NDA 20-687 MIFEPREX (mifepristone) Population Council (Mifeprex Approval Memorandum), available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111366.pdf

Furthermore, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.[17] The2011 REMS for Mifeprex incorporated the restrictions under which the drug was approved. Indeed, there is substantial overlap between the requirements of subpart H and the statutory criteria for REMS set out in Title IX.

Given all of the above, the Mifeprex NDA was appropriately approved in 2000.

B. The French and U.S. Clinical Trials of Mifeprex Provided Substantial Evidence to Support Approval

You contend that the studies on which the Population Council relied in support of its NDA for Mifeprex do not meet the statutory and regulatory requirements for the quality and quantity of scientific evidence needed to support a finding that a new drug is safe and effective (Petition at 24).

Our review of Mifeprex was thorough and consistent with the FD&C Act and FDA regulations, including the requirements under section 505(d) of the FD&C Act that: (1) there be adequate tests to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling (section 505(d)(1)) and (2) there be substantial evidence that the drug will have the effect it purports or is recommended to have under the conditions of use prescribed, recommended, or suggested in the labeling (section 505(d)(5)). The Mifeprex NDA was thoroughly reviewed, and the drug product was found to be safe and effective for its approved indication. In addition, as noted in the Mifeprex Approval Memorandum (at 1), FDA's Reproductive Health Drugs Advisory Committee (Advisory Committee) voted 6 to 0 (with 2 abstentions) on July 19, 1996, that the benefits of Mifeprex exceeded the risks. As set forth below, we disagree with your claims concerning the clinical trials that form the basis for the approval of Mifeprex.

1. The Clinical Trials Used to Support the Mifeprex NDA Were in Accordance With the FD&C Act and Applicable Regulations

You argue that because neither the French clinical trials nor the U.S. clinical trial of mifepristone were blinded, randomized, or concurrently controlled, these trials were inadequate to establish the safety and effectiveness of Mifeprex (Petition at 24-25 and 32-34). In addition, you assert in the response you submitted on October 10, 2003, to the comments in opposition to the Petition submitted by the Population Council and Danco (Response to Opposition) that the clinical trials of Mifeprex were not historically controlled but instead were uncontrolled.[18] You state that the

[17] 73 FR 16313 (Mar. 27, 2008).

[18] Response to Opposition at 5. You also state that because the Mifeprex regimen was the first drug regimen that FDA approved to induce abortions, the applicant should have compared the new drug regimen to surgical abortions performed during the first 49 days after a woman's last menstrual period (Response to Opposition at

applicant did not describe any historical control group in the French clinical trials, and did not indicate that any of the scientific guidelines for selecting a proper control group before beginning a historically controlled study were used for these trials (id. at 5-6). You also reject the applicant's claim that the available information on surgical abortion constitutes historically controlled data (id. at 6).

We disagree with your conclusion that the French and U.S. clinical trials of mifepristone were not clinically and legally adequate to support the approval of Mifeprex. The data from these three clinical trials (a large U.S. trial and two French trials) constitute substantial evidence that Mifeprex is safe and effective for its approved indication in accordance with section 505(d) of the FD&C Act. The labeling approved in 2000 for Mifeprex was based on data from these three clinical trials and from safety data from a postmarketing database of over 620,000 women in Europe who had had a medical termination of pregnancy (approximately 415,000 of whom had received mifepristone together with misoprostol).[19]

The U.S. trial of Mifeprex involved 2,121 subjects enrolled at 17 sites. Of these, 827 had an EGA of ≤ 49 days and were included in the efficacy evaluation.[20] Medical termination of pregnancy was complete (without the need for surgical intervention) in 762 of these subjects (92 percent).[21] Sixty-five of the subjects in the U.S. trial who were evaluable for efficacy were classified as having had a "treatment failure." The reasons for treatment failure (and number of subjects experiencing each) were: incomplete pregnancy termination (n = 39), still pregnant (n = 8), subject request for surgical intervention (n = 5), and medical indication (bleeding, n = 13).[22] The two French trials enrolled a total of 1,681 subjects providing effectiveness outcomes. Among the French subjects, the success rate for medical termination of pregnancy was 95.5 percent.[23]

In the U.S. trial, 859 subjects with an EGA of ≤ 49 days were evaluated for safety. Among these subjects, there were no deaths, one transfusion, and nine instances in which subjects received intravenous fluids.[24] The safety profile of the patient group in the French trials with an EGA of ≤ 49 days did not differ significantly from the safety profile of the same patient group in the U.S.

5, note 20). The fact that a drug might be the first one approved for a particular indication is not a factor in determining what type of control is adequate for a clinical trial of that drug for that indication. As discussed above, FDA's regulations provide for a variety of different types of controls (see 21 CFR 314.126(b)), and do not require comparison of a proposed drug product to an active control group to establish the safety and effectiveness of the drug. Therefore, the clinical trials to support the approval of Mifeprex were not required to have a surgical comparator arm.

[19] Mifeprex labeling, Sept. 28, 2000, PRECAUTIONS, Teratogenic Effects: Human Data, *Pregnancy,* available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf.

[20] Mifeprex Approval Memorandum, supra note 16, at 1; Medical Officer's Review, supra note 12, at 10.

[21] Medical Officer's Review, supra note 12, at 11 (Table 1) and 16.

[22] Id. at 11 (Table 1).

[23] Mifeprex Approval Memorandum, supra note 16, at 1.

[24] Medical Officer's Review, supra note 12, at 12-13.

trial, and the percentage of patients in the French and U.S. trials requiring hospitalization and blood transfusion and experiencing heavy bleeding was comparable.[25] There were no deaths in the French trials.[26]

Section 505(d) of the FD&C Act states, in part, that FDA must refuse to approve an application if the Agency finds that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the drug's proposed labeling. Section 505(d) defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."

As stated in 21 CFR 314.126(a), the purpose of conducting clinical investigations of a drug is to distinguish the effect of the drug from other influences, such as a spontaneous change in the course of the disease or condition, placebo effects, or biased observation. Reports of adequate and well-controlled investigations serve as the main basis for determining whether there is substantial evidence to support the claims of effectiveness for a drug.

We agree that randomization and the use of concurrent controls are two principal means of ensuring that clinical trial data are reliable and robust. However, that does not mean that in order to be adequate and well-controlled, a clinical trial must use a randomized concurrent control design. Section 314.126(b) lists the characteristics of an adequate and well-controlled study. Contrary to your assertion (Petition at 24), FDA regulations do not require that a study be blinded, randomized, and/or concurrently controlled. Among the characteristics of an adequate and well-controlled study is that it uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect (§ 314.126(b)(2)). A historical control is one of the recognized types of control (§ 314.126(b)(2)(v)), and one in which the results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment in comparable patients or populations (id.). Unlike some other types of control (e.g., placebo concurrent control (§ 314.126(b)(2)(i)) or dose-comparison concurrent control (§ 314.126(b)(2)(ii))), use of a historical control does not include randomization or blinding. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances, including studies in which the effect of the drug is self-evident.[27] Thus, in the proper setting,

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[25] Id. at 18.

[26] FDA, May 21, 1996, Statistical Review and Evaluation (May 21, 1996, Statistical Review), at 4 and 7, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf.

[27] 21 CFR 314.126(b)(2)(v). We note your contention that the effects of the regimen approved in 2000 are not self-evident because "[t]he Sponsor's focus on this dyadic set of possibilities (failure (0) or success (1)) obscures a whole range of less easily measurable, but critically important, outcomes," including "tissue retention, life-threatening hemorrhaging, persistent bleeding, infection, teratogenicity, pain, continued fertility, and psychological effects" (Response to Opposition at 8). We disagree with your argument. From a clinical perspective, there are two outcomes associated with the use of Mifeprex for medical abortion: either there is a complete abortion (without the need for surgical intervention) or there is not. The "outcomes" you

historically controlled trials can be considered adequate and well-controlled, and there is no need for the other types of control listed in § 314.126(b)(2).[28]

The use of historical controls in the Mifeprex clinical trials was appropriate for two reasons. First, the natural history of a viable pregnancy is adequately documented (a pregnancy continues on average for 40 weeks' gestation).[29] Second, the effect of Mifeprex is dramatic, occurs rapidly following treatment, and has a low probability of having occurred spontaneously.[30] Furthermore, contrary to your assertion (Petition at 32-34), the use of a historical control in these circumstances is consistent with ICH's guidance for industry, *E10 Choice of Control Group and Related Issues in Clinical Trials* (E10 Guidance).[31] The E10 Guidance addresses external controls (including historical controls) that are used in externally controlled trials to compare a group of subjects receiving the test treatment with a group of patients external to the study, rather than with an internal control group consisting of patients from the same population assigned to a different treatment.[32] The guidance states that the "external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome)."[33]

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cite are complications that can be associated with all abortions (including surgical abortion, missed abortion (non-viable pregnancy that has not been expelled from the uterus), and spontaneous abortion).

[28] You cite to a statement in the May 21, 1996, Statistical Review regarding the two French trials that "[i]n the absence of a concurrent control group in each of these studies, it is a matter of clinical judgement whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy" (Petition at 27). FDA's finding that Mifeprex was safe and effective for its labeled indication was based on data from three trials, one in the U.S. and two in France, as well as from safety data from a database of over 620,000 women in Europe who had had a medical termination of pregnancy (and approximately 415,000 of whom had received the combination of mifepristone and misoprostol). The Medical Officer's Review, supra note 12, also states that the "U.S. clinical trials confirm the safety and efficacy of mifepristone and misoprostol found in the pivotal French studies for women seeking medical abortions with gestations of 49 days duration or less" (Id. at 18-19). As stated previously, it is up to the physician and his/her patient to decide whether a medical or surgical abortion is preferable and safer in the patient's particular situation.

[29] MacDonald, PC, NF Gant, et al., 1996, Williams Obstetrics (20th ed.), Appleton and Lange, at 151.

[30] Although sources and studies differ somewhat, the 92% success rate following mifepristone/misoprostol use far exceeds the rate of spontaneous abortion (spontaneous miscarriage). One source states: "No less than 30% and as much as 60% of all conceptions abort within the first 12 weeks of gestation, and at least half of all losses go unnoticed. Most recognized pregnancy losses occur before 8 weeks' gestation, and relatively few occur after 12 weeks" (Fritz, M and L Speroff, 2011, Clinical Gynecologic Endocrinology and Infertility (8th ed.), Lippincott Williams & Wilkins, Philadelphia, at 1193). Other sources indicate that 15% of all pregnancies between 4-20 weeks of gestation spontaneously abort (See Speroff, L, et al., 1989, Clinical Gynecologic Endocrinology and Infertility (4th ed.), Williams and Wilkins, Baltimore, at 535; see also Stenchever, MA, 2001, Comprehensive Gynecology (4th ed.), Mosby, at 414). According to the National Library of Medicine, "[a]mong women who know they are pregnant, the miscarriage rate is about 15-20%. Most miscarriages occur during the first 7 weeks of pregnancy." (Miscarriage, available on the MedlinePlus Web site at http://www.nlm.nih.gov/medlineplus/ency/article/001488.htm.

[31] E10 Guidance, available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, at 6.

[32] Id.

[33] Id.

Moreover, the E10 Guidance clearly states that, notwithstanding certain limitations of external controls, including the possibility of bias, external controls can be appropriate under circumstances where the effect of the treatment is dramatic and the usual course of the disease or condition is highly predictable.[34] In other words, historical controls can be appropriate in circumstances such as medical termination of early pregnancy. The use of the expected rate of spontaneous abortion during early pregnancy as the control in the Mifeprex clinical trials was appropriate and fully consistent with FDA regulations and guidance. The applicant could rely on the data from the three trials to support approval because they were adequate and well-controlled, using a historical control.[35]

It is not uncommon for the drug product review divisions in FDA's Center for Drug Evaluation and Research (CDER) to accept for filing and approve applications that rely on clinical trials employing historical controls to support approval for drug products in which the outcome of the condition is well known and the effect of the drug is anticipated to be markedly different from that of a placebo. Examples include FDA's approval of numerous oncology drug products, including, for example, Xalkori (crizotinib) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test, and Adcetris (brentuximab vedotin) for the treatment of patients with Hodgkin lymphoma and a rare lymphoma known as systemic anaplastic large cell lymphoma. Other examples include iPlex (mecasermin rinfabate [rDNA origin] injection) for treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH; Myozyme (alglucosidase ALFA) for use in patients with Pompe disease (GAA deficiency); Ferriprox (deferiprone) for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate; Voraxaze (glucarpidase) for treatment of toxic (>1 micromole per liter) plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function; and Elelyso (taliglucerase alfa) for injection for use as a long-term enzyme replacement therapy in patients with Type 1 Gaucher disease. Similarly, it is not unusual for the CDER review divisions to accept for filing applications relying on historically controlled clinical trials. Examples of reproductive drug products for which a historical control is often relied on in the drug approval process include contraceptive drug products (e.g., most birth control pills, Mirena intrauterine device, NuvaRing (an intravaginal hormonal contraceptive), and Implanon (an implanted hormonal contraceptive)) and menopausal hormonal therapy products with the addition of a progestin to prevent endometrial cancer secondary to unopposed estrogen stimulation.

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[34] Id. at 27.

[35] We disagree with your statement that the sponsor's failure to identify precisely a historical control group is fatal to its claim that the trials supporting the approval of Mifeprex were historically controlled (Response to Opposition at 5-6). In situations where an investigational product is anticipated to have an effect that is readily discernible and greatly exceeds that which would be expected otherwise, the historical control may be relied upon without explicitly describing it as such. Examples of situations where this arises include, as here, the use of a drug for early medical abortion, given that the majority of pregnancies continue to term, and the use of a drug as a contraceptive, given that the pregnancy rate in sexually active women between 18 and 35 years old in the absence of contraception for one year is well documented at approximately 85% (Hatcher, RA, et al., 2012, Contraception Technology (20th ed.), Ardent Media, Inc., at 780.

You state that FDA did not conduct a statistical review of the results of the U.S. clinical trial (Petition at 29). The Agency, however, concluded that the clinical results of the supporting U.S. clinical trial were "similar enough to the results of the European studies" (the studies used to support the original approval of Mifeprex in Europe) that a statistical evaluation of the results of the U.S. trial was not required.[36]

You maintain that the Mifeprex approval is not in accordance with Agency guidance[37] on when only one effectiveness trial may be necessary for approval because: (1) mifepristone had not been approved for any use in any population in the United States and (2) no one had ever presented to FDA any evidence from adequate and well-controlled trials regarding any use for mifepristone.[38] As stated above, our approval of Mifeprex was based on not one but three studies that met the requirements of § 314.126. Therefore, Agency guidance concerning reliance on only one effectiveness trial is not relevant to the approval of Mifeprex.

You argue that FDA's acceptance of the French and U.S. clinical trial data violated § 314.126(e), which states that uncontrolled studies or partially controlled studies are not acceptable as the sole basis for approval of claims of effectiveness (Petition at 34-36). As explained above, the Mifeprex clinical trials were neither uncontrolled nor partially controlled. They were historically controlled, and the use of an historical control was appropriate under § 314.126(b)(2)(v). Consequently, § 314.126(e) is inapplicable.

Citing § 314.500, you contend that the approval of Mifeprex under subpart H was improper because FDA did not require the concurrent testing of mifepristone with surgical abortion to test the proposition that mifepristone provides a meaningful therapeutic benefit over the standard method for terminating pregnancies (Petition at 37-40). You maintain that Mifeprex is the only drug that we have approved under § 314.520 (approval with restrictions to assure safe use) without requiring "that safety and efficacy be scientifically demonstrated through blinded, comparator-controlled, and randomized clinical trials" (Petition at 37).

Nothing in subpart H requires that an applicant conduct comparative clinical trials in order to demonstrate that a drug product provides meaningful therapeutic benefit to patients over existing treatments. Furthermore, nothing in the concept of "meaningful therapeutic benefit" requires concurrent testing of a proposed drug with an existing treatment.[39] We have approved other drugs

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[36] FDA Memorandum to NDA 20-687 re: Statistical comments on Amendment 024, Feb. 14, 2000, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf.

[37] FDA guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Effectiveness Guidance), available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[38] Petition at 31-32 (citing Effectiveness Guidance at 5-17).

[39] You state that "[c]onducting a concurrently-controlled randomized trial comparing surgical abortion with the mifepristone-misoprostol regimen is readily achievable" (Petition at 32, note 145). You add that "[t]here are study designs that would have also allowed for blinding" (Id.). Assuming, arguendo, that it may have been feasible to design a randomized, concurrently-controlled study, such study was not required under our regulations; as described previously in this response, the clinical trials supporting the approval of Mifeprex

under subpart H based on clinical trials that do not directly compare the drug to an existing therapy, including Gleevec (imatinib mesylate), Tracleer (bosentan), and Xyrem (sodium oxybate). We also note that the latter two referenced drug products, Tracleer (bosentan) and Xyrem (sodium oxybate), were approved under the restricted distribution provisions at 21 CFR 314.520. As previously explained in this response, Mifeprex was deemed to have in effect an approved REMS under Title IX of FDAAA. The Mifeprex REMS, which was approved in June 2011 and is still in effect, incorporated the subpart H restrictions under which the drug was approved.

As evidenced by the foregoing, the studies supporting the 2000 approval of Mifeprex were consistent with the FD&C Act and FDA regulations, including § 314.126 and subpart H.

2. There Is No Need for an Audit of the French Clinical Data

You assert that FDA allowed "tainted data" to support the Mifeprex NDA by failing to require a comprehensive audit of the French clinical trial data after discovering violations of good clinical practices (Petition at 40-41). You maintain that we should therefore conduct a complete audit of all of the French clinical trial data to determine whether other trials must be conducted (Petition at 41 and 89).

We disagree with your characterization of both the French data and FDA's reliance on that data. You reference the Form FDA 483 issued on June 28, 2006, to Dr. Elisabeth Aubeny, as well as the Summary of Findings related to that Form FDA 483. It is not uncommon to have trial sites receive a Form FDA 483, listing the FDA investigator's observations regarding non-compliance with good clinical practice, at the conclusion of an inspection. The investigator will draft an Establishment Inspection Report (EIR) that reviews the violations noted and will recommend an action, taking into consideration the nature of the inspectional findings, any actions that occurred following the findings, and Agency policy. For products regulated by CDER, compliance reviewers in the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations (previously, the Division of Scientific Investigations) review the EIR, the Form FDA 483, and the evidence collected during the inspection, as well as any written response submitted timely by the inspected party, to determine whether the recommended action is appropriate and is supported by adequate evidence. This review evaluates each violation's effect on the timeliness, accuracy, and/or completeness of the data collected from the site to ascertain if the data are reliable. In this particular case, although there were violations cited on the Form FDA 483 and discussed in the EIR, the violations were determined not to affect the reliability of the data provided by that site. The statement you quote from the Summary of Findings reflects this conclusion. We note that, although the French studies were not performed under a U.S. investigational new drug application (IND), this is typical of many approved drugs that originally were developed or studied outside the United States, and is fully permissible under 21 CFR 312.120 (Foreign clinical studies not conducted under an IND) (including the version of the provision in effect at the time of the 2000

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were historically controlled, which was appropriate under § 314.126(b)(2)(v). Furthermore, your suggestion that there are study designs that would have allowed for blinding raises ethical issues that go beyond the scope of your Petition and this response.

approval of Mifeprex). FDA concluded that the French trials were conducted in accordance with good clinical practice,[40] and the Agency was able to validate the data from those studies.

It is worth noting that in 1996, when the Advisory Committee reviewed the French data without considering the U.S. data, the committee voted 6 to 2 that the French data alone demonstrated efficacy and 7 to 0 (with one abstention) that the French data supported safety.[41] The subsequent approval of Mifeprex was based not only on the data from the two French trials but also on the data from the large Phase 3 U.S. trial. The Advisory Committee received a report on the U.S. trial (the article by Spitz, et al., referenced in note 12 above) and had no comments.

For the foregoing reasons, there is no scientific or regulatory need for us to further review the French clinical data on Mifeprex.

3. Your Request for an Audit of the U.S. Clinical Data

In addition to your request that FDA conduct a full audit of the data from the French trials, you request that FDA conduct a full audit of all data from the U.S. trial (Petition at 1-2 and 89). Other than one footnote referring to a letter from the NDA sponsor to FDA (Petition at 89, note 384), you have provided no information supporting this request. Accordingly, we do not address this request further, other than to note that we do not believe there is any scientific or regulatory need to further review the U.S. clinical trial data relied on for approval of the Mifeprex NDA.

C. FDA Lawfully Approved Labeling for Mifeprex for Use with Misoprostol

You contend that FDA's "de facto" approval of misoprostol for use with Mifeprex as part of a medical abortion regimen was unlawful because the holder of the only approved NDA for misoprostol[42] did not submit a supplemental NDA for this new use (Petition at 41-45). You further

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[40] The regulations in effect at the time of the Mifeprex approval in 2000 refer to FDA accepting such studies when they are "well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community" FDA has generally interpreted that language as incorporating the principles of "good clinical practice" (see, e.g., ICH guidance for industry, *ICH E6 Good Clinical Practice: Consolidated Guidance* (E6 Guidance), available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm), which is the term used in the current regulations. The E6 Guidance states that GCP:

> is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that clinical trial data are credible

(E6 Guidance at 1).

[41] Mifeprex Approval Memorandum, supra note 16, at 1.

[42] Two abbreviated new drug applications (ANDAs) for misoprostol have been approved since Mifeprex was approved: ANDA 076095 (IVAX Pharmaceuticals, Inc., approved July 10, 2002) and ANDA 091667 (Novel Laboratories Inc., approved July 25, 2012).

argue that FDA not only sanctioned, but participated in, the promotion of an off-label use of misoprostol by overseeing the creation of Mifeprex promotional materials that discuss the off-label use of misoprostol and by disseminating information about the off-label use in documents such as the press release announcing Mifeprex's approval (Petition at 46-47).

The approval of Mifeprex was based on evidence from three adequate and well-controlled clinical trials using the treatment regimen of administration of mifepristone on day one, followed approximately 48 hours later (i.e., on day three) by the administration of misoprostol (unless a complete abortion has already been confirmed before that time). Neither the FD&C Act nor FDA regulations require the submission of a supplemental NDA by the sponsor of the misoprostol NDA for the use of misoprostol as part of the approved treatment regimen for Mifeprex. In this situation, the "drug product" subject to section 505(b) of the FD&C Act (21 U.S.C. 355(d)) was Mifeprex.[43] The NDA for Mifeprex appropriately contained the full reports of investigations which have been conducted to show whether or not "such drug" is effective in use (§ 505(b)(1) of the FD&C Act), and FDA appropriately found that the Mifeprex NDA met the approval requirements in § 505(d) of the FD&C Act.

There are a number of drug products that FDA has approved as safe and effective in combination with another drug for a use that was not sought by the applicant of the second drug product, and for which the Agency did not require any change in the labeling of the second product (i.e., that the second product's labeling include the indication for use with the newly approved drug product). Examples of approved drug labeling that refer to the concomitant use of another drug without there being a specific reference to the combined therapy in the previously approved labeling for the referenced drug include the following:

- Xeloda (capecitabine) for treatment of metastatic breast cancer in combination with Taxotere (docetaxel) after failure of prior anthracycline-containing therapy[44]

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[43] In the Response to Opposition, you reference a July 2, 2002, letter submitted by the Population Council to Docket 01E-0363 re: Determination of Regulatory Review Period for Purposes of Patent Extension; Mifeprex (Response to Opposition at 12-13). In its July 2, 2002, letter, the Population Council made several statements regarding what it believed should be considered "the approved human drug product" for purposes of 21 CFR 60.22(a)(1), for purposes of patent term restoration. In the Agency's October 24, 2002, notice amending FDA's previous determination of the regulatory review period for Mifeprex (67 FR 65358), we addressed — and rejected — the Population Council's assertions. We stated that "[t]he applicant tries to characterize Mifeprex as mifepristone 'in combination with another active ingredient' in an attempt to take advantage of portions of the definition of 'human drug product' in 35 U.S.C 156(f), that is, a human drug product means 'the active ingredient of a new drug * * * as a single entity or in combination with another active ingredient.' The applicant points to the definition of 'combination product' at 21 CFR 3.2(e) in this effort. A more useful description of a drug 'in combination with another active ingredient' is found at 21 CFR 300.50 (two or more drugs combined in a single dosage form). Mifeprex is not mifepristone 'in combination with another active ingredient.' Mifeprex is single entity mifepristone" (67 FR 65358, note 2).

[44] We note your assertion that when Xeloda and Taxotere are used together, each is being used for an FDA-approved use (Response to Opposition at 11). Taxotere (docetaxel) was approved on May 14, 1996; its current labeling states that it is indicated as a single agent for treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy, and in combination with doxorubicin and cyclophosphamide as adjuvant treatment of patients with operable node-positive breast cancer. Xeloda (capecitabine), which

- Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin for *H. pylori* eradication
- Persantine (dipyridamole) as an adjunct to coumarin anticoagulants for prevention of postoperative thromboembolic complications of cardiac valve replacement
- Herceptin (trastuzumab) in combination with paclitaxel for treatment of metastatic breast cancer
- Vistide (cidofovir) administered with probenecid for treatment of CMV retinitis in patients with AIDS
- Daraprim (pyrimethamine) for treatment of toxoplasmosis when used conjointly with a sulfonamide

You maintain that the labeling for Mifeprex is misleading because it directs physicians to use misoprostol for a purpose that FDA never approved and because it creates the false expectation that misoprostol is approved for medical abortion (Petition at 47). We disagree that the labeling for Mifeprex is misleading by virtue of the fact that it includes instructions for the use of misoprostol as part of the approved treatment regimen for Mifeprex. The Mifeprex labeling appropriately describes the clinical trial treatment regimen in which Mifeprex was shown to be safe and effective. The labeling for Mifeprex makes clear that Mifeprex tablets contain mifepristone, not misoprostol, and although the Indication and Usage section in the 2000 labeling does address the use of misoprostol in a regimen with Mifeprex, the labeling is clearly addressed to Mifeprex.

You claim that Mifeprex is misbranded because, per 21 CFR 201.6(a), the references to misoprostol in the Mifeprex labeling constitute a false or misleading representation that misoprostol itself is approved for medical termination of pregnancy (Petition at 48). In addition, you contend that Mifeprex is misbranded under section 502(j) of the FD&C Act (21 U.S.C. 352(j)) because it is unsafe when used as directed in the 2000 approved labeling (id.).

The references to misoprostol in the Mifeprex labeling do not render Mifeprex misbranded as described in § 201.6(a) because the labeling does not make any false or misleading representations with regard to misoprostol. We determined, and the labeling reflects, that Mifeprex is safe and effective for the termination of early pregnancy when used in combination with misoprostol. The approval was based on evidence from adequate and well controlled clinical trials in which misoprostol was administered two days after mifepristone to help stimulate uterine contractions; accordingly, the approved labeling describes the use of Mifeprex in combination with misoprostol.

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originally was approved on April 30, 1998, for the treatment of metastatic breast cancer that is resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, is currently approved (in addition to other indications) for use in combination with docetaxel for treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy. The indication to which this response refers is the concomitant use (i.e., use in combination) of the two drugs, a use that is not referenced in the labeling for Taxotere. Your arguments with respect to Actos (pioglitazone) in combination with a sulfonylurea, metformin, or insulin; Viread (tenofovir disproxil fumarate) in combination with other antiretroviral agents; and Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin (id.) are similarly inapposite.

Additionally, the approved labeling in no way implies that misoprostol alone would be safe and effective for the termination of pregnancy. Thus, the statements in the labeling are neither false nor misleading with regard to the use of misoprostol.

With regard to section 502(j) of the FD&C Act, Mifeprex is not misbranded under that provision because, as discussed in the following section, the approved regimen for Mifeprex is not "dangerous to health when used in the dosage or manner; or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof."

D. Mifeprex Is Safe for Its Approved Use and the Conditions of Approval Do Not Lack Essential Safeguards

You contend that FDA "approved mifepristone for use in a deregulated regimen that lacks key safeguards" (Petition at 5). You claim that in 2000, the Population Council repudiated distribution restrictions that it had proposed in 1996, and that FDA subsequently approved a regimen that does not embody restrictions sufficient to address legitimate safety concerns (Petition at 49). You note that the February 18, 2000, Mifeprex approvable letter stated that restrictions (per § 314.520) on the distribution and use of Mifeprex were needed to ensure safe use of the drug but that in March 2000, the Population Council said such restrictions were unwarranted (Petition at 51-52). You claim that we later yielded to the applicant on several important issues (Petition at 54-55).

FDA has found that Mifeprex is safe and effective for its intended use. It is true that, before the 2000 approval of Mifeprex, FDA and the applicant were not always in full agreement about the distribution restrictions. It is not unusual for such differences to emerge during the course of the review process for a proposed drug product. We ultimately determined that the distribution restrictions stated in the approval letter were appropriate to ensure the safety of Mifeprex for its intended use.[45] Three adequate and well-controlled clinical trials supported the safety of Mifeprex for its intended use, and over 15 years of postmarketing data and many comparative clinical trials in the United States and elsewhere continue to support the safety of this drug product.[46] Further, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Following is our response to the specific safety issues you raise in the Petition.

1. Ultrasound Dating

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[45] We note your reference in your Response to Opposition to the statement by the Reproductive Health Drugs Advisory Committee that it had concerns about the distribution proposal discussed at the July 19, 1996, meeting (Response to Opposition at 4 (referencing the minutes from the 1996 Reproductive Health Drugs Advisory Committee meeting)). In light of FDA's determination in 2000 that the distribution restrictions stated in the approval were appropriate to ensure that Mifeprex was safe for its intended use, as well as the 2011 approval of the Mifeprex REMS, the Committee's reservations in 1996 are not applicable.

[46] See, e.g., Raymond, EG, et al., 2013, First-Trimester Medical Abortion With Mifepristone 200 mg and Misoprostol: A Systematic review, Contraception, 87:26-37 In this article, 87 trials were reviewed and 91 references were cited.

You maintain that the Mifeprex regimen is unsafe because it does not require ultrasound examination. Specifically, you maintain that the use of transvaginal ultrasound is necessary to accurately date pregnancies and to identify ectopic pregnancies, and you note both that Mifeprex was approved in 2000 only for women through 49 days' gestation and that it is contraindicated for women with a confirmed or suspected ectopic pregnancy (Petition at 57-61).

Although the protocol for the U.S. clinical trial required a transvaginal sonogram (TVS) for each patient at Visit 1 and stated that the test should be used "as indicated" at Visits 2 and 3, this does not mean that a TVS is essential to ensure the safe use of Mifeprex.[47] As stated in the Mifeprex Approval Memorandum, during the review process, the Agency carefully considered the role of ultrasound.[48] In the clinical trials, ultrasound was performed to ensure proper data collection on gestational age, but in clinical practice, pregnancies can also be (and frequently are) dated using other clinical methods. (As discussed in section II.F below, safeguards employed during clinical trials are not always essential for safe use of the approved drug product.) As part of the restricted distribution of Mifeprex put in place in 2000, each provider must have the ability to accurately assess the duration of pregnancy and to diagnose ectopic pregnancy. We determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider.

You claim that the only way to date a pregnancy accurately enough to exclude EGA > 49 days is by using TVS (Petition at 58). That is incorrect. As noted above, using TVS (or any other method) does not ensure complete accuracy in dating a pregnancy. In most cases, a provider can accurately make such a determination by performing a pelvic examination and obtaining a careful history, which would include the following: date of last menstrual period, regularity of menses, intercourse history, contraceptive history, and (if available) home pregnancy test results.[49] If in doubt, the provider can order an ultrasound and/or a blood test measuring the quantitative beta-human chorionic gonadotropin (hCG) to further assist in dating the gestational age.

Furthermore, use of a TVS does not guarantee that an existing ectopic pregnancy will be identified. As of April 30, 2015, there were 89 unduplicated reports in FDA's Adverse Event Reporting System (FAERS) database of ectopic pregnancy in women in the United States who had received mifepristone for termination of pregnancy since the approval of Mifeprex in the United States. In

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[47] We note that the French clinical trials did not require an ultrasound examination; rather, the decision as to whether an ultrasound was needed was left to the discretion of the investigator.

[48] Mifeprex Approval Memorandum, supra note 16, at 5.

[49] See, e.g., Fielding, SL, et al., 2002, Clinicians' Perception of Sonogram Indication for Mifepristone Abortion up to 63 Days, Contraception, 66:27-31 (discussing the results of a prospective study of 1,016 women in a medical abortion trial at 15 sites that concluded that "clinicians correctly assessed gestational age as no more than 63 days in 87% of women. In only 1% (14/1013) of their assessments did clinicians underestimate gestational age. We conclude that the clinicians felt confident in not using ultrasound in most cases").

42.7% (38 of89) of the reported cases, an ultrasound was completed. Of the 38 cases that had an ultrasound completed, 55.3% (21 of 38) showed no changes indicative of ectopic pregnancy.[50] In light of the fact that Mifeprex is contraindicated for women with a confirmed or suspected ectopic pregnancy, we believe it is reasonable to expect that the women's providers would not have prescribed Mifeprex if a pelvic ultrasound examination had clearly indicated an ectopic pregnancy; this strongly suggests, therefore, that ultrasound examinations were falsely negative for ectopic pregnancy in these women. The currently approved labeling for Mifeprex reflects this, stating that the "presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifeprex."[51]

2. Physician Training and Admitting Privileges

You contend that the administration of Mifeprex should have been restricted to physicians who have formal training in both pharmaceutical and surgical abortion and who have admitting privileges to emergency facilities (Petition at 62-65).

Although we did not restrict the administration of Mifeprex to physicians with the specific requirements you list in your Petition, we did conclude in 2000 that Mifeprex had to be provided by a physician who, among other qualifications, either (1) has the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or (2) has made plans to provide such care through other qualified providers and facilities.

During the clinical trials for Mifeprex, the principal investigators were trained in surgical abortions and were able to conduct any necessary surgical interventions.[52] The protocol for the U.S. trial was designed such that the studies were conducted at 17 centers where the principal investigators could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures.

During the NDA review process, the issue of physician qualifications and certification was thoroughly discussed within the Agency, with the applicant, and with an outside consultant with expertise in early pregnancy termination. Although the distribution of Mifeprex was not restricted to any particular medical specialist, the Agency did determine in 2000 that certain restrictions were

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[50] Seventeen cases were identified as having an ultrasound with a possible ectopic pregnancy. Fourteen of these 17 (82.3%) cases noted appropriate follow-up procedures, such as additional hCG monitoring, ultrasounds, appointments, or emergency room referral, while two cases did not include any additional follow-up information. In the remaining case, a diagnosis of a heterotopic gestation (simultaneous ectopic pregnancy and intrauterine pregnancy) was noted.

[51] Mifeprex labeling (Mar. 29, 2016) available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. .

[52] Additionally, it is common in drug development that the clinical investigators who conduct pivotal Phase 3 clinical trials have more specialized training than may be necessary to ensure the safe use of a drug post-approval. Examples are trials for male erectile dysfunction (typically conducted by urologists), hypertension (internists), depression (psychiatrists), and endometriosis (gynecologists).

necessary under § 314.520. In accordance with this determination, the Prescriber's Agreement for Mifeprex stated the following:[53]

> Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:
>
> - Ability to assess the duration of pregnancy accurately.
> - Ability to diagnose ectopic pregnancies.
> - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have [sic] made plans to provide such care through others, and are [sic] able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
> - Has read and understood the prescribing information of Mifeprex….

As noted in the Mifeprex Approval Memorandum, the requirement that a physician certify, by signing the Prescriber Agreement, that he or she has the qualifications described in that Agreement limited the physicians who would be eligible to receive Mifeprex from the sponsor to those who are familiar with managing early pregnancies.[54] Because only such qualified physicians would be using or would oversee the use of Mifeprex, we concluded that there was no need for special certification programs or additional restrictions. Additionally, as noted in the Mifeprex Approval Memorandum, in the U.S. clinical trial of Mifeprex, 11 out of roughly 850 patients needed surgical intervention to treat bleeding, and three of these patients were treated by non-principal investigators such as emergency room physicians and a non-study gynecologist.[55] These data suggested that patients would receive any needed surgical intervention from either their physician or another physician with the needed skills.[56] The Mifeprex Approval Memorandum also pointed out that the Mifeprex labeling and the Medication Guide approved at that time highlight that surgery may be needed and that patients must understand whether the provider will furnish any necessary medical intervention or whether they will be referred to another provider and/or facility.[57]

In addition, one of the Phase 4 commitments accompanying the approval of Mifeprex was a cohort-based study of safety outcomes when Mifeprex is prescribed by physicians with the skills for surgical intervention compared to physicians who refer patients for surgical intervention. In a February 2008 submission, the applicant stated that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful

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[53] Mifeprex labeling (June 8, 2011), Mifeprex (mifepristone) tablets, 200 mg, Prescriber's Agreement, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020687s014lbl.pdf.

[54] Mifeprex Approval Memorandum, supra note 16, at 5.

[55] Id.

[56] Id.

[57] Id.

study to assess this specific issue. After review of this submission, the Agency: (1) concurred with the applicant regarding the non-feasibility of conducting a meaningful study and (2) concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. Accordingly, on September 26, 2008, the Agency released the applicant from this commitment.

The provisions of the currently approved labeling (including the REMS) that relate to provider training and admitting privileges are substantially similar to the labeling provisions approved in 2000. Under current labeling, healthcare providers who administer Mifeprex must be licensed to prescribe, and must have the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also (1) be able to provide any necessary surgical intervention, or (2) have made arrangements for others to provide for such care. Healthcare providers must be able to ensure that women have access to medical facilities for emergency care, and must agree to other responsibilities, including reviewing and signing the Patient Agreement Form with the patient and providing each patient with a copy of the signed Patient Agreement Form and the Medication Guide.[58]

3. "Dear Health Care Provider" Letter and FDA "Mifepristone Questions and Answers"; Adverse Events Discussed in Response to Opposition

You maintain that your concerns about the safety of Mifeprex are validated by the April 19, 2002, "Dear Health Care Provider" letter issued by Danco and by statements in the "Mifepristone Questions and Answers" (Mifepristone Q&A) document (placed on FDA's Web site on April 17, 2002) about reports of serious adverse events, including ruptured ectopic pregnancies and serious systemic bacterial infections (Petition at 65-71). You argue that FDA understated the possibility that the Mifeprex regimen caused the serious adverse events referred to in the letter and inappropriately attempted to link those events to the unapproved vaginal administration of misoprostol (Petition at 67-68).

The fact that Danco and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 (or that a subsequent Dear Health Care Provider letter and a Dear Emergency Room Director letter were issued on September 30, 2004) does not imply that the approved Mifeprex regimen is unsafe. It is not uncommon for drug sponsors to issue "Dear Health Care Provider" letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, "[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely."[59] The intent of the two "Dear Health Care Provider" letters and the "Dear Emergency Room Director" letter was to provide health care personnel with new safety information regarding the use of Mifeprex. Similarly, when these letters were issued, we posted Mifepristone Q&A documents to

[58] Mifeprex REMS, available at http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=35

[59] See Historical Information on Mifepristone (Marketed as Mifeprex), available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm.

address questions that might arise as a result of the issuance of the letters. We disagree that we have in any way "inappropriately attempted to link" the adverse events to the intravaginal use of misoprostol. Rather, the April 2002 Mifepristone Q&A document accurately stated that in all of the adverse event cases at that time,[60] the misoprostol was given vaginally not orally; that we did not know what role, if any, the use of Mifeprex and vaginal misoprostol may have in the development of serious infections; and that FDA had not reviewed data on the safety and effectiveness of vaginal administration of misoprostol.

You maintain that it is particularly important for FDA to respond to these adverse events because the clinical trials in support of Mifeprex allegedly did not adhere to the Agency's scientific methodology for such trials (Petition at 70). As explained above, however, the clinical trials supporting the approval of Mifeprex were adequate and well-controlled, and they provided substantial evidence of the safety and effectiveness of the drug product in accordance with the FD&C Act and FDA regulations.

In your Response to Opposition, you state that the serious adverse events reported to date are consistent with concerns expressed before approval (Response to Opposition at 16). You refer to the death of Holly Patterson on September 17, 2003, after she had taken Mifeprex and misoprostol to terminate her pregnancy. You state that Ms. Patterson's apparent death from a serious systemic bacterial infection after taking Mifeprex is "not the first such death since FDA approved Mifeprex," referring to a fatality due to serious systemic bacterial infection mentioned in the April 2002 "Dear Health Care Provider Letter" (Response to Opposition at 16-17). You also question whether adverse events for Mifeprex will be adequately reported to FDA (Response to Opposition at 18).

As with all approved drug products, we continue to monitor the safety of Mifeprex. Since the approval of Mifeprex, the Agency has issued two public health advisories (one in July 2005[61] and one in March 2006[62]) and posted multiple MedWatch safety alerts (in November 2004[63] and July 2005, the latter with updates in November 2005 and March 2006[64]). As referenced above, Danco has issued two Dear Health Care Provider letters and one Dear Emergency Room Director letter. Furthermore, since you submitted your Response to Opposition, Danco has revised the labeling for

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[60] The April 2002 Mifepristone Q&A document refers to cases of ectopic pregnancy, sepsis, and heart attack.

[61] Available at, http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051734.htm.

[62] Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051196.htm.

[63] Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm166463.htm.

[64] Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111339.htm.

Mifeprex (including the prescribing information, the Medication Guide, and the Patient Agreement), in November 2004, December 2004, July 2005, and April 2009[65] to provide prescribers and women with additional information about infection, vaginal bleeding, and ectopic pregnancy.

The boxed warning for Mifeprex currently states the following:

> Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.
>
> • Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis.
>
> • Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding.
>
> Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MIFEPREX REMS Program.
>
> Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting or diarrhea) for more than 24 hours after taking misoprostol.
>
> Advise the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe MIFEPREX, so that the provider knows that she is undergoing a medical abortion.

[65] The Mifeprex labeling also was revised in June 2011 when the REMS was approved. In addition, as described above, FDA is today approving a supplemental NDA submitted by Danco that proposed modified labeling for Mifeprex. See Mifeprex labeling (Mar. 29, 2016) available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.

The WARNINGS section of the Mifeprex labeling states, in part, the following:

[With respect to infection and sepsis:]

> As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.
>
> A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

[With respect to uterine bleeding:]

> Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion.
>
> Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.
>
> Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in women who bleed heavily.
>
> Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfu¬sions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to $\leq 0.1\%$ of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

[With respect to ectopic pregnancy:]

> MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.
>
> Women who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

The Agency has regularly completed a cumulative summary of U.S. postmarketing adverse events reported for the use of mifepristone for medical termination of pregnancy. From the approval date of Mifeprex (September 28, 2000) through October 31, 2012, we received 2,740 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy,[66] including 57 reports of severe infections[67] and 416 incidences of blood loss requiring transfusion. From November 1, 2012, through April 30, 2015, we received 984 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy, including 9 reports of severe bacterial infections and 134 incidences of blood loss requiring transfusion.[68] As of April 30, 2015, 89 ectopic pregnancies associated with the use of mifepristone in the United States had been reported since the approval of Mifeprex. As of July 24, 2015, 17 U.S. deaths had been reported since the approval of Mifeprex. Deaths were associated with sepsis in 8 of the 17 reported fatalities (7 cases tested positive for *Clostridium sordellii*, and 1 case tested positive for *Clostridium perfringens*).[69] Seven of the eight fatal sepsis case reported vaginal misoprostol use;

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[66] This represents data from the FDA's previous adverse event reporting system, which was known as AERS.

[67] Severe infections generally involve death or hospitalization for at least 2-3 days, intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, and any other physical or clinical findings, laboratory data or surgery that suggest a severe infection.

[68] This represents data from the current FDA Adverse Event Reporting System (FAERS), which was implemented in September 2012 and replaced AERS. FDA migrated all of the data from the previous reporting system (AERS) to FAERS. FDA validated and recoded product information as the reports from the AERS database were migrated to the FAERS database. In addition, the FAERS database features a new search functionality that is based on the date FDA initially received for the case; this facilitates more accurate follow-up for cases that have multiple reports and multiple receipt dates. For these reasons, there may be differences in the case counts between AERS and FAERS.

[69] We note your statements in your October 10, 2003, Response to Opposition Comments that the presence of retained products of conception can lead to the development of intrauterine or systemic infection and that Mifeprex might potentiate this possibility through negative effects on immune system function or normal protective mechanisms (Response to Opposition at 17). Regarding retained products of conception and the emergence of infections, based on autopsy and/or ultrasound reports, there were no retained products of conception in any of the eight deaths associated with infections (sepsis). With respect to your claim that Mifeprex might increase the likelihood of infection by adversely affecting immune system function, although

one case reported buccal misoprostol use. Seven of the nine remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; and a delayed onset of toxic shock-like syndrome. In the eighth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. In the ninth case, infection was ruled out and the final autopsy report listed pulmonary emphysema as the cause of death. [70]

We disagree with your assertion that adverse event reporting for Mifeprex is "spotty" and that, as a result, the database for post-approval adverse events for Mifeprex is incomplete (Response to Opposition at 18). You are correct that reporting to the Agency's MedWatch program is voluntary, and we acknowledge that there is always a possibility with any drug that some adverse events are not being reported. We believe, however, that the potential for underreporting of serious adverse events associated with the use of Mifeprex for medical abortion has been very low because of the restricted distribution of the product and because healthcare providers have agreed in writing to report any hospitalizations, transfusions, or other serious adverse events associated with the drug to the sponsor, which is required under FDA's regulations to report all adverse events, including serious adverse events, to the Agency (see 21 CFR 314.80, 314.81). As with all drugs, we will continue to closely monitor the postmarketing safety data on Mifeprex.

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published experimental data from animal models suggest that this is a theoretical possibility, the overall event rate of serious infections does not support this. If Mifeprex were adversely affecting immune system function, we would expect to see a much higher rate of serious infections from more common organisms, as well as a higher number of deaths in Europe (where mifepristone has been approved for over 24 years) and in the United States. Contrary to your statements, data from the medical literature and findings by the CDC suggest that the critical risk factor in the reported cases of sepsis is pregnancy itself (see Miech, RP, 2005, Pathophysiology of Mifepristone-Induced Septic Shock Due to *Clostridium sordellii*, Ann Pharmacother, 39:1483-1488). In May 2006, FDA, along with the CDC and the National Institute of Allergy and Infectious Diseases at the National Institutes of Health held a workshop on emerging clostridial disease. The issue of immunosuppression also was discussed at length during this public workshop. It was clear from the presentations at the workshop that *C. sordellii* causes rapid and serious clinical illness in settings other than medical abortion, including among pregnant women who have recently undergone spontaneous abortion or term delivery. The fact that cases of *C. sordellii* have been identified both in pregnant women who have undergone medical abortion and those who have not supports the idea that the physiology of pregnancy may be a more plausible risk factor for *C. sordellii* illness than having undergone a medical abortion with Mifeprex.

[70] FDA is aware of 11 additional deaths of women in foreign countries who used mifepristone for the termination of pregnancy. This included one death associated with sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial, and 10 deaths identified from post-marketing data. These 10 fatal cases were associated with the following: sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure"; thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes a jejunostomy feeding tube, and severe cystic fibrosis; *Clostridium septicum* sepsis (from a published literature report).

E. Withdrawal of the Approval for Mifeprex Based on Current Use Is Not Appropriate

You claim that Mifeprex abortion providers have disregarded the restrictions in the approved regimen "without any reaction from FDA, the Population Council, or Danco" (Petition at 71). You also claim that "common departures from the approved regimen" have included (1) offering the regimen to women with pregnancies beyond 7 weeks and (2) eliminating the second of the three prescribed visits to the health care provider (Petition at 72-74). You argue that we should withdraw approval of Mifeprex under § 314.530(a)(4) due to the failure of the Population Council and Danco to adhere to the postmarketing restrictions in the approval letter (Petition at 71).

In the Response to Opposition, you suggest that some providers have not met their obligations because many prescriber Web sites (1) advertise the Mifeprex regimen as being available for patients whose pregnancies have progressed beyond 49 days and (2) indicate that patients take misoprostol at home rather than at the provider's office (Response to Opposition at 19-20). Thus, you maintain that many prescribers have allowed patients to make false statements and that the applicant is obligated to stop sales to these prescribers (id. at 20). You claim that prescribers have disregarded the requirements imposed with the 2000 approval of Mifeprex to provide patients with the Medication Guide, obtain their signatures on the Patient Agreement, and give them the opportunity to read and discuss these documents (id. at 20-21). You state that because some prescribers, with the applicant's tacit approval, have permitted patients to sign the Patient Agreement while effectively directing them not to adhere to its requirements, the applicant cannot be described as meeting its obligations (id. at 21).

FDA is aware that medical practitioners may use modified regimens for administering Mifeprex and misoprostol. However, FDA does not believe that it is appropriate to initiate proceedings under 21 CFR 314.530 or section 505(e) of the FD&C Act to withdraw the approval of Mifeprex based on available information regarding the distribution of Mifeprex.

The Mifeprex approval letter included nine items that the applicant and/or prescriber were obligated to follow. As stated earlier in this response, Mifeprex has been subject to a REMS which incorporated these restrictions, including by appending a Prescriber's Agreement outlining required qualifications and guidelines prescribers must agree to follow. Specifically, the Prescriber's Agreement required each physician to attest to possessing certain necessary skills and abilities related to managing early pregnancy to ensure safe use of the drug.[71] The Prescriber's Agreement also contained responsibilities that prescribers must carry out.[72] The Prescriber's Agreement stated that prescribers must have read and understood the prescribing materials.[73]

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[71] Prescriber's Agreement, supra note 53, at 1.

[72] Id. at 1-2.

[73] Id. at 1.

The 2000 Prescriber's Agreement also required that the prescriber (1) provide each patient with a copy of the Medication Guide and the Patient Agreement, (2) fully explain the procedure to the patient, and (3) give the patient the opportunity to read and discuss the Medication Guide and Patient Agreement.[74] The Medication Guide and the Patient Agreement stated the approved dosage and administration of Mifeprex. FDA has no evidence, nor have you provided any evidence, that prescribers have not signed the Prescriber's Agreement, or that women either have not been given the opportunity to read and discuss the Patient Agreement or have not signed the Patient Agreement.

As noted above, restrictions on the distribution and use of Mifeprex substantially similar to those approved in 2000 remain in place today.

F. Safeguards Employed in Clinical Trials Are Not Necessarily Essential Conditions for Approval

You maintain that we effectively approved a drug regimen that we had not tested because the Mifeprex regimen approved in 2000 does not include important safeguards employed in the U.S. clinical trial (e.g., governing physician training, use of ultrasound, 4-hour post-misoprostol monitoring, physician privileges at facilities that provide emergency care) (Petition at 75-76). You argue that we should not have extrapolated conclusions about the safety and effectiveness of the Mifeprex regimen from data generated under trial conditions that do not mirror the approved regimen (id.).

We disagree with your assertions. Furthermore, your implication that the approved conditions of use for a drug product must mirror those used in the clinical trials supporting its approval is incorrect. As discussed above with respect to ultrasound dating and physician qualifications, safeguards employed in clinical trials are often not reflected in approved drug product labeling nor are they necessarily needed for the safe and effective use of the drug product after approval. Many clinical trial designs are more restrictive (e.g., additional laboratory and clinical monitoring, stricter inclusion and exclusion criteria, more visits) than will be necessary or recommended in postapproval clinical use; this additional level of caution is exercised until the safety and efficacy of the product is demonstrated. For example, in menopause hormonal therapy trials, specialists perform periodic endometrial biopsies to establish the safety of long-term hormone use. Once the safety of the product has been established, these biopsies are not recommended in the approved product labeling, nor are they routinely performed in actual use with the approved product. During our review of the clinical data submitted in support of an NDA, we make an assessment of the procedures employed during the clinical trials and the conditions under which the drug was studied. This assessment is reflected in the approved labeling for the drug product.

Upon reviewing the data submitted in support of the Mifeprex NDA, we concluded in 2000 that restrictions requiring ultrasound dating of gestational age of the pregnancy and limiting access to Mifeprex to physicians trained in surgical abortions and capable of performing surgical intervention if complications arise subsequent to use of Mifeprex were not necessary to ensure its safe use (see discussion in section II.D above).

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[74] Id.

G. FDA Appropriately Concluded That Studies of Mifeprex in Pediatric Patients Were Unnecessary

You maintain that our 2000 approval of Mifeprex violated regulations requiring that new drugs be tested for safety and effectiveness in the pediatric population (Petition at 76). You state that although we stated in the September 28, 2000, approval letter that the application was subject to the Pediatric Rule (21 CFR 314.55), we waived the requirement without explanation (Petition at 78). You contend that the Mifeprex application was not in accordance with any of the three provisions under which an applicant may obtain a waiver under 21 CFR 314.55(c)(2) of the pediatric study requirement, for the following reasons:

- 21 CFR 314.55(c)(2)(i) does not apply because FDA maintained that Mifeprex represented a meaningful therapeutic benefit over existing treatments and because Mifeprex can be expected to be used in a substantial number of pediatric patients.

- 21 CFR 314.55(c)(2)(ii) does not apply because pediatric studies of Mifeprex would not have been either impossible or highly impractical because a large population of pediatric females becomes pregnant each year and the female population is evenly distributed throughout the country.

- 21 CFR 314.55(c)(2)(iii) does not apply because FDA stated that there was no reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen than older females (Petition at 79-82).

As an initial matter, we reject your contention that the Population Council did not provide evidence from any adequate and well-controlled adult studies of Mifeprex, and that therefore it was inappropriate to rely on the submitted adult studies under § 314.55(a) with respect to the use of Mifeprex in the pediatric population (Petition at 82). As discussed above, the Mifeprex approval was based on three adequate and well-controlled clinical trials.

Our conclusion that studies of Mifeprex in pediatric patients were not needed for approval was consistent with FDA's implementation of the regulations in effect at that time.[75] We determined that there were sufficient data from studies of mifepristone. Therefore, the Mifeprex approval letter should have stated our conclusion that the pediatric study requirements were waived for pre-menarchal patients and that the pediatric study requirements were met for post-menarchal pediatric patients, rather than stating that we were waiving the requirements for all pediatric age groups.[76]

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[75] FDA was enjoined from enforcing 21 CFR § 314.55 under *Ass'n of Am. Physicians& Surgeons v. FDA*, 226 F. Supp. 204 (D.D.C. 2002). However, on December 3, 2003, the President signed into law the Pediatric Research Equity Act of 2003 (PREA 2003), Public Law 108-155, which gave FDA the statutory authority to require pediatric studies of drugs when such studies are needed to ensure the safe and effective use of drugs in children. PREA 2003 stated that any waivers or deferrals that were granted under the Pediatric Rule were considered to be granted under PREA 2003 (see Section 4 of Public Law 108-155).

[76] FDA's implementation of the Pediatric Rule was still at a relatively early stage in September 2000 and the Agency was not always precise regarding the language used in approval letters to distinguish between situations where studies were waived and where studies were not needed because the requirements were met.

It is still our scientific opinion, based on the medical literature and over 15 years of use in the United States, that there is no biological reason to expect menstruating females under age 18 — compared to women age 18 and older — to have a different physiological outcome with the Mifeprex regimen.[77]

H. The Mifeprex Approval Letter Included Appropriate Phase 4 Commitments

You state that although the Population Council agreed in 1996 to perform Phase 4 studies with six different objectives, the Mifeprex approval letter included only two Phase 4 study obligations (Petition at 85-86). You allege that the changes in its Phase 4 commitments were largely in response to the Population Council's unwillingness to explore the "ramifications" of the Mifeprex regimen (Petition at 87). You maintain that this alleged "curtailment" of Phase 4 study commitments was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (Petition at 88).[78]

We disagree with your assertions. Our process for determining the appropriate Phase 4 studies for Mifeprex adequately addressed our concerns and reflected typical Agency-applicant interactions to reach consensus on appropriate postmarketing studies.[79] It is common for proposed Phase 4 commitments to evolve during the application review process. As you note (Petition at 85), in 1996, the Population Council committed to six postmarketing studies with the following objectives:

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[77] In the Mifeprex Approval Memorandum, the Office Director stated, "FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients" (Mifeprex Approval Memorandum, supra note 16, at 7).

[78] We note that post-marketing studies are not required for approvals under 21 CFR 314.520.

[79] You also state that, "[a]s a general rule, the clinical trials required by FDA to support an NDA are adequate to establish short-term drug safety and effectiveness. The standard pre-approval clinical trials, however, are typically incapable of providing either the amount or type of data necessary to assess a drug's long-term effects" (Petition at 84). This argument is not relevant to Mifeprex, which is approved for medical termination of pregnancy. Mifeprex is not approved for long-term or chronic use, which is an important factor in assessing the need to study long-term effects of a drug. Long-term safety for a single-dose medication is generally not a concern. However, FDA routinely monitors postmarketing safety data for all approved drugs. Mifeprex is no exception. FDA's Office of Surveillance and Epidemiology continuously monitors available safety data from use of mifepristone for termination of pregnancy both within and outside of the United States and has not identified any long-term safety signals. The Mifeprex adverse events reported are consistent with product labeling and with what can be expected with spontaneous and surgical abortions. Furthermore, as explained in this response, since Mifeprex's approval, safety concerns and adverse events have been monitored through enhanced surveillance and reporting by certified prescribers, and we have required a REMS for Mifeprex including a Medication Guide, elements to assure safe use, an implementation system that requires the sponsor to assess the performance of certified distributors, and a timetable for submission of assessments of the REMS. We also continue to closely monitor the post-marketing safety of mifepristone for termination of pregnancy for any new or long-term signals.

(1) Monitor the adequacy of the distribution and credentialing system.

(2) Follow-up on the outcome of a representative sample of Mifeprex-treated women who have surgical abortion because of method failure.

(3) Assess the long-term effects of multiple use of the regimen.

(4) Ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

(5) Study the safety and efficacy of the regimen in women under age 18, women over age 35, and women who smoke.

(6) Ascertain the effect of the regimen on children born after treatment failure.

As stated in the Mifeprex Approval Memorandum (at 7), during the final review of the Mifeprex NDA in 2000, items 1, 2, 4, and 5 above were revised and integrated into a single Phase 4 study to assess whether, for providers who did not have surgical intervention skills and referred patients for surgery, clinical outcomes were similar to those of patients under the care of physicians (such as those in the clinical trials) who possessed surgical skills. Based on a revised protocol, this Phase 4 study would monitor the adequacy of provider qualifications (item 1) and collect data on safety outcomes and method failures (item 2) and return of patients for their follow-up visits (item 4). Because patients would not be restricted to a specific age range or smoking status, information to address item 5 also would be obtained. In a second Phase 4 study, the applicant would examine the outcomes of ongoing pregnancies (i.e., method failures) through a surveillance, reporting, and tracking system (item 6). Thus, although the approval letter listed only two Phase 4 studies, those two studies incorporated all but one element of the six studies listed in the September 18, 1996, approvable letter concerning the Mifeprex NDA. (As discussed below, the remaining study was not included for logistical and practical reasons.)

As mentioned in section II.D.2 above, for the first Phase 4 study, which addressed items 1, 2, 4, and 5 above, the applicant reported in a submission in February 2008 that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful study to assess this specific issue. We agreed with the applicant regarding the non-feasibility of conducting a meaningful study and concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. In September 2008, we released the applicant from this postmarketing commitment.

For the second Phase 4 study, which addressed item 6 above, based on the reporting of ongoing pregnancies during the first 5 years of Mifeprex distribution, the applicant provided updates in January 2006 and November 2007. Danco reported that only one to two pregnancies per year were followed for final outcomes, and explained that the small number was due, in part, to the requirement that the patients consent to participation after seeking a pregnancy termination. In January 2008, because of the lack of an adequate number of enrolled women, and based on subsequent reports, we released the applicant from this postmarketing commitment.

In addition, as noted in the Mifeprex Approval Memorandum (at 7), we agreed with the Population Council both that it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug and that the pharmacology of mifepristone does not suggest any carryover effect after one-time administration. Accordingly, we did not include item 3 as a Phase 4 commitment in the September 28, 2000, approval letter. However, we note that data from many other studies reported in the medical literature using mifepristone for, e.g., fibroids, uterine myoma, meningioma, psychiatric illnesses, and Cushing's disease, in much higher daily and lower daily doses for chronic use (months) have not raised any major safety issues.[80]

III. REQUEST FOR STAY AND REVOCATION OF APPROVAL

You request that we immediately stay the approval of Mifeprex, thereby halting all distribution and marketing of the drug pending final action on your Petition (Petition at 2). You cite 21 CFR 10.35 as the basis for your request for a stay (Petition at 1). In addition, you urge us to revoke the approval of Mifeprex because of the purported legal violations and safety concerns set forth in your Petition (Petition at 2).

As described above, we are denying your Petition. Therefore, your request for a stay pending final action on your Petition is moot.

For the reasons set forth in section II of this response, we conclude that you have not presented any evidence that the applicable grounds in 21 CFR 314.530 have been met with respect to Mifeprex. Furthermore, you have not provided any evidence that any of the applicable grounds in section 505(e) of the FD&C Act have been met for Mifeprex.[81] Therefore, you have not provided any evidence that would serve as a basis for seeking to withdraw the approval of Mifeprex.

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[80] See, e.g., Tristan, M, et al., 2012, Mifepristone for Uterine Fibroids (Review), Cochrane Library, 8:1-47; Esteve, JL, et al, 2013, Mifepristone Versus Placebo To Treat Uterine Myoma: A Double-Blind, Randomized Clinical Trial, Int J Womens Health, 5:361; Spitz, IM, et al., 2005, Management of Patients Receiving Long-Term Treatment With Mifepristone, Fertil Steril, 84:1719; Blasey, CM, TS Block, JK Belanoff, and RL Roe, 2011, Efficacy and Safety of Mifepristone for the Treatment of Psychotic Depression, J Clin Psychopharmacol, 31:436; Fleseriu, M, et al., 2012, Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome, J Clin Endocrinol Metab, 97:2039.

[81] You have not presented any clinical data or other information demonstrating that Mifeprex is unsafe for use under its approved conditions for use, either on the basis of evidence available to the Agency at the time of approval or when also considering evidence obtained subsequent to approval. In addition, you have not provided any new evidence that, when evaluated with the evidence available at the time of Mifeprex's approval, shows that there is a lack of substantial evidence that the drug will have its intended effect.

IV. CONCLUSION

We appreciate and share your concerns about the need to appropriately manage the risks associated with the use of Mifeprex. Our concerns about the potential complications associated with Mifeprex led to its approval in accordance with 21 CFR 314.520. It was deemed to have in effect a REMS in 2007, and it has had an approved REMS since 2011.[82]

For the reasons set forth above, your request that we immediately stay the approval of Mifeprex is moot, and we deny your request that we revoke approval of the Mifeprex NDA. In addition, we deny your request that we conduct an audit of all records of the French and U.S. clinical trials supporting the Mifeprex approval. As with all approved new drug products, we will continue to monitor the safety of Mifeprex and take any appropriate actions.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[82] As of today's approval of Danco's supplemental NDA, the Medication Guide is no longer part of the REMS. However, the Medication Guide will remain as part of approved patient labeling and will be required to be provided to the patient under current Medication Guide regulations.

EXHIBIT 32

2020 Letter from ACOG & SMFM to FDA about
Mifepristone REMS
(Apr. 20, 2020)
("2020 ACOG-SMFM Letter")

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

April 20, 2020

Stephen M. Hahn, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue NW
Silver Spring, MD 20993

Re: Docket Number: FDA-2020-D-1106; Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals

Dear Commissioner Hahn:

On behalf of more than 60,000 of the nation's primary care obstetrician-gynecologists and subspecialty and high-risk obstetric practitioners dedicated to advancing women's health, thank you for your recent action to suspend enforcement of Risk Evaluation and Mitigation Strategy (REMS) requirements for certain drugs with laboratory testing or imaging requirements for the duration of the COVID-19 public health emergency. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine urge the U.S. Food and Drug Administration (FDA) to immediately expand this policy to REMS and Elements to Assure Safe Use (ETASU) requirements for certain prescription drugs requiring in-person health care professional administration, where treatment could safely occur through telehealth or self-administration. In addition, physicians who provide such services in accordance with current clinical guidelines during this pandemic should not be held liable.

Obstetrician-gynecologists are serving on the front lines responding to the COVID-19 crisis. In order to provide the safest care for their patients and themselves, in-person visits are limited to emergency and essential physically necessary visits. We support the FDA's acknowledgment that REMS-required health care professional in-person dispensation is difficult because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. Under these circumstances, undergoing in-person clinic administration in order to obtain a drug subject to a REMS can put patients and others, including health care professionals and their families, at risk for COVID-19 transmission. As referenced in ACOG Committee Opinion #798, *Implementing Telehealth in Practice*, evidence suggests that telehealth provides comparable health outcomes when compared with traditional methods of health care delivery without compromising the patient–physician relationship.[1] Telehealth has quickly become integrated into nearly every aspect of obstetrics and gynecology. During this pandemic, it is essential to use telehealth services to limit COVID-19 transmission.

It is critical that the FDA promptly expand its recent policy to apply to the REMS and ETASU requirements for certain drugs requiring in-person dispensation, especially mifepristone. The current REMS and ETASU requirements for mifepristone are outdated and serve as a barrier to accessing this safe, effective medication. Further, they cause unnecessary delays in obtaining time-sensitive health care, without supporting improvements to patient safety or outcomes. During this federally declared public health emergency, these antiquated and superfluous requirements put patients and their physicians at risk, with no demonstrated benefit. As noted in the ACOG Position Statement, *Improving Access to*

Mifepristone for Reproductive Health Indications, mifepristone has been used by over 3 million women in the United States since FDA approval in 2000 and strong evidence exists regarding the safety of mifepristone for medication-induced abortion and medical management of early pregnancy loss.[2,3,4,5]

Restricting access to mifepristone interferes with the ability of obstetrician–gynecologists and other women's health clinicians to deliver the highest quality care for their patients, especially during the COVID-19 pandemic. Abortion is an essential component of comprehensive health care and is a time-sensitive service for which a delay of several weeks, or in some cases days, may increase the risks or potentially make it completely inaccessible.[6] Temporarily waiving REMS and ETASU requirements that certain drugs be dispensed in-person by certain medical professionals is particularly important for patients who suffer from other medical conditions and are at higher risk of serious complications from COVID-19, as well as those in rural areas for whom hours of travel for in-person administration would disallow social distancing recommendations and travel advisories.

In addition, we urge you to consider waiving the requirement for health care professional administration of subcutaneous depot medroxyprogesterone acetate (DMPA). Several studies have shown patient interest in self-administration and increased continuation of DMPA via subcutaneous at-home delivery.[7,8,9] In a period when limiting patient interactions with the health care system is essential to prevent COVID-19 transmission, it is in our patients' best interest to have unencumbered access to the contraceptive method of their choice, including DMPA.

Ensuring the safety of patients and physicians during the COVID-19 pandemic requires policy changes such as those already enacted by FDA to waive the REMS requirements for certain drugs with laboratory testing or imaging requirements. We strongly urge FDA to further protect patients and their health care professionals from the risk of transmission by promptly expanding the existing policy to waive REMS and ETASU requirements that certain drugs be dispensed in-person by certain medical professionals. Thank you for your consideration. We are available to answer any questions you may have regarding these issues.

Sincerely,

Maureen G. Phipps, MD, MPH, FACOG
Chief Executive Officer
American College of Obstetricians and Gynecologists

Judette Louis, MD, MPH
President
Society for Maternal-Fetal Medicine

Matt J. Granato, LL.M., MBA
Chief Executive Officer
Society for Maternal-Fetal Medicine

[1] Implementing telehealth in practice. ACOG Committee Opinion No. 798. American College of Obstetricians and Gynecologists. Obstet Gynecol 2020;135:e73–9.
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EXHIBIT 33

Students for Life of America, Citizen Petition to FDA
(Dec. 13, 2022)

Citizen Petition

December 13, 2022

The undersigned submits this petition under 21 C.F.R. § 10.30 and Section 505-1 of the Food Drug and Cosmetic Act (21 U.S.C. § 355-1) to request the Commissioner of the Food and Drug Administration (FDA) to modify the Risk Evaluation and Mitigation Strategy (REMS) regarding mifepristone (Mifeprex® or RU-486) (hereinafter, "Mifepristone") and restore the REMS regarding Mifepristone, that were curtailed in 2016 and 2021, back to the REMS that were formally enacted in 2011.

A. ACTION REQUESTED

This Petition makes one request. We request that the 2021 and 2016 modifications to mifepristone's REMS be reversed and the REMS as they were in 2011 be restored.

Reverse the 2021 and 2016 Mifepristone REMS modification and restore the REMS as they were in 2011.

The REMS for Mifepristone were modified by the FDA in 2021 and 2016. This petition requests that the FDA reverse this modification by requiring that:

1) Mifepristone only be administered, in a regimen with misoprostol, for the termination of intrauterine pregnancy, for up to 49 days (7 weeks) gestation;

2) Mifepristone only be administered by or under the supervision of a physically present physician (to reduce instances of telehealth prescriptions to only those that are absolutely necessary);

3) the use of Mifepristone and misoprostol for the termination of pregnancy necessitate three office visits by the patient: the first to be an ultrasound to rule out ectopic pregnancy, determine the gestational age of the child, to determine if the patient is Rh-negative, and to actually issue Mifepristone. The second, to determine that the termination has been successful, and to make sure that there are no remaining tissues in the body that could lead to infection. The third, as a follow-up to make sure there are no further complications;

Additionally, Mifepristone should be administered only after ectopic pregnancy has been ruled out, and the gestational age of the fetus has been determined. Mifepristone use should be contraindicated for patients who do not have convenient access to emergency medical care. This use should be as limited as possible. Telehealth should not be an option to all women, but only to women in absolute need under extreme circumstances that would make access to a medical care facility impracticable, with a substantial risk that the woman would die without immediate administration of Mifepristone.

To alter the Mifepristone REMS, a formal study should be required. This study should include outcomes for at-risk populations, patients under the age of 18, patients with repeat

Mifepristone abortions, patients who have limited access to emergency room services, patients who self-administer misoprostol, patients who did not have an ultrasound to rule out ectopic pregnancy, patients who did not have an ultrasound to determine the gestational age of the fetus, patients who were prescribed Mifepristone over telehealth, and patients who did not see a physician before or after Mifepristone was administered over telehealth.

Reinstituting the limiting of dispensing of Mifepristone to patients in clinics, medical offices, and hospitals, by or under the physical supervision of a certified prescriber and only up to 49 days (7 weeks) gestation can only benefit women's health. The 2021 and 2016 modifications promulgated by the FDA claimed that the data supported modification of the REMS to reduce the burden on patient access and the health care delivery systems and that the overall benefits of the product outweighed the risks. The modifications to the Mifepristone REMS program should be reversed, reinstituting the requirement that mifepristone be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement"); adding a requirement that pharmacies that dispense the drug be certified; requiring three office visits along with prescription; and only prescribing up to 49 days (7 weeks) gestation. The petitioner requests that the FDA revoke these changes as these modifications are detrimental to the health and safety of women seeking abortions.

B. STATEMENT OF GROUNDS

The FDA should restore and strengthen elements of the Mifepristone regimen and prescriber requirements approved in 2016 and 2021. Mifepristone should be prescribed only up to 49 days (7 weeks) gestation and administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy. Mifepristone should only be prescribed by a physically present physician, and telehealth dispensing should be limited to patients with no other legitimate option.

Mifepristone should only be administered, in a regimen with misoprostol, for the termination of intrauterine pregnancy, for up to 49 days (7 weeks) gestation.

In 2016, FDA increased the maximum gestational age for Mifeprex use for abortion from 49 days (7 weeks) to 70 days (10 weeks), and changed the method of administration of misoprostol from oral to buccal (*i.e.*, in the cheek pouch). However, drug-induced abortion[1] regimens demonstrate an increase in complications and failures after 49 days' gestation.

In a 2011 study of thousands of patients, the majority of whom had a drug-induced abortion using what is now the Mifeprex regimen, the rate of infection and the rate of failure requiring surgical intervention increased with gestational age.[2] The American College of Obstetricians

[1] The terms "Medication abortion," "medical abortion," "chemical abortion," and "drug-induced abortion" [or termination of pregnancy] share the same meaning and refer to the use of abortion-inducing drugs, rather than surgery, to induce abortion. The current FDA-approved regimen uses two drugs, mifepristone (a.k.a. Mifeprex or RU-486) and misoprostol.

[2] Mentula MJ, Niinimaki M, Suhonen S, Hemminki E, Gissler M, and Heinkinheimo O, *Immediate Adverse Events after Second Trimester Medical Termination of Pregnancy: Results of a Nationwide Registry Study,* Human Reproduction 26(4), 927-932 (2011).

and Gynecologists (ACOG) has stated: "the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days."[3]

Further, a 2015 meta-analysis examined all the existing publications on buccal administration of misoprostol, 20 studies in all, from November 2005 through January 2015. The failure rate of the buccal misoprostol regimen increased as the gestational age increased, especially at gestational ages greater than 49 days.[4] The current FDA label also acknowledges this fact.[5]

Given the serious risks of failure, hemorrhage, infection, and ongoing pregnancy that increase as pregnancy advances, the gestational limit for the Mifeprex regimen should have never been increased, and now should be restored back to 49 days (7 weeks).

Mifepristone should be administered by or under the supervision of a physically present certified physician who has ruled out ectopic pregnancy and Rh negativity.

The 2000 Mifepristone regimen required Mifepristone to be "provided by or under the supervision of a physician" who meets qualifications discussed in this section below.[6] However, the 2016 regimen replaced "physician" with "healthcare provider," thus permitting non-physicians to apply to be certified prescribers.[7] Given the regimen's serious risks, the FDA should limit the ability to prescribe and dispense Mifepristone to qualified, licensed physicians. Physicians are better trained to diagnose patients who have contraindications to Mifepristone and to verify gestational age.

In the Mifepristone label, the FDA emphasizes that "Mifepristone is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)" because of the drug's "risks of serious complications." In a bold-print box, the FDA states that before prescribing Mifepristone, a provider must inform a patient: about the risks of serious events; whom to call and what to do if certain symptoms occur; and to take the Medication Guide with her if she visits an emergency room or healthcare provider who did not prescribe Mifepristone, so that she receives appropriate, informed care.[8]

Chemical abortions were first approved by the FDA on September 28, 2000. A chemical abortion, also known as a medical abortion, is a two-step regime. The first is taking RU-486, a synthetic steroid also known as mifepristone. This drug cuts off the production of progesterone in the woman's body, effectively starving the fetus. The second step requires taking misoprostol. This drug then expels the fetus from the woman's body. This drug was initially created to treat

[3] ACOG Practice Bulletin 143: Medical Management of First-Trimester Abortion, p. 5 (Mar. 2014, reaffirmed 2016).
[4] Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet. Gynecol 126 (1) July 2015 12-21.
[5] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[6] Mifeprex 2000 label, Dosage and Administration, emphasis added.
[7] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[8] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

stomach ulcers. Importantly, the FDA rarely promotes off label uses of medications. Misoprostol has never been approved by the FDA as an abortifacient.

When the FDA approved chemicals abortions, it did so under an accelerated process for drug approval under 21 C.F.R. § 314(H). Before chemical abortions were approved, this approval process had only been used on 30 drugs, all of which were for HIV/AIDS, cancer, and other debilitating diseases. Because chemical abortions were approved under this method, it did not have to go through testing for long-term effects that other drugs have to. This raises red flags as this drug could potentially cause more serious adverse side effects to women.

There was a small trial in the U.S. before this was approved. Clinical trials were conducted on 2,121 women from September 1994 to September 1995 at 17 abortion facilities. The Population Council and the New England Journal of Medicine reported that the most frequent side effect was bleeding and cramping; 56 women underwent surgical intervention for excessive bleeding; four women received blood transfusions; the average duration of bleeding and spotting was 13 days; gastrointestinal side effects of the drugs, such as nausea, diarrhea, and vomiting were documented; eight percent of women did not abort with the medication and were encouraged to have a surgical abortion; and five percent of the women never completed the study.[9]

On the FDA's website the side effects for a chemical abortion are stated as: "cramping and vaginal bleeding are expected effects of the treatment regimen. In some cases, very heavy vaginal bleeding will need to be stopped by surgical procedure, which can often be performed in a healthcare providers office. Other common side effects of the treatment regimen include nausea, weakness, fever/chills, vomiting, headache, diarrhea, and dizziness in the first day or two after taking the two medicines." Still to this day, we don't know if there are any long-term effects on women who opt for a chemical abortion even though it has been over 22 years since initial approval. The medication that is used to complete chemical abortions had not changed since introduction in 2000. However, the guidelines promulgated for its safe consumption have continually been diminished.

The FDA revisions imposed in 2021 permit mail-order telehealth abortions. This runs in contravention to the doctor's code of ethics which requires doctors to examine patients in person at least once before giving them medication with potentially life-threatening side effects. Now women can procure Mifepristone without medical guidance or oversight that would otherwise verify the gestation of the child. This is relevant to know if the chemical abortion will even be effective, to test for Rh negativity, to rule out ectopic pregnancies, and it makes it next to impossible to track the side effects of the chemical abortions.

The 2016 Mifepristone REMS provided that "Mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber."[10] Many providers today are promoting and performing

[9] Irving M. Spitz et al. *Early Pregnancy Termination with Mifepristone and Misoprostol in the United States*, New England Journal of Medicine 338, no. 18 (1998): 1241-1247.
[10] Mifeprex 2016 REMS, emphasis added, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2016-03-29_REMS_full.pdf.

"telemedicine abortions," where the certified prescriber's "supervision" of the dispensing of Mifepristone is limited to a videoconference.[11] This practice demonstrates a flagrant disregard for FDA safeguards.

To ensure true supervision, the FDA should require certified prescribers to be physically present when Mifepristone is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifepristone. This requirement would be consistent with other requirements in the Mifepristone Label and REMS.

In reality, a de-emphasis on follow-up care increases risks of post-abortion complications. Mifepristone's regimen in 2000 required that women return approximately 14 days after ingesting mifepristone. This was considered necessary to ensure that all pregnancy tissue had been passed.[12] This determination is crucial, because retained pregnancy tissue can lead to continued bleeding and serious intrauterine infections. The return visit permits healthcare providers to ensure that a patient is not experiencing these or other complications from the abortion procedure, and that Rh negative patients are administered Rhogam to protect future pregnancies.

Abortion advocates argue that three clinic visits make accessing abortion-inducing drugs more difficult for patients with transportation challenges; however, ACOG acknowledges that drug-induced abortion is contraindicated for patients who "are not available for follow-up contact or evaluation."[13] Surgical abortion is a better choice for these patients, because it "[d]oes not require follow-up in most cases."[14]

Drug-induced abortion is optional. If a woman does not meet the criteria necessary to use abortion-inducing drugs, then surgical abortion is still an option. For women with transportation difficulties, an abortion provider can complete surgical abortion "in a predictable period of time," and the procedure "[d]oes not require follow-up in most cases."[15]

Efforts to promote abortion-inducing drugs to women in rural areas where access to emergency medical care is scarce are detrimental to women's health. It is better for a patient in a remote region to have a surgical abortion, "which requires a single visit, and is less likely to result in serious or life-threatening complications."[16]

In the Mifepristone label, the FDA emphasizes that "Mifepristone is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)" because of the drug's "risks of serious complications." In a bold-print box, the FDA states that before prescribing

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[11] See Planned Parenthood Releases New Educational Video on Telemedicine Abortion (Feb. 6, 2018), https://www.plannedparenthood.org/about-us/newsroom/press-releases/planned-parenthood-releases-new-educational-video-on-telemedicine-abortion.
[12] Mifeprex 2000 label, Day 14: Post-Treatment Examination.
[13] ACOG Practice Bulletin 143, p. 6.
[14] *Id*.
[15] ACOG Practice Bulletin 143, p. 3 & Box 1.
[16] Donna Harrison, M.D. & Michael J. Norton Testimony before the Iowa Board of Medicine, p. 9 (Aug. 21, 2013), citing Postmarket Drug Safety Information for Patients and Providers, Questions and Answers on Mifeprex, https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm492705.htm.

Mifepristone, a provider must inform a patient: about the risks of serious events; whom to call and what to do if certain symptoms occur; and to take the Medication Guide with her if she visits an emergency room or healthcare provider who did not prescribe Mifepristone, so that she receives appropriate, informed care.[17]

Thirty-four states permit only physicians to prescribe Mifepristone,[18] with nineteen states requiring the provider to be physically present with the patient.[19] For example, the law in Alabama states that the physical presence and care of a physician are necessary because "the failure and complications from medical abortion increase with advancing gestational age, because the physical symptoms of medical abortion can be identical to the symptoms of ectopic pregnancy, and because abortion-inducing drugs do not treat ectopic pregnancies but rather are contraindicated in ectopic pregnancies."[20]

Lawmakers in these states recognize that abortion providers cannot diagnose contraindications and cannot adequately care for their patients through a videoconference. Fundamentally, telemedicine "may be legitimate when it comes to discrete, document-based tasks such as reading X-rays," but it "is not the standard of care when it comes to abortion or the management of miscarriage."[21]

The 2016 regimen significantly diminished doctor-patient interaction. While the 2000 Mifeprex label required three patient visits with the abortion provider, women may now obtain Mifeprex at a clinic and self-administer it at home. They are no longer required to return to the clinic for the administration of misoprostol, which prevents abortion providers from ensuring that they take the drugs at the correct times. Further, providers may now "confirm" that a patient's drug-induced abortion was successful without a clinic visit,[26] increasing the possibility that Rh-negative patients will not receive administration of Rhogam, which is necessary to prevent serious risks in subsequent pregnancies. The failure to test for Rh-negativity could lead to infertility.

The 2016 regimen directs that patients be given or prescribed misoprostol to take 24 to 48 hours after taking Mifeprex. However, without monitoring, a patient may take misoprostol before 24 hours have passed since she consumed Mifeprex, rendering the regimen ineffective and increasing the likelihood that she will experience a failed drug- induced abortion and require surgery.

Using buccal misoprostol sooner than 24 hours after administering mifepristone leads to a significantly increased failure rate. In one study investigating the timing of buccal misoprostol after Mifepristone, nearly one out of every three to four women who took buccal misoprostol

[17] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[18] Donovan MK, *Self-Managed Medication Abortion: Expanding the Available Options for U.S. Abortion Care*, Guttmacher Policy Review, Vol. 21, p. 44 (2018).
[19] *Id.*
[20] Ala. Code § 26-23E-7.
[21] Harrison & Norton Testimony, p. 3.

shortly after Mifepristone failed to abort.[22] The failure rate ranged from 27% to 31%, depending on the pregnancy gestation.[23] Given these results, the authors of this study strongly recommended that buccal misoprostol not be taken immediately after Mifepristone because of the very high abortion failure rate.[24] However, with home administration of misoprostol, healthcare providers have no control over when their patients consume the drug.

A woman may also choose to swallow misoprostol rather than keep the pill between her cheek and gum for 30 minutes, converting a "buccal" administration into an "oral" administration. An oral administration of misoprostol following the lower dose of Mifepristone in the current regimen is not as effective in ending the pregnancy.

Further, waiting until 24 hours after Mifepristone to administer misoprostol does not guarantee success, and the failure rate of buccal misoprostol is higher than that under the 2000 regimen. A comprehensive systematic review and meta-analysis of the existing studies of the 2016 regimen found that women who take misoprostol earlier than 48 hours after Mifepristone are more likely to fail the regimen.[25]

Under the 2000 regimen, doctors were also able to provide care to patients during the most challenging and painful time in the drug-induced abortion. According to the World Health Organization, up to 90% of women will abort within 4-6 hours after taking misoprostol.[26] The 2000 regimen permitted a patient to be in a clinic for this period of time, during which she would be under the observation and care of medical personnel. This observation period is for "both patient safety and compassion. This is the time when women should be in a place where their bleeding can be monitored, their vital signs can be observed by trained medical personnel, and they can receive sufficient pain medication during the most difficult part of the expulsion."[27]

In-person contact with a healthcare provider is critical to post-abortion care as well. Abortion providers should perform a "follow-up [physical exam] after the use of mifepristone in order to confirm abortion and rule out life-threatening infection."[28] Before the FDA approved the 2016 regimen, the follow-up visit was considered "very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred."[29] In fact, the 2000 label provided that "[e]ach patient must understand the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking

[22] Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD, *Oral Mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study*, Contraception 76 (2007) 215-220.
[23] *Id.*
[24] *Id.*
[25] Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet. Gynecol 126 (1) July 2015 12-21.
[26] World Health Organization, *Safe Abortion: Technical and Policy Guidance for Health Systems* 45.
[27] *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015) ¶ 136.
[28] Harrison & Norton Testimony, p. 18.
[29] Mifeprex 2000 label, Day 14: Post-Treatment Examination.

Mifeprex."[30] ACOG's current policy explains that:

> Women are not good candidates for medical abortion if they … desire quick completion of the abortion process [or] are not available for follow-up contact or evaluation.[31]

In addition to ensuring for all drug-induced abortion patients that the uterus has been emptied of retained tissue and that they are not suffering from infection, the follow-up examination is particularly critical for Rh-negative patients. These patients must be administered Rhogam in order to prevent Rh isoimmunization in subsequent pregnancies. Without follow-up, women will not receive the Rhogam after the abortion, greatly increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies.[32]

Nonetheless, abortion advocates strongly supported the reduction in required visits, and continue to advocate for the elimination of direct provider-patient contact. Gynuity Health Projects (an organization that "has been at the forefront of efforts to increase women's access to medical abortion in settings throughout the world")[33] has conducted at least three domestic and five international studies[34] on eliminating pelvic ultrasound or exam after drug-induced abortion. Following one study, researchers determined that "[s]emi-quantitative pregnancy tests … could be used in lieu of transvaginal ultrasound and/or serum hCG at clinic-based follow-up or by women themselves for home-based follow-up."[35] This ignores the risks outlined above.

In a more recent study, researchers asserted that the "common practice of scheduling a clinical contact after every medical abortion may not be necessary to ensure safety; enabling patients to determine for themselves whether or not a contact is needed can be a reasonable approach."[36] They reached this conclusion even with 26% of participants failing to provide

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[30] Mifeprex 2000 label, Information for Patients.
[31] ACOG Practice Bulletin 143, p. 6.
[32] ACOG Practice Bulletin 181: Prevention of Rh D Alloimmunization (Aug. 2017);
and SOGC Clinical Practice Guidelines: Prevention of Rh Alloimmunization (No. 133, Sept. 2003).
[33] See Gynuity Health Projects, Medical Abortion, https://gynuity.org/programs/medical-abortion.
[34] See, e.g., Self-Assessment of Medical Abortion Outcome Using Serial Multi-level Pregnancy Tests [NCT02570204] (Sept. 2015 – Dec. 2016), https://www.clinicaltrials.gov/ct2/show/NCT02570204?term=Self-Assessment+of+Medical+Abortion+Outcome+Using+Serial+Multi-level+Pregnancy&rank=1; Exploring the Role of At-home Semi-Quantitative Pregnancy Tests for Medical Abortion Follow-up [NCT01150279] (Aug. 2009 – May 2014), https://www.clinicaltrials.gov/ct2/show/NCT01150279?term=Exploring+the+Role+of+At-home+Semi-Quantitative+Pregnancy+Tests+for+Medical+Abortion+Follow-up&rank=1; De-Medicalizing Mifepristone Medical Abortion [NCT00120224] (May 2005 – Apr. 2007), https://www.clinicaltrials.gov/ct2/show/NCT00120224?term=De-Medicalizing+Mifepristone+Medical+Abortion&rank=1.
[35] Lynd K, et al., *Simplified Medical Abortion Using a Semi-Quantitative Pregnancy Test for Home-Based Follow-up*, Int J Gynaecol Obstet. 2013 May;121(2):144-8.
[36] Raymond EG, et al., *Self-assessment of Medical Abortion Outcome Using Symptoms and Home Pregnancy Tests,* Contraception *97* (2018) 324-28.

sufficient follow-up information.[37]

Gynuity researchers also conducted a recent systematic review of existing studies on "the accuracy and acceptability of a strategy for identifying ongoing pregnancy after medical abortion treatment using a low-sensitivity pregnancy test (LSPT)." While the researchers acknowledged that "the LSPT strategy had *moderate* sensitivity for identifying ongoing pregnancy" and "the LSPT itself had a limited role in the detection of treatment failures [*i.e.*, ongoing pregnancy] in the studies," they stated that the "LSPT strategy shows promise for reducing the need for in-person follow-up after medical abortion. A range of home-based options should be validated to meet the varied needs of women and abortion providers in diverse settings."[38]

In reality, a de-emphasis on follow-up care increases risks of post-abortion complications. As discussed above, the 2000 regimen's requirement that women return approximately 14 days after ingesting mifepristone was considered necessary to ensure that all pregnancy tissue had been passed.[39] This determination is crucial, because retained pregnancy tissue can lead to continued bleeding and serious intrauterine infections. The return visit permits healthcare providers to ensure that a patient is not experiencing these or other complications from the abortion procedure, and that Rh negative patients are administered Rhogam to protect future pregnancies.

Abortion advocates argue that three clinic visits make accessing abortion-inducing drugs more difficult for patients with transportation challenges; however, as noted above, ACOG acknowledges that drug-induced abortion is *contraindicated* for patients who "are not available for follow-up contact or evaluation."[40] Surgical abortion is a better choice for these patients, because it "[d]oes not require follow-up in most cases."[41]

Drug-induced abortion is a longer process that requires more attention and care from healthcare providers. Three visits to a physician in the interest of patient safety should not be sacrificed for the convenience of healthcare providers or even their patients.

Limit The Dispensing Of Mifepristone Over Telehealth

Mifepristone should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy and instances of administration over telehealth be limited to only those situations where a patient has no clear alternative.

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[37] *Id.*
[38] Raymond EG, et al., *Low-sensitivity Urine Pregnancy Testing to Assess Medical Abortion Outcome: A Systematic Review,* Contraception (2018), https://doi.org/10.1016/j.contraception.2018.03.013 (emphasis added).
[39] Mifeprex 2000 label, Day 14: Post-Treatment Examination.
[40] ACOG Practice Bulletin 143, p. 6.
[41] *Id.*

As mentioned above, the original Mifepristone regimen required Mifepristone to be "provided by or under the supervision of a physician" who meets qualifications discussed in this section below.[42] However, the 2016 regimen replaced "physician" with "healthcare provider," thus permitting non physicians to apply to be certified prescribers.[43] Given the regimen's serious risks, the FDA should limit the ability to prescribe and dispense Mifepristone to qualified, licensed physicians. Physicians are better trained to diagnose patients who have contraindications to Mifepristone and to verify gestational age.

The previous Mifepristone REMS requires that Mifepristone "be dispensed to patients only in clinics, medical offices and hospitals, by or under the supervision of a certified prescriber." That prescriber must be capable of assessing the duration of a pregnancy accurately, diagnosing ectopic pregnancies, and providing or referring for surgical intervention in cases of incomplete abortion or hemorrhaging.[44]

Abortion advocates, however, want prescription of Mifepristone to increase to pregnant patients over the Internet or phone, with the drug available at pharmacies or through the mail, and through advance provision (i.e., before a patient is pregnant). Eliminating and relaxing the REMS to facilitate Internet or telephone prescriptions is dangerous to women and adolescent girls. This must be reversed to ensure the appropriate care for the health of women and adolescent girls. Healthcare providers prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs. Further, as discussed above, Rh-negative patients must be administered Rhogam in order to prevent Rh isoimmunization in subsequent pregnancies. Without direct patient contact, women will not receive the Rhogam after the abortion, greatly increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies and lead to potential infertility.[45]

Telemedicine abortion further distances women from the practitioners responsible for caring for them, and modification of the REMS in 2021 by FDA further absolved abortion providers of responsibility for the well-being of their patients. Promoting telemedicine abortion to women and adolescent girls in rural areas with limited access to healthcare is extremely dangerous—they will have little recourse if they face known and predictable emergency complications such as severe hemorrhage.[46]

Previous Mifepristone REMS, provided that "Mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, *by or under the supervision of a certified prescriber*."[47] Yet, abortion providers today are increasingly

[42] Mifeprex 2000 label, Dosage and Administration, emphasis added.
[43] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[44] Mifeprex Risk Evaluation and Mitigation Strategy (REMS), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2016-03-29_REMS_full.pdf.
[45] ACOG Practice Bulletin 181: Prevention of Rh D Alloimmunization (Aug. 2017); and SOGC Clinical Practice Guidelines: Prevention of Rh Alloimmunization (No. 133, Sept. 2003).
[46] Harrison & Norton Testimony, p. 9.
[47] Mifeprex 2016 REMS, emphasis added, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2016-03-29_REMS_full.pdf.

promoting and performing "telemedicine abortions," where the certified prescriber's "supervision" of the dispensing of Mifepristone is limited to a videoconference. This practice demonstrates a flagrant disregard for FDA safeguards.

In allowing this disconnect between patients and prescribers, the FDA is creating circumstances that could lead to patient abandonment. According to the National Library of Medicine, patient abandonment "is considered a breach of duty and is defined as unilateral termination of the physician-patient relationship without providing adequate notice for the patient to obtain substitute medical care."[48] Further, the "patient-physician relationship becomes established when a physician affirmatively acts in a patient's care through the patient's diagnosis and/or treatment. This relationship is also established if the physician agrees to diagnose and/or treat the patient. A physician-patient relationship is often created when the "professional services of a physician are rendered to and accepted by another person for the purposes of medical or surgical treatment."[49] By definition then, the prescribing of Mifepristone by a medical provider to a patient establishes a physician-patient relationship. The level of care implicit in this relationship is thus abrogated in an unacceptable way when the prescription of Mifepristone is conducted solely via telehealth.

To ensure true supervision, the FDA should require certified prescribers to be physically present when Mifepristone is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifepristone. This requirement would be consistent with other requirements in the Mifepristone label and REMS. In some situations, it is possible that a woman may *not* take the abortion drugs in the manner prescribed, nor obtain the follow-up care that is recommended. With a doctor-patient relationship limited to online chats, she has virtually no accountability or support as she navigates a complicated procedure. The responsibility of the provider of the drugs to follow up with the patient is obviated as well.

In the Mifepristone label, the FDA emphasizes that "Mifepristone is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)" because of the drug's "risks of serious complications." In a bold-print box, the FDA states that before prescribing Mifepristone, a provider must inform a patient: about the risks of serious events; whom to call and what to do if certain symptoms occur; and to take the Medication Guide with her if she visits an emergency room or healthcare provider who did not prescribe Mifepristone, so that she receives appropriate, informed care.[50]

A provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional contraindications (i.e., circumstances that make a treatment or medication *unadvisable*) to Mifepristone use. These physical contraindications include pelvic infections, ovarian masses, cardiac arrhythmias, and liver abnormalities.[51] A physician bears responsibility to diagnose and rule out contraindications prior to Mifepristone use. It is inadequate to entrust this critical care to another healthcare provider who is not trained in diagnosis. Further, a healthcare provider who is

[48] https://www.ncbi.nlm.nih.gov/books/NBK563285/.
[49] *Id*.
[50] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[51] Harrison & Norton, p. 3.

not physically accessible to a patient cannot provide adequate follow-up care to patients, as required by the FDA Mifepristone regimen.

Abortion complications are also more frequent when women abort at home, without the oversight of a healthcare provider. A 2018 combined retrospective and longitudinal follow-up study of complications related to induced abortion in Sweden determined that "[t]he complication frequency [of drug-induced abortion] was significantly higher among women <7 gestational weeks who had their abortions *at home*."[52]

The 2000 Mifeprex label stated:

> Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.[53]

This critical language was excluded from the 2016 Mifeprex label. Yet, studies comparing the outcome of surgical versus drug-induced abortion have clearly demonstrated that Mifeprex abortions have a greater risk of hemorrhage, infection, continued pregnancies, retained tissue and need for emergency reoperation than surgical abortions. ACOG acknowledges that "[c]ompared with surgical abortion, medical abortion takes longer to complete, requires more active patient participation, and is associated with higher reported rates of bleeding and cramping," and has lower success rates.[54]

The FDA, in "Questions and Answers on Mifeprex" categorizes women who should not take Mifeprex, specifically the agency states:

> A woman should not take Mifeprex if it has been more than 70 days since the first day of her last menstrual period, or if she: has an ectopic pregnancy (a pregnancy outside of the uterus) has problems with the adrenal glands (the glands near the kidneys) is currently being treated with long-term corticosteroid therapy (medications) has had an allergic reaction to mifepristone, misoprostol or similar drugs has bleeding problems or is taking anticoagulant (blood thinning) drug products has inherited porphyria has an intrauterine device (IUD)

[52] Carlsson I, Breding K, and Larsson PG, *Complications Related to Induced Abortion: a Combined Retrospective and Longitudinal Follow-up Study*, BMC Women's Health (2018) 18:158, p. 4 (emphasis added).
[53] Mifeprex 2000 label, Contraindications.
[54] ACOG Practice Bulletin 143, p. 3 & Box 1.

in place (it must be removed before taking Mifeprex).[55]

And yet, with the proliferation of telehealth prescription, it is less and less likely that the prescribing "healthcare provider" will have first-hand knowledge that the patient will not have these complications or is otherwise less able to the tests necessary to rule out any of these complications.

Drug-induced abortion is optional. If a woman does not meet the criteria necessary to use abortion-inducing drugs, then surgical abortion is still an option. For women with transportation difficulties, an abortion provider can complete surgical abortion "in a predictable period of time," and the procedure "[d]oes not require follow-up in most cases."[56]

Efforts to promote abortion-inducing drugs to women in rural areas where access to emergency medical care is scarce are detrimental to women's health. It is better for a patient in a remote region to have a surgical abortion, which requires a single visit, and is less likely to result in serious or life-threatening complications.

CONCLUSION

Mifepristone carries risks of life-threatening hemorrhage, infection, continued pregnancy, retained tissue, need for emergency surgery, and death. The 2011 regimen provided significantly more protections for patients than the 2016 regimen or the 2021 regimen. FDA should restore and strengthen elements of the Mifepristone regimen and provider requirements, including: limiting Mifeprex use to 49 days' (7 weeks) gestation; requiring that Mifepristone be administered only by or under the supervision of a physically present physician; requiring three office visits by a patient who has been prescribed Mifepristone; and clarifying that Mifepristone use is contraindicated for patients who do not have convenient access to emergency medical care. The agency should restore the original Mifepristone REMS, and return to limiting the dispensing of Mifepristone to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

C. ENVIRONMENTAL IMPACT

Petitioner is categorically excluded from conducting an environmental impact statement under 21 C.F.R. § 25.30, 25.31, 25.32, 25.33, or § 25.34 or an environmental assessment under 21 C.F.R. § 25.40.

D. ECONOMIC IMPACT

Petitioner will submit information upon request of the Commissioner following review of this petition.

[55] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifeprex
[56] ACOG Practice Bulletin 143, p. 3 & Box 1.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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Marissa Thompson, Bethany Lutheran College

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Damien	Murphy
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Eden	Logan
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Linda	Hoeck
Lindsay	Rupprecht
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Bradley	Smith
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Susan	Misa
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Shirl	Assal
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Gene	Gazzara
Linda	Gray
Sharon	Kurtz
Jack	Thomas Clinton
Jenny	Boyd
Jeffery	Ensley
Junius	Graham

Karen	Dunaway
Kenn	Claude Blankenship
Linda	Love
Elizabeth	Dozier
Joann	P Williamson
Michael	Moore
Mary	horne
Paul	Christopher
Amy	Ritter
Mary	Elizabeth Waugh
A.	Pierce
Maria	Speight
Johnnie	Stephens
Kitty	Parker
Michelle	M Schneider
Kate	McKeehan
Emmafae	Lemons
Keely	Gililland
Isaac	Monteleone
Marjorie	Liedtke
Yesenia	Rodriguez Ruiz
Angela	Lukens
Benjamin	Sell
Alison	Sims
Claire	Hibbs
Donna	Stowell
Erma	Thomas
Matthew	Sprague
Jennifer	Tyler
Joshua	Cruice
John	Puffer
Kris	Ellen Pinckney
Laura	Howard
Lisa	M
Lawrence	Nagle
Betty	Murdock
James	Thomas Putman
Jenna	Dolbare
Sondra	Dayton
Susan	Pomranky

Susan	Sutphin
Samuel	Jason Hooker
Paul-Leon	Tuzeneu
Suzy	Ravitch
Bill	Kilgore
Janice	Breedlove
Anita	Zeiser
Alan	M Becker
Sandra	Munoz
Anna	Simmacher
Olivia	Tamez
April	Morley
Anita	Shirley
Briana	Vasquez
Bryan	Malatesta
Julie	Bush
Carol	Bannerman
Lavinia	Calota
Carla	Smith
Carolyn	McClugage
Claire	Pace
Colleen	Luikart
Dale	johnson
Dennis	Mattli
Jonathon	Delaney
Delia	Tuttlebee
Donna	Hart
Donna	Bogema
Donna	Caster
Erika	Salazar
Elizabeth	Georgette Moreno
Ellie	Contreras
Joy	Gautney
Gaylon	George
Gerry	Brundage
Imelda	Valadez
James	Austin Pinedo
Janis	Hillin
John	J GILLULY
John	Courtney

James	Guillory
Karen	Werner
Joanna	Kennedy
Gary	Kent Boyd Jr
Kaylyn	Madany
Karen	Bingman
Riley	Sisco
Margaret	A Foland
Elizabeth	Moon
Marcy	Bloomfield
Mary	Cashion
Mark	Douglas Nightingale
Melanie	Mattil
Gloria	A Pope
Miles	Bedlan
Mindy	Villegas
Monika	Montecillo
Claire	Mullan
Samantha	Rhodes
Noel	Brinkerhoff
Jerome	ILTIS
Pamela	Littlepage
Peggy Ann	Weesner
David	Porter
Paula	Cordova
Rebekah	David
Dave	Cross
Rita	Cross
Robert	Parlee
Loretta	Bosley
Ramona	Krenek
Ronald	Samek
Richard	Razvillas
Annaliese	Schultz
Lorran	Rodriguez
Stanley	J Sramek
Alex	Alaniz
Adam	McManus
Virginia	Choate
Tommy	Chatlosh

Teresa	Rodriguez
James	Theisen
Tia	Viera
Cristina	Flores
Craig	Vernieu
Gail	Watts
Dorothy	Hussey
Jerusha	Welborn
Lacey	Lofgreen
Tami	Higbee
Linda	Paulson
Reggie	Voyce
Ry	MORAN
Elijah	Hatch
Allyson	Harris
Christine	strasser
Everett	Michael Griffiths
Lacie	Knight
Gene	Dwyer
Gray	Turner
Maryann	Hagan
Vicky	Hepperle
Janice	Towne
Karen	Lahr
Nina	P Newton
Carl	Walker
Patricia	E. Battle
Raymond	Eugene Grant
Rudolph	Gasser
C	Marks
Susan	Healy
Tiffany	Dickson
Wanda	Wylam
Abigail	Rose Sheerer
Havana	Tidball
Phyllis	Claire D Dant
Beatriz	Cintron
Angelica	De la Fuente
Arona	Vashon
Betty	Webb

Colleen	Connors
Daniel	Bickel
Dawn	Black
Ruth	Waldram
Elizabeth	Juhnke
Elaine	Adams
Fritzie	M Wolfe
Heidi	Amdahl
Janice	C Wheat
Judy	Odell
Suellen	Johnston
Karen	Munz
Lorna	Griffith
Angela	Black
Mary	Kasprzyk
Robert	Walling
Pamela	Garand
Paul	McClintock
Patrick	Kirlin
Patrick	Russell
Rodney	Barker
Sarah	Bissell
Michael	and Kimberly Nolan
Rena	Morrill
Virginia	Amidon
Wendy	Sleisher
Jo	Connors
Bob	Carubia
Bridget	Robinson
Mary	Elizabeth
Donna	Trippett
Mary	S. Riley
Rebecca	Perez
Annette	Wiemann
Candy	Anderson
Earl	Pappenfuss
Glenn	Schueffner
Kaila	Haws
Irene	Robaidek
Cathy	Burt

Joan	Van Abel
Lily	Yu
Linda	Gabriel
Mallory	Keefe
Eva	Melenchuk
Michael	Rohde
Paul	Margan
Peter	Schaettle
Patrick	Haines
Philip	Helwig
Philip	L. Potratz
Pam	Kramer
Roger	Rohe
Roseann	Schmidt
Susan	DECKER
Timothy	Dutcher
John	Thomas Wells
Ann	Heller
Becky	Weber
Blake	Brodjeski
Denny	Christenson
Kim	Hakenjos
Karen	J. Murawski
Rebecca	Wensink
Betty	Holliday
Joseph	Michael Donnelly
Margaret	Erickson
Dana	Kinion
Michael	Peach
Judy	A. Cook
William	sturdevant
Nathan	Fitzpatrick
Zentura	Zentura
James	Willingham
Nahid	Amini
Eleni	Ruiz
Adrian	John Woollen
Kenneth	Abbott
Abby	Ettinger
Audrey	Coltrane

Abigail	McDuff
Abigail	LaFave
Anne	Blackburn
Amanda	Sorlie
Adsam	Robitaille
Adelle	Garner
Adria	Paya
Adrian	Vance
Aerik	La Fave
Aeryn	Elisabeth Anderson
Ariana	galicia
Genevieve	mary czech
Annette	Hirl
Aidan	Clarke
Aislynne	Van Oirschot
Anne	Kinskey
Amalia	Bauza
Alicia	Gonzalez
Allison	Cruz
Bobby	Jean
Allyson	Moseley
Althea	Sanny Vader
Amanda	Ficken
Marian	Lyon
Ashley	Grooms
Ann	Marie
Amyjo	Pleune
Andre	DZIERZYNSKI
Andrew	Davies
Aneka	Maurer
Angela	Jean Brown
Judy	Diciaccio
Angie	Griffin
Christina	Frazell
Anna	Romanchik
Melody	Pegis
Anna	Schumacher
Amy	Hoff
Arianna	Milbrand
Anna	Reese

Ann	Zacharias
Annie	McGregor Meek
Phyllis	Bassett
Alison	Gordon
Virgilio	A. Buhain
Aleena	Jenea Rivera
Angela	Rizzo
Armel	Valenzuela
Abigail	Hammitt
Ashley	Rahar
Ashley	Resto
Rachel	Mechling
Blake	Elsberry
Edie	Baars
Beverly	Lopp
Barbara	Beatty
Sarah	Jane
Roger	Bautista
Stroffe	Brandi
Rebecca	Jackson
Rebekah	Bull
Shana	Thomas
Bella	Silva
Betty	Morrison
Bianca	Saliba
Harry	Parker
Becky	Palmer
Blanche	Lefebvre
Joseph	Vasta
Bryan	M Nogaki
Mary	Lou Hesser
Barbara	Agresta
Bonnie	Knudsen
Bonnie	Norman
Emily	Gramley
Brandie	Campbell
William	Thomas Bray
Brettany	Schonert
Brittany	Boller
Anne	Brown

Bryan	Kelsen
Brynn	Turner
Phillip	Talarico
Maria	Buczek
Biviana	Carreon Valdez
Andrea	Cartwright
Kirk	Smith
Carol	A. Hood
Carleton	Black
Carmela	Cavero
Carmen	Parks
Carol	Baker
Roger	Joyal
Caryn	Spaniel
Cari	Asjes
Cassandra	Cobb
Catherine	Caroul
Catherine	Mary
Chris	Blount
Constance	M. Canute
Clarie	Denise Calicdan
William	Threlkeld
Callie	Grett
Stephanie	Kapp
Chandler	Barnato
Charles	Sproull
Carmel	Saliba
Chelsea	Meza
Chels	Rowe
Cherilyn	Cherilyn
Cheryl	L. Lambert
Lindsay	Beck
Chris	More
Cindy	Biery
Cindy	Aguirre
Vincenza	Agosta
Cynthia	Velky
Claire	Moore
Christina	Mesker
Elizabeth	Schantz

John	Robertson
Charity	Saweikis
Anbarasu	Jerald
Colleen	Kunsemuller
Dean	Schlueter
Chris	Cola
Charles	Otterpohl
Wayne	H. McNiel
Cristian	Alfaro
Charles	Sicola
Lisa	Holstein
Alison	Curtin
Cindi	Weeks
Cynthia	Peters
Stephen	Richardson
Dave	Miles
Jeanne	Kjellman
Dale	Nacke
Kathleene	Daly
Danae	Agnew
Danalyn	Alvarez Perez
Daniel	Ridder
David	Duppler
Davis	Posey
Deacon	Brian Zeman
Ken	Carpenter
Dorothy	Downing
Joan	Sessions
Dean	Clark
Deanna	Bridges
Debra	Ann Spence
Debrah	Kelley
Carmela	Deguara
Denise	Henderson
Carol	Denty
Devin	Andrews
Deb	Graber
David	Laub
David	Hofstra
Dave	Huizing

Diana	Ramirez
Dulce	Diaz
Sharon	Finecey
Denise	Rhodes
Daniel	Moore
Dominique	Muggeridge
Donald	Schatte
Donna	L. Graham
Ruth	Stoehr
Edward	J. Dowd
Jeanette	Owens
Gemma	Downey
John	Dulph
Bev	Martin
Jameela	Thomas
Cecilia	Keen
Andrew	Gillis
Denise	B. Slaven
David	Traut
Cliff	Schiewerden
Jerome	Matthews
Dustin	Slaton
Diane	Lebari
Dylan	Isaac Thaut
Emily	Simmons
Elizabeth	Knight
Elizabeth	A Nelson
Judah	Eaton
Evanan	Church
Erica	Chartier
Edgar	Manuel Chacón Lizano
Eva	A. Garay
Eric	Holsopple
Eileen	Ealy
Emily	Klein
Karen	Locker
Julie	Elander
Elizabeth	Bergeron
Elizabeth	Boriszek
Elizabeth	Abdool

Laura	Probst
Elizabeth	Earl May
Collyn	Hunt Gomez
Christy	Meyers
Erica	Marie Faucher
Emil	Ember
Emily	Medlyn
Emma	Leigh Hamilton
Emma	Hood
Emma	Jaquess
Enyer	Delgado
Elizabeth	Rankin
Erica	Mulford
Erica	Smith
Erik	Andersen
Erin	Myers
Ernest	Robillard
Esther	Attebery
Dee	Kelley
Faith	Zenaty
Fernando	Aizpun
Kolbe	Williams
Francis	Oberembt
Frances	Buchanan
$Frederick	Cohen
Aurora	Hampton
Mike	Fenton
Karla	Alvarado
Peter	Rappold
Christine	Gookin
Nancy	Bucca
Alicia	Thompson
Frank	B. Kady Jr.
Frances	Schmitz
Freda	Smouter
Gary	Henderson
Joseph	Martins
Tom	Sodano
Gabrielle	Vega
Elizabeth	Jean Hughes

Gabriela	Garcia
George	Berry
Gary	Anderson
Gregory	Antonik
Diana	Garcia
Gary	Raffle
Gaye	Drummond
George	Branscom
Gilbert	Cormier
Georgia	Farrish
Tim	Giles
Gillian	Owens
Gina	Schmittdiel
Mikell	Schoonover
Glenda	Patterson
Glen	Zimmerman
Grace	McAlary
Carolyn	S Gardner
Nancy	Baum
Kaitlyn	Schmitt
Kara	Schoepfer
Grace	Bergman
Gracelyn	Mosier
Annabelle	Gray
Katlynn	Green
Gregory	Smith
Gerald	Hicks
Patricia	Kumiega
Gabriel	Moreno
Deanne	Wikler
Catherine	Gwinner
Kerrie	Lynn Schlenker
Beau	Rodriguez
Hailee	Clifton
Hailey	Lennon
Carol	Theriault
Hannah	Kern
Hannah	Felch
Ida	Bolding
Caroline	Jordon

Gerard	Hartze
Harvey	B. Rachlin
Pamela	Faulkner
Nola	Kuester
Mary	Fairbairn
Heidi	Ngai
Anna	Roth
Ana	Paulson
Holly	Hanson
Hannah	Ferrin
Heather	Sargent
Paige	Hoban
Debra	Hoots
Hannah	Swartz
Lynne	Howell
Hannah	Janae Dean
Hoa	Vuong
Ian	Thompson
Tim	Kelley
Ronald	Draper
Nancy	M. Draper
David	Antoff
Isabel	Rothstein
Ashlie	Villafuerte
Isabella	Torres
Janine	Micke
Joyce	Carrico
Jacqueline	R. Krozy
Abigail	Allen
James	Fetty
Janaye	Pieczynski
Jane	Griffin
Janet	Cross
Janet	Waksmunski
Janice	Weber
Janie	Widman
Juan	Arguedas
Julia	Stamerro
Cynthia	Alfonso
Mae	Johnson

Jean	Vinyard
Gerard	Schmidt
Jeffrey	Aaron Borchardt II
Jeff	Frasieur
Jen	Brown
Jennifer	Larson
Jessica	Phillips
Jessica	Iwema
Jennifer	Hansley
James	Gokey
James	Harris
Jean	Hillberg
Linda	Stankiewicz
Joan	Null
Julianne	Wiley
Janet	Masline
Jim	Dobratz
John	Hammerbacher
Julia	Monk
Jean	Walkowski
Joy	M. Monroe
Juliana	Nordhoff
Joanna	Hobbs
Joann	Georgostathis
Joaquin	Gutierrez del Alamo
Joleen	Peterson
Joseph	Rebman
Michael	Brigadier
Joe	Wierzbicki
John	Gavin
John	E. Alexander
John	Kowalak
Dean	Allan Johnson
Patrick	Johnston
Jonathan	Dewey Wilkerson
Jordyn	Robinson
Josephine	Mortrud
Joseph	Bertin
Joyce	Simkin
Joyce	Hudgins

Starr	Powell
Patty	Straus
Jessica	Summers
Berl	Thompson
Sarah	Tomac
Hannah	Judson
Judith	Soller
Judy	Owensby Goad
Judy	Branscom
Julianna	Gallion
Charles	T and Julie R Arnold
Julio	Colmenares
Jennifer	Viviano
Jeremy	Day
Jolene	Wojcik
Jessica	Freeman
Ken	kruger jr
Kadynce	Owens
Blair	Kampoivtz
Kamy	Lee Treat
Kandace	maynard
Karina	Ortiz
Alia	Muellerleile
Katherine	Manning
Kate	Lessard
Kathleen	Gaber
Kathleen	RUTH GOLDSMITH-KILLING
Kathleen	M. Knospe
Katie	Palmatier
Katie	Gardner
Katie	Pace
Kayleen	Corrigan
Kathleen	B. Long
Kristen	Newcomer
Les	Greaser
Kathleen	Jenkins
Keaton	Dillard
Keili	Danielle Stevens
Kelly	Hellmuth

Kenna	Holt
Kristina	Kaufer
Kathryn	Haveman
Kim	Allmon
Nicole	Dodge
Kimberly	C. Martinez
Steve	King
Kira	O'Neal
Kirah	Fillmore
Kirk	Watts
Patricia	Doss
Katie	Bollinger
Kathy	Kelly
Kathrine	M Kolanko
Kristine	Schneider
Kay	West
Kevin	Nishimuta
Kenna	Thornton
Katherine	Ray
Kristina	Cobb
Karen	Salamon
Karen	Harris
Karen	Sipes
Katherene	Skinner
Kary	Taylor
Katherine	(Katie) Ramsey
Kenrith	Williams
Loisel	Barrios
Lacie	Barnes
London	Abigail Farnsley
Suzanne	Landis
Melanie	Hopkins
Launa	Meyer
Laura	Cheshire
Lauren	Parker
Lauren	Thurman
Diane	McGovern
Andrew	Leese
Katie	Lemon
Leonard	Reiland

Wilma	Lenz
Leslie	Holcomb
Linda	Gibbs
L.	GUNDIQUE
Luke	Brehm
Liana	Moore
Emily	Powell
Lily	Crosby
Lily	Sutton
Delaney	Tracy
Linda	BABB
Lindsey	Blount
Lindsey	Peter
Lisa	Johnson
Lisa	Burns
Lisabeth	Lipp
Lisa	Dahmer
Lisa	Hall
Olivia	Dean
Helen	Mary McBlain
Judith	Rangel
Larry	Garber
Lisa	COOLEY
Lois	A. Carter
Stephen	Gravel
Lorne	David Digges
Loretta	Nicholas
Louise	Cox
Louise	Perrotta
Megan	Luby
Luca	Castellanza
Lucy	Papaik
Luiz	Carlos
Lynda	Elliott
Lyndon	Griarte
Lynne	Perlik
Miss	Lynn Marie K
Mary	Brummell
Mark	Hagey
Martha	Ruschkamp

Samuel	Maclay
Madelyn	Peterson
Maryann	Derrick-Green
Madison	Selva
Maira	Tripp
Kristina	Gonzales
Sheree	Mann
Pinky	Mendoza
Maria	Kim
Jane	Klorer
Marian	Ross
Maria	P. Angelucci
Mariele	Lopez
H.R.	Martin
Marvin	Putman
Mary	T. Dombrovski
Mary	Hyska
Mary	Olson
Mary	Adams
Matalin	Shaver
Matt	Donald
Matthew	Snyder
Terrie	May
Mercedez	Barker
Marilyn	Stadtmueller
Moira	C. Dowling
Mckenna	Freeland
Maureen	Morton-Navarro
Marilyn	Lengyel
Mary	A. DURKIN
Kathleen	Mulhair
Monica	Ferris
Megan	Willis
Megan	Reinsfelder
Melinda	Movius
Melodie	Padgett
Michael	Morris
Mervyne	Greene
Gail	Dierkes
Mary	Cetera

Michael	Murray
Michael	Hinderscheid
Michael	van Holst
Michele	Cheever
Michelle	Lewis
Mikayla	Hill
Michalene	L. Lovato
Richard	Miles
Carlee	Miller
Mirna	Jajow
Michael	Gilbert
Jeanne	Ann White
Mary	Kay Neal
Michael	Dooley
Muriel	Korson
Margaret	Mary
Marilyn	Muscanere
Mary	Ann
Melvin	Molitor
Mary.	Leonard
Rosalynd	Perlick
Mona	Pilane
Maureen	Nash
Monica	Holland
Shannon	Moodry
William	Smith
Morgan	Matreci
Kary	Kahle
Matthew	Maurer
Lynda	True
Christina	Valadez
Julie	Kidwell
Mary	Lind
Michelle	Tripp
Olivia	Mullins
Mary	Venckus
Mark	Waters
Michael	Ingle
Mary	Partee
Bill	L. Manville

Natalie	Kurtz
Nadine	Schanilec
Nancy	Zaengle
Nancy	Yeats
Neida	Johnson
Augusto	Cesar
Nathan	Watry
Diana	Nelson
Mary	Ann
Nick	Unverferth
Nicole	Waters
Nicole	Dellas
Nicole	Maurer
Malielani	Min
Jacqueline	Aldrich
Nicole	Phipps
Mary	F. Norton
Natasha	Mosier
Noel	Perez
Noelle	Reagan
Jeff	Norton
Naomi	Murray
Michelle	Viljoen
Olivia	Cloer
Ciaran	O'Meara
Rocky	Rocha
Malorie	Summer
Órlaith	Ryden
Pamela	Hayward
Pamela	Burrell
Mary	R. Partin
Pauline	Self
Richard	Pauls
Phil	Stiver
Robert	Pierce
Martha	Maturi
Larry	Cotten
Keanna	Martin
Mary	Lou
Peggy	Kurtz

Robert	Collins
Portia	Horst
Emma	Brewer
Janet	Price
Pauline	Myers
Joseph	G. Sandoval
Pro-Life	Richardson
Rocky	Gray
Rebecca	Drinks
Ronnie	Rose
Robert	Chapman
Reagan	Marie Woody
Rebekah	Stepp
Crystal	Howley
Andrew	Reder
Regina	Calderon
Regina	Singleton
Renu	Carroll
Tyler	Revolinski
Robert	Reynolds
Ryan	Horning
Richard	Burkett
Rick	Hill
Kim	Hoog
Rosemary	Graham
Michael	Rosenthal-English
Royce	Clough
R.	Pescador
Renee	Show
Richard	Tuma
Sean	Hayes
Ruth	Merklinger
Ruthie	Johnson
Ruth	Nicolaus
Ryan	Leanor
Sharon	Larks
Sharon	Sackett
Sandra	Evarts
Olivia	David-Eagan
Bridget	Schlafley

Samantha	Cote
Charla	Moreno
Sara	Tracey
Sarah	Smith
Sarah	Brown
Sara	Yunger
Sara	Martin
Linda	Zimmerman
Scott	Bathke
Stephen	Brown
Alfred	Scott Jr.
Jeff	Weber
Sharon	Dakin
Sue	Gibson
Sarah	Tamburro
Dave	Pickrell
Susan	Gardy
Peter	Shaddock
Debbysue	Dettloff
Sharon	Ziegler
Mary	C. Shaw
Shellie	Silcott
Roberta	Sibbald
Larry	Simmons
Shelly	J. Taylor
Sydney	Keleske
Sharon	E. McCormick
Stacey	Manzi
Susan	Henebery
Kerri	Smith
Michael	Korn
Susan	Stepien
Sharon	Luke Sogut
Susan	Pingel
Jeanette	Rerucha
Stacey	R. Saia
Sally	Hess
Scott	Sprout
Patricia	Stack
Darlene	M. Champagne

Stasi	Ventura
Stasia	SCHWARTZ
Anastasia	Crain
Stephanie	Bennion
Stephaney	Roberson
Stephanie	Spandet
Stephanie	Veloso
Margaret	Stevenson
Eva	Stevy Young
Roy	Green
Jeff	Stoner
Sue	Jones
Sue	Shoemaker
Richard	Harrison
Susan M	Barker
Sukhdev	Contee
Ryleigh	Sullivan
Audrey	Summers
Susan	Hahn
Susan	M Walsh
Suzanne	Harmon
William	Sweeney
Allison	Howard
Sheila	Wisocky-Lord
Sylvia	Bertolini
Sylvia	bartosek gee
Sylvia	Galan
May	Tran
Maria	Tabellini
Lily	Ho
Tamra	Wright
Tarena	Mowrey
Taylor	Osowski
Tracy	Hernandez
Theresa	Bonopartis
Tiffany	Wilson
Antoinette	Disney
Tamara	Rutgers
Teresa	M Breault
Terri	L Monahan-Mitchell

Terry	Stam
Tressa	Hammond
Patricia	Munn
Theresa	Howard
Theresa	L. Greene
Timothy	Alberts
Timothy	Haunsperger
Christina	Haug
Valentina	Bernero
Jill	Campione
Delphene	Osborn
Thomas	Moran
Teresa	Robinson
R.	Thomas Conrad
Tony	Hamilton
Tonya	S Smith
Mike	Brown
Debra	Horton
Tim	Opper
Trace	Flax
Travis	bechtold
Terry	Hughes
Tresha	Rivere
Toby	Cobb
Thomas	X. Brown
Carol	Kemp
Melissa	Ducommun
Breanne	Wall
Virginia	Mantela
Valerie	Beukema
Valerie	Iacovangelo
Victoria	Whitmore
Vincent	Lagrotteria
Vickie	Giles
Veronica	Santini
Victoria	Leigh
Wendy	Pham
Cheryll	Klompien
William	Vandergriff
William	Baize

Amanda	Wildon
Wendy	Ridder
Kathleen	Worlund
Susang-Talamo	Family
Galen	W. Yoder
George	Akula
Yuerong	Hu
Abigail	Nolla
Zara	Elizabeth Dina
Claire	Sabroe
Linda	Webster
Zulmarie	Pagan-Panzardi
Robert	C Zunino
Zvonimir	Gašpar

EXHIBIT 34

2023 FDA Letter to Students for Life of Am. denying
2022 SFLA Petition, Docket No. FDA-2022-P-3209
(Jan. 3, 2023)



Kristan Hawkins, President
Students for Life of America
1000 Winchester Street, Suite 301
Fredericksburg, VA 22401

Kristi Hamrick, Chief Media & Policy Strategist
Students for Life of America
1000 Winchester Street, Suite 301
Fredericksburg, VA 22401

January 3, 2023

Re: Docket No. FDA-2022-P-3209

Dear Ms. Hawkins and Ms. Hamrick:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on December 13, 2022, on behalf of Students for Life of America and other signatories (Petition). In the Petition, you request that the "2021 and 2016 modifications to mifepristone's REMS be reversed and the REMS as they were in 2011 be restored." Specifically, you request that:

(1) FDA reverse the 2021 and 2016 modifications to the risk evaluation and mitigation strategy (REMS) for mifepristone[1] by requiring that:

a. "Mifepristone only be administered, in a regimen with misoprostol, for the termination of intrauterine pregnancy, for up to 49 days (7 weeks) gestation" (Petition at 1).
b. "Mifepristone only be administered by or under the supervision of a physically present physician" (Petition at 1).
c. "the use of Mifepristone and misoprostol for the termination of pregnancy necessitate three office visits by the patient" (Petition at 1).

[1] Mifepristone products for medical termination of intrauterine pregnancy through 70 days gestation are subject to a single, shared system REMS known as the Mifepristone REMS Program. We note that on December 16, 2021, FDA completed its review of the Mifepristone REMS Program and determined, among other things, that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification. On December 16, 2021, FDA sent REMS Modification Notification letters to the applicants for Mifeprex and the approved generic version of Mifeprex, Mifepristone Tablets, 200 milligrams. Following receipt of these letters, the applicants prepared proposed REMS modifications and submitted them to FDA. On January 3, 2022, FDA approved the REMS modifications.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

(2) "Mifepristone use should be contraindicated for patients who do not have convenient access to emergency medical care," and "[t]his use should be as limited as possible" (Petition at 1).

(3) "Telehealth should not be an option to all women, but only to women in absolute need under extreme circumstances that would make access to a medical care facility impracticable, with a substantial risk that the woman would die without immediate administration of Mifepristone" (Petition at 1).

(4) "To alter the Mifepristone REMS, a formal study should be required" (Petition at 1).

The actions you request in your Petition are the same or substantially the same as the actions requested in the March 29, 2019 citizen petition submitted by the American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG) and the American College of Pediatricians (ACP) (FDA-2019-P-1534) (AAPLOG/ACP petition), which were addressed in FDA's December 16, 2021 response to that petition.[2] Your Petition does not provide any new data or evidence beyond what was provided in support of the AAPLOG/ACP Petition. FDA carefully considered the information submitted in the AAPLOG/ACP Petition and issued a detailed response. The December 16, 2021 citizen petition response is available at regulations.gov.

For the reasons explained above, we deny your Petition.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2023.01.03 09:41:02 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[2] Available at https://www.regulations.gov/document/FDA-2019-P-1534-0016.

EXHIBIT 35

2021 FDA Center for Drug Evaluation & Research
Director Patrizia Cavazzoni Letter to
Dr. Graham Chelius
(Dec. 16, 2021)

December 16, 2021

Graham Chelius, M.D.
The Society of Family Planning
The California Academy of Family Physicians

Dear Dr. Chelius:

This letter is to inform you that FDA has completed its review of the Mifepristone Risk Evaluation and Mitigation System (REMS) Program.[1] The agency has determined that the Mifepristone REMS Program continues to be necessary to ensure that the benefits of the drug outweigh the risks. However, we have determined that it must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. See 21 USC 355-1(g)(4)(B). The modifications to the REMS will consist of: (1) removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement"); and (2) adding a requirement that pharmacies that dispense the drug be specially certified.

A REMS Modification Notification letter has been sent to both Applicants subject to the Mifepristone REMS Program. The letter describes the modifications and directs the Applicants to submit prior approval supplements within 120 days. We have also answered a related citizen petition from the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians. That response will be posted in the public docket (Docket No. FDA-2019-P-1534; available at www.regulations.gov).

Sincerely,

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[1] We also note your letter of September 29, 2021 to us on this subject.

EXHIBIT 36

Oral History Interview with Ruth B. Merkatz
(Oct. 16, 2019)

U.S. FOOD & DRUG ADMINISTRATION

Oral History Interview with
Ruth B. Merkatz, PhD, RN, FAAN
Director of the Office of Women's Health
1994-1996

FDA Oral History Program
Final Edited Transcript
October 16, 2019

Table of Contents

Table of Contents 2

Oral History Abstract 3

Keywords 3

Citation Instructions 3

Interviewer Biographies 4

FDA Oral History Program Mission Statement 4

Statement on Editing Practices 4

Index 5

Interview Transcript 8

Curriculum Vitae 60

Appendix A: Speech to North American Menopause Society 82

Oral History Abstract

Ruth B. Merkatz, PhD, RN, FAAN, was the first Director of the FDA Office of Women's Health (1994-1996), and before that served as a Special Assistant on Women's Health Issues to Commissioner David Kessler (1991-1994). During her tenure at the FDA she not only stood up the Office of Women's Health and established its research program, but helped the agency to grapple with issues ranging from women's participation in clinical trials, gender differences in health, silicone breast implant safety, the Mammography Quality Standards Act, HIV/AIDS in women, contraceptive labeling, etc. After leaving FDA in late-1996, Dr. Merkatz served as Director of Women's Health at Pfizer, Inc. and later as the Director of Clinical Development in Reproductive Health at the Population Council.

Keywords

women's health; clinical trials; contraception; HIV/AIDS; mammography; gender differences in health; silicone breast implants

Citation Instructions

This interview should be cited as follows:

"Ruth B. Merkatz Oral History Interview," History Office, U.S. Food and Drug Administration, Department of Health and Human Services, October 16, 2019.

Interviewer Biographies

Vanessa Burrows is an historian who holds a Ph.D. in the History of Public Health and Medicine from the City University of New York's Graduate Center (2015). She joined the FDA History Office in January 2017, where she focuses on the history of medical consumerism, regulatory policy and digital history. She has a background in documentary film, public history and higher education, and her prior work includes associate producer of the 2018 film *Power to Heal: Medicare and the Civil Rights Revolution*. Her research on the history of socially determined health inequities, dynamics of health literacy and the political economy of medical research has been published in the *Journal of American History* and the *Oxford Research Encyclopedia of Psychology*.

FDA Oral History Program Mission Statement

The principal goal of FDA's OHP is to supplement the textual record of the Agency's history to create a multi-dimensional record of the Agency's actions, policies, challenges, successes, and workplace culture. The OHP exists to preserve institutional memory, to facilitate scholarly and journalistic research, and to promote public awareness of the history of the FDA. Interview transcripts are made available for public research via the FDA website, and transcripts as well as audio recordings of the interviews are deposited in the archives of the National Library of Medicine. The collection includes interviews with former FDA employees, as well as members of industry, the academy and the legal and health professions with expertise in the history of food, drug and cosmetic law, policy, commerce and culture. These oral histories offer valuable first-person perspectives on the Agency's work and culture, and contribute otherwise undocumented information to the historical record.

Statement on Editing Practices

It is the policy of the FDA Oral History Program to edit transcripts as little as possible, to ensure that they reflect the interviewee's comments as accurately as possible. Minimal editing is employed to clarify mis-starts, mistakenly conveyed inaccurate information, archaic language, and insufficiently explained subject matter. FDA historians edit interview transcripts for copy and content errors. The interviewee is given the opportunity to review the transcript and suggest revisions to clarify or expand on interview comment, as well as to protect their privacy, sensitive investigative techniques, confidential agency information, or trade secrets.

Index

abortion, 9, 36, 45
adverse events, 18, 20
advisory committee, 12, 36, 57
  reproductive health, 36
Albert Einstein University, 10, 48
amlodipine (NORVASC), 47
Annovera, 37
Anthony, Marietta, 29
artificial heart valves, 54
Association for the Accreditation of Human Research Protection Programs, 40
Atorvastatin (LIPITOR), 47
Bagley, Grant, 26, 57
Berman, Rachel Sherman, 30
biographical background, 8
breast cancer, 8, 33
breastfeeding, 8, 11
budget, 35
Burlington, Bruce, 26
Bush, George H., 36
Bush, George W., 46
cardiac disease, 18
cardiovascular disease, 9, 21, 22, 46, 47
Carter, Linda, 26
Case Western Reserve, 9
Centers for Disease Control and Prevention, 23
Cleveland, Ohio, 9
clinical trials
  minority participation, 18
  women's participation in, 3, 13, 14, 15, 17, 18, 19, 21, 22, 27, 29, 30, 31, 32, 35, 36, 38, 41, 42, 45, 49, 52, 53, 58
Clinical Trials in Women Committee, 30
Clinton, Bill, 29, 46
condoms, 51
conferences
  FDA Making a Difference in Women's Health, 46
  Gender Effects on Product Development, 43
  Women's Health Across the Lifespan, 31
Congressional appropriations, 24
Congressional Women's Caucus, 23, 33, 45
consumer advocacy, 22
contraceptive devices, 53
Department of Health and Human Services, 3, 12, 15, 16, 23, 25, 33
  Office of the Assistant Secretary for Health, 32
  Women's Health Coordinating Committee, 23
drug approval, 20
education, 8, 9, 10, 21
epilepsy, 22
FDA Consumer, 46
Food and Drug Administration, 1, 3, 4
  Center for Devices and Radiological Health, 15, 26, 34, 35, 42, 54
  Center for Drug Evaluation and Research, 15, 16, 26, 27, 30, 50, 56
    Division of, 37
  Office of Constituent Health Affairs, 26, 57
  Office of Consumer Affairs, 39
  Office of External Affairs, 25, 26
  Office of Special Health Issues, 26
  Office of the Commissioner, 11, 26, 27, 55
  Office of Women's Health, 22, 23, 24, 27, 29, 39, 40, 42, 44, 45, 50, 53, 54, 56, 58
Food and Drug Administration Modernization Act, 49
gender differences
  medication dosage, 18
gender differences in health, 54
Government Accountability Office, 14, 21
Gross, Mary, 26, 28
Health Resources and Services Administration, 23
Healy, Bernadine, 13
heart disease, 14, 31, 47

Heart Parties, 47
Henderson, Marsha, 41, 56
Henney, Jane, 26
HIV/AIDS, 3, 10, 14, 19, 20, 21, 27, 36, 49, 51, 52
Holston, Sharon Smith, 25
Hou, Florence, 35
Kennedy, Ted, 34
Kessler, David A., 3, 10, 11, 13, 15, 20, 23, 27, 36, 59
Kirschstein, Ruth, 14
Korfman, Phil, 36
Kweder, Sandra, 43
Legato, Marianne, 46
listeriosis, 53
Lowey, Nita, 33
Mammography Quality Standards Act, 3, 34
McCarthy, Jane, 57
Menopause Society, 30
mental health, 9, 31
Mikulski, Barbara, 13, 14, 23, 33, 34
Murphy, Dianne, 26
National Institutes of Health, 13, 14, 32, 36, 38, 52
  Office of Women's Health Research, 12, 14, 23
New England Journal of Medicine, 16, 29
New York City, 9, 10, 23
  The Bronx, 10, 14
Nightingale, Stuart, 26
nonoxynol-9, 51
Norplant, 37
nursing, 8
Nursing of Women in the Age of Liberation, 9
obstetrics and gynecology, 8, 9, 10
oral contraceptives
  labeling, 37, 50
outreach, 30, 55
ovarian cancer, 36
Parklawn Building, 50
Peck, Carl, 26
Pendergast, Mary, 15, 26, 38, 45, 59
Pfizer, 3, 44, 47, 48
Physicians' Health Study, 21
Plan B, 45
Population Council, 3, 37, 38, 52
pregnancy
  drug labeling, 44
  drug use in, 29, 44
pregnancy discrimination, 17
Pregnancy Discrimination Act, 16
pregnancy registries, 44
recruitment to FDA, 10, 11
Roe v. Wade, 410 U.S. 113 (1973), 9, 39
Roussel-Uclaf, 38
RU-486, 38, 39
Scheman, Carol, 25
Schroder, Patricia, 33
sertraline (ZOLOFT), 44, 47
Shalala, Donna, 38
Sheppard, Audrey, 28, 39, 49, 56
silicone breast implants, 3, 11, 12, 13, 14, 20, 21, 33, 43, 49, 53, 57
Sobel, Sol, 36
Special Advisor to the Commissioner of Food and Drugs, 33
Summers, Elyse, 27, 28, 40
Take Time to Care, 29, 39
Taylor, Michael, 27
Temple, Bob, 15, 27, 28, 49
thalidomide, 13
Toigo, Terry, 26, 27
Trapnell, Carol, 52
United Automobile Workers v. Johnson Controls, 499 U.S. 187 (1991), 16, 17
United States Agency for International Development, 38
United States Supreme Court, 17
Washington, D.C., 11, 20, 48
Wenger, Nanette, 46
Williams, Roger, 26
women's health, 9, 11, 12, 13, 20, 21, 23, 24, 32, 33, 35, 42, 43, 47, 53, 55
Women's Health Equity Act, 24
Women's Health Initiative, 36
WomenHeart, 47
Wood, Susan, 11, 27, 44, 56

Woodcock, Janet, 27
World Health Organization, 38
Wykoff, Randy, 51
Yeates, Nancy, 27
Yen, Lillian, 35
zudovudine (AZT), 19

Interview Transcript

VB: This is an addition to the FDA Oral History Collection. I am Vanessa Burrows for the FDA History Office here with Ruth Merkatz, the first director of the FDA Office of Women's Health. It's October 16, 2019.

I'd like to just start off by asking you a little bit about your background, growing up, your education, and how you developed an interest in women's health that brought you to the FDA.

RM: Well, in terms of my background, I guess, I would say that I've always been involved in health care. My father was a physician, a general practitioner, and he had his office in the house. Although I had two brothers, he always called upon me to help him when patients came to the office off-hours or in the middle of the night or on weekends. So, I think I developed an interest in health when I was very young and saw what, the practice of medicine and dealing with health issues for families of different means was all about.

I actually then studied nursing as part of my liberal arts preparation at Cornell. And very early on in my nursing career, I did a lot of work caring for women patients, many of whom had breast cancer and had mastectomies back when there were very few options for women who may have wanted reconstruction or in terms of how they might deal with their body image. I then shifted into officially caring for women in the maternity cycle, providing obstetrical care. I was one of the early teachers, for prepared childbirth, and I, also, worked very closely with the moms in terms of breastfeeding back when breastfeeding was not very popular in the United States.

I also had an opportunity early in my career to care for women having in New York State who were seeking abortions. This is before *Roe v. Wade* was enacted into law, but New York State had already passed a law that enabled women to have a first trimester to have abortion. I was at a hospital where we actually set up a unit for women -- they came from all over the country to have abortions because they weren't able to have them in other parts of the United States. Actually, the very first paper I wrote dealt with the experience of setting up a unit in a hospital to provide safe abortion. I continued working in women's health here in New York City at the New York Hospital-Cornell.

And then as a family, we moved to Cleveland, Ohio mainly for my husband's work and some exciting opportunities he had to regionalize care of pregnant women and try to improve outcomes. I started doing graduate work in nursing at Case Western Reserve. I focused on women's health in my graduate work and had very forthright and very forward-thinking faculty who encouraged me in thinking out of the box, so to speak, about women's health. We actually wrote a book together, several of us. It was called *Nursing of Women in the Age of Liberation,* and we touched on subjects that most people would not have touched on at that particular time, e.g. feminist themes. We focused on theoretical aspects of caring for women as well as some of the challenges that women faced in health care.

So, I had very good schooling and was able to think quite broadly about some of the issues that women were facing in their health. While women's health seemed to focus mainly on reproductive health, there were many other aspects of health for women that needed attention whether it was cardiovascular disease, mental health disease. These were really important issues for women. But at the time, I focused on the care of women who were at high risk for poor pregnancy outcomes, and that, in fact, is what I did my thesis on.

And then having spent 10 years in the Midwest, we actually came back to New York where my husband was offered the chair of the department of obstetrics and gynecology at Albert Einstein in the Bronx. I began to work in the Bronx in the nursing department at the hospital. I don't know if you recall exactly date-wise, but certainly, I remember that when I came back, something had hit the Bronx that we didn't even talk about in the Midwest, and that was HIV. The Bronx was actually an epicenter of HIV in the United States. I actually cared for a woman who came into our special unit for high-risk pregnant women with a very bad case of pneumonia and a very bad case of vaginal herpes. I became very concerned about her, what was going on and after speaking with her at length about her lifestyle, I suspected -- even though it wasn't talked about -- suspected that she had HIV. I asked the physicians to please do an HIV test, and sure enough, this woman had HIV. So, that was my introduction to the world of HIV, which became a very important part of my nursing career in the 1980s and very important for my work when I landed at the FDA.

While I was continuing to active work in nursing, I was also working on doing a PhD in nursing research. I had started that in Cleveland, but I finished it here in New York. I did a lot with ethics as part of my doctoral study and worked on the bioethics committee at the hospital. It was there that I got to know Dr. David Kessler who was the medical director at the hospital where I was working. We tackled some very challenging cases together and with the other members of the committee; we worked together quite a bit in caring for patients at the hospital and I think sharing ways of thinking and approaches to health care.

Then just to fast-forward, as you know, Dr. Kessler became the head of the FDA, the commissioner of the FDA. He was appointed -- I believe it was -- in 1990; he went down to the FDA. And it just so happened that my husband who had been chairing the department of

obstetrics and gynecology at Einstein, planned on going to Washington for a year to do a sabbatical. He was going to be a Robert Wood Johnson Policy Fellow, and I decided that it was a great opportunity for me to go to Washington as well and actually planned to work at Georgetown University. They had a special research area on breastfeeding, and because I had always done a lot of work on breastfeeding, I thought that would be a very good research opportunity for me.

But then Dr. Kessler, because we had worked together very closely while he was the medical director at Einstein, contacted me and told me that women's health was very important at the FDA. It was really heating up in Washington, that there were many issues that were extremely important for the FDA that they were going to be grappling with -- for example, the issue of breast implants. He wondered whether I might be interested in coming down and meeting some of the people that he worked very closely with on his staff just as an exploratory interview to see whether there might be anything that I could work on or that would be a fit.

Since I was going down to Washington, and I thought it could be a wonderful opportunity, I interviewed with a number of people in the Office of the Commissioner. They explained to me that this was sort of unchartered territory for the FDA to have a special focus on women's health, but there were a lot of issues that were heating up -- as I mentioned, breast implants being front and center at that particular time. This is 1991. I must say I didn't have to think too hard. After I went down to the FDA to meet with some of the folks that interviewed me, I was very excited -- it was humbling in a way to think that someone with my beginnings in my Dad's office in a little town and a nursing background would be asked to come down and work directly in the Office of the Commissioner and try to work on issues of women's health.

And so, in September of 1991, I went down to the FDA, and originally, it was going to be for a year since my husband had to go back after his one-year sabbatical was up and so I originally thought I would just stay down there for a year. Well, I quickly learned that there was so much to do and there was opportunity for meaningful change in approaches to women's health. It didn't take me many months before I realized that in a year's time, there wasn't an awful lot that one could actually accomplished, but I would do my best.

The issue that I focused on almost exclusively when I first got down there was the issue of breast implants because they were getting ready to have some very important advisory committee meetings to review the four applications from companies that had their applications filed for review of the breast implants. More than four companies had filed for breast implant approval, for the FDA to give its approval, but only four were deemed fileable, i.e. had adequate information so that FDA could conduct a full review. I had a chance to review, myself, some of the documents that were part of the dossiers of the various companies and very much participated in the advisory committee meetings that became worldwide events. There were thousands of people that showed up for these hearings. It was broadcast all over the world, and it was quite an important event in women's health. It also, I think, really set the stage for the FDA realizing how important women's health was in and of itself.

Before the breast implant controversy erupted, there already was a focus on women's health. within the Department of Health and Human Services. There had been a committee that had started in the '80s. There had been very important reports that had come out describing women's health across the lifespan and some of the challenges that women faced in various periods of their life. And importantly, the Office of Women's Health Research was established at the NIH.

At the same time that David Kessler was appointed as the FDA Commissioner, Bernadine Healy became the head of the NIH. It was the first time a woman headed up the NIH. Dr. Healy and Dr. Kessler communicated with one another about women's health, and I actually had the privilege of meeting with Dr. Healy. Dr. Kessler brought me to a meeting with Dr. Healy where we talked about not only about what the NIH was doing but what we were going to be doing at FDA to be part of a real effort to raise awareness about issues in women's health.

The other thing that was going on at the same time -- and it was almost like a perfect storm in a way – besides breast implants, we had leaders in Congress like Barbara Mikulski who, I believe, marched on the NIH -- organized a march demanding that women be in clinical trials. So, this is when the issue of women in clinical trials starts and became a major focus for me and my work at FDA. The FDA, as you probably know, had a longstanding ban on the participation of women in the early phases of human clinical trials -- clinical trials being phase 1, phase 2, phase 3, the human trials. Phase 1 being the small trials that are primarily for safety, phase 2 being larger where they're looking at safety and efficacy and dose-finding and then, of course, the large phase 3 trials for further evidence of safety and efficacy before a new drug can be considered for approval for use and become commercially available.

To go back, the FDA has this long-standing ban that came about in 1977 as a result of concerns about exposing women who might become pregnant to any drugs that haven't been tested. And this comes about as a result of the thalidomide tragedy where the FDA was the hero in terms of preventing thalidomide from coming into the United States. So, the FDA, based on their good record keeping thalidomide out of the market, took it to the point of wanting to really protect -- quote "protect women" -- from exposure to any drugs that they didn't know very much about.

The NIH had gotten into quite a bit of political difficulty over the fact that they had conducted a very large study, with taxpayer dollars, on heart disease without including any women. That's what I think triggered Barbara Mikulski and other members of Congress to demand that the NIH put women into their clinical trials especially for trial on heart disease. No one talked about the fact that heart disease was the number one killer of women. They talked about heart disease in men; they didn't talk about heart disease in women. So, all of this was, as I said, almost the perfect storm. We had breast implants, then we had this issue of women in clinical trials. We had what was going on at NIH starting an Office of Women's Health Research. And the GAO from out of Congress did a study of women on clinical trials at the FDA, and their results also pointed to the fact that women were not being included to any great extent especially in the phase 1 and phase 2 clinical trials.

Then, to add to this perfect storm comes my experience with having worked in the Bronx the epicenter of HIV, women with HIV. Women with HIV were getting no attention whatsoever, and women with HIV were being excluded from the clinical trials, and women with HIV just like men with HIV were dying. The men with HIV were very well organized, and they had a lot of money. The women with HIV, for the most part, were very poor women who were getting contracting HIV through sharing needles and through sexual transmission. There was one group however, that was organized and headed by a very dynamic woman by the name of Terry McGovern -- this was the HIV Law Project -- and they started demanding that there be changes made in getting women into clinical trials. Shortly after I arrived, there was one meeting headed by another great woman, a real pioneer, and she was from the NIH. Her name was Ruth Kirschstein. But together with others from NIH and other Federal agencies including the

Department at HHS we started having meetings about how we were going to get women into clinical trials.

RM: Yes, from the department of HHS. I, of course, was reporting back to David Kessler, and I also worked very closely with Mary Pendergast who was the senior advisor to David. And together, we started to think about what we needed to do at the FDA to change the policy to get more women into clinical trials.

VB: Was there resistance?

RM: Oh yes, there was. You know change is always difficult no matter what it is, and... But I think we tried very hard to be strategic and mindful that bring about major change is not easy… change can be difficult, and you have to have very good reasons for making changes, not just make changes because, well, everybody else is doing it.

So, we organized a committee within the FDA, members from the Center for Drugs, the Center for Devices, and we started meeting with the committee to talk about what we needed to do. We had some outside groups involved as well and decided internally within the agency that we needed to abandon that 1977 policy of women not being able to be in the clinical trials in phase 1 and phase 2. Actually, I don't know if I have all the names of the people that were on the committee. But Bob Temple for example, was involved, very instrumental and made sure

that everything we did was grounded in science, which was one of the three cornerstones of the change we tried to bring about.

VB: I was going to ask --

RM: It was very important that we had the leadership of the Center for Drugs supportive …. we knew that it wasn't going to happen without the leadership of the Center for Drugs being supportive.

VB: It occurs to me that there was another turning point in '91, and I wonder if it had an impact on the agency's thinking about the '77 guidelines, and that was the UAW case against the Johnson Controls which led to the Pregnancy Discrimination Act?

RM: We had a conference, and that case was very important -- we discussed the legal issues and implications of the case a lot in addition to the ethical and the scientific/medical points of view. Those three, it was a triangle -- medical/scientific, legal and ethical -- we detailed these three perspectives in the article that was published in the *New England Journal of Medicine* in 1993. We also discussed these at conferences we had at FDA in conjunction with our sister agencies within HHS --

VB: Pregnancy Discrimination.

RM: The Act as interpreted by the Supreme Court in the *UAW v. Johnson Controls* was very much a factor in convincing everyone that that the restriction at FDA needed to be reconsidered. From a legal point of view, the Supreme Court determined that prohibiting the blanket exclusion of pregnant women from jobs they're qualified to perform solely because working conditions pose a potential risk to exposed fetuses constituted discrimination. Although the purposes of clinical trials are manifestly different from the purposes of employment, the court's emphasis on the woman's right to participate in decisions about fetal risk underscored the principles of autonomy and informed consent. So, it was both the ethics and the legal aspect of the case that were really, really important in the agency's decision to lift that restriction.

VB: So, you brought everybody together at the table and were able to formulate this really strong case for why it was time to reverse that policy?

RM: Right.

VB: Were there any people that needed further convincing that you needed --

RM: The hardest issue was from the scientific point of view. We were asked to provide examples of where the dosing of a drug needs to be different for women than for men based on what pharmacokinetic data, and cases like that were difficult to find. There wasn't very much information. So, I would say that the scientific argument was the hardest one at that point, especially at the agency. When it came to drugs for cardiac disease for example, where is it going to be different from men than it is for women in terms of how much the dose should be or what the effects will be? And those are still some challenges, but nevertheless, I think that when it comes to issues of safety, e.g. describing the side effects, the adverse events that occur with a drug, you must include women, and it's not just women. You need to have people with different phenotypes. That's why the agency now really stresses the importance of not only a balance in terms of sex but also by age and by race and also shy away from weight restrictions. Because there are some phenotypical aspects of race that are going to be important in the metabolism of drugs. And so using the issue of women, making sure that women were in clinical trials really raised the bar overall for representation of groups within the population of volunteers for clinical trials.

This issue is still a challenge the 1993 announcement that we're removing the ban and then came the guidance document was just the beginning…. making sure that when a new drug application is submitted to the agency, that the center that's reviewing that application really does its job in reviewing the data that the sponsor is supposed to submit on how the drug works by sex. And whether there actually have been enough women recruited into the clinical trials in order to have a valid analysis done is another important component. Removing the restriction was very important, and it was the beginning, but it was the beginning of really trying to have full disclosure of how drugs work in men and women as well as in the elderly for example.

Often, there are inclusion-exclusion criteria in the protocols for new drugs that have an age limit so that can make it very difficult sometimes to understand how a drug might work in someone who's elderly whose kidneys may not be functioning as well as someone who's much younger.

VB: Um-hm. In the course of all the discussions that you had that went into revising these guidelines, you mentioned early on that one of the things on your radar was women with HIV and how they were treated in general as men's HIV advocacy groups were really pushing FDA to revise treatment guidelines for investigation of new drugs and innovate new approval pathways and so forth. How do women benefit from this in the late '80s/90s when '77 guidelines excluded most from entering into the early phases of clinical trials?

RM: They didn't benefit initially -- while there was an expedited review of AZT, for example so that they didn't have to complete phase 3 clinical trials before it was approved, there hadn't been women in those AZT trials. For anyone diagnosed with HIV in the 80s, there were no approved therapies for women. If they were diagnosed with HIV, the only outcome would be death. They had no hope because they weren't able to get into any of the clinical trials. Finally, the women actually marched on the FDA. I was in the office when all of a sudden, I heard this noise outside, and I go to the window, and sure enough, they're marching. They were saying things to get them (FDA), to get women into the clinical trials, and it was, "Get the facts, call Ruth Merkatz." I'll never forget it.

We had also had a town hall before that where women with HIV, women activists were so angry and understandably angry at -- and it wasn't just FDA, it was all of us who were

involved in women's health in Washington at the time. I was on the podium; they started throwing rolls of toilet paper. I wasn't angry at them -- I empathized with them, but I was angry at the system. For me, it didn't require that kind of action to make me realize we had to do something because the facts were obvious, but still, it was very dramatic.

VB: Not to shift back and forth in time but when David Kessler asked if you'd be interested in this opportunity, was this on your radar? Did you realize that you were going to be leading the charge to...?

RM: No, absolutely not. I mean, I knew I was going to be involved in breast implants. When I was first invited down to the FDA to interview, I sat in on one early meeting on breast implants. It was a public meeting. I knew that there was a lot going on with HIV and trying to get new drugs approved, but, honestly, I wasn't aware of this whole issue of women in clinical trial., I think that was a reflection on how uninformed I was about how critical the actions of the FDA for women. But I think in general the public is very ill-informed about how drugs come to market. In fact, after I left FDA, I started going around to the different medical and nursing schools in New York talking about how drugs get approved and how we get the drugs, what's important to know about the drugs that we take for granted – that we use. In medical schools, for example, most physicians don't get this in their education. Nurses don't get it. Sometimes, they don't know that they're supposed to report serious adverse events or how to report.

Next week, I'm doing a webinar on the drug development process for family planning fellows. And it's something I want to continue to do because the important elements that go into development of new drugs aren't well known or understood.

VB: Yes, that's great. So, you knew you were going to be working on breast implants, and you had an inkling that there would be women and HIV issues, but what was it that really attracted you to the job? You said it was an amazing opportunity, what did you see in the job?

RM: Before I went into nursing, I was a government major in college, a subject I loved. I thought, "What a great opportunity to really see how the government works firsthand and to do it in relation to health to issues that I had been working on throughout my career; issues such as reproductive health, contraception, pregnancy, well-being, as well as breast and gynecologic cancers. I knew that that was something that would, certainly, be an important component of working on women's health at the FDA since they were in the business of reviewing and approving new methods of contraception whether it was a drug or a device. But I'll be honest; I myself wasn't fully aware of the way clinical trials were structured and their impact for women.

VB: Um-hm. You also mentioned the Physicians' Health Study and how that drew everyone's awareness to this problem and led to the GAO study and other reports. It also shone a light on the lack of data on women and cardiovascular disease. Did you anticipate that fleshing

out a research agenda and contributing to work on women and cardiovascular disease was going to be on your plate when you got to the FDA?

RM: No. I have to say that was not something I had focused on either before I went to the FDA because my career had been focused primarily around reproductive health. I wasn't that involved with the impact of cardiovascular disease for women at that point in my career. But I quickly became very involved with the issue of cardiovascular disease in women and other diseases as well.

I had the very good fortune of interacting with many different consumer advocacy groups at the FDA. For example, I worked closely with the group focused on seizure disorders, epilepsy, the issue of women with epilepsy and whether the drugs to treat epilepsy were being studied in those women. That became a big issue. We had two important conferences on inclusion of women in clinical trials for drugs in development. Women with epilepsy were always there to talk about how they needed to be represented in the clinical trials for drugs for epilepsy, and who would've thought about that? It wasn't just cardiovascular disease where men outnumbered by far the number of participants in the clinical trials, but there were other conditions as well.

VB: So, you had a variety of things and really important issues on your plate in the first two years that you were there. When did the proposal for the FDA to create an Office of Women's Health first come up? How did that idea germinate?

RM: Well, one thing that happened is -- as I think I mentioned -- I was just going to stay for a year when I went down to FDA. I was going to go back to NY with my husband. I remember talking to Dr. Kessler and saying, "A year is just an opener. We've just gotten started. I can't believe how many really important issues there are to focus on." The way I saw it and the way that other people saw it too, there's a little piece here and there were pieces all over the agency, but there wasn't a central focus to try to bring them together in a cohesive manner. I certainly may have mentioned it to Dr. Kessler that I thought an office would be good, but there was also a lot of discussion within the HSS Women's Health Coordinating Committee. They were going to create an Office of Women's Health in HSS. The office at the NIH was leading the pack, but through our coordinating committee I think all of the women's health

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representatives on the coordinating committee from the various DHHS agencies had the same "aha" if you will. In all the like agencies we concluded that we needed an Office of Women's Health to coordinate activities. to prioritize and bring people together to focus on women's issues that were different from men's. There are unique aspects in women's health that have important implications for the work of the agencies whether it was the FDA, CDC, HRSA or the overall HHS department. And so, ultimately, all the agencies created Offices of Women's Health.

But there was also an important group within Congress, the Women's Caucus. They were supportive of an Office of Women's Health. Barbara Mikulski, for example, who was such a champion of women's health, she was very supportive of creating an office of women's health and using Congressional funds. Because the Office of Women's Health at the FDA came

through legislative language -- and I think they were previously appropriated funds -- that they were able to utilize Congressional language to create an Office of Women's Health at the FDA.[1]

VB: So, it was through the budget process?

RM: Yes.

VB: I can't recall, but in the original or subsequent Women's Health Equity Act if there was a call for the creation of Offices of Women's Health?[2]

RM: What year was that?

VB: 1990 was the first one.

[1] The FDA Office of Women's Health was established as a delegation of HHS authority in July 1994 (see *Federal Register*, vol. 59, no. 144 (July 28, 1994): 38482).

[2] The Women's Health Equity Act of 1990 called for the creation of the National Institutes of Health Office of Women's Health Research and the Department of Health and Human Services Office of Women's Health. The bill did not pass, though it was resubmitted multiple times in subsequent Congresses. Many provisions of the Women's Health Equity Act were incorporated into other legislation.

RM: Honestly, I'd have to go back and look that up myself. I'm sorry; (laughter) I don't remember.

VB: I can give myself that homework. So, as the idea started spreading throughout HHS, by 1994, it was a reality at FDA. I suppose you had the hard work to figure out exactly how you're going to set up that office and who you're going to recruit to help you with it. I don't know if you recall how many FTEs you had or --?

RM: I sent you that picture. I think that was the office at the time. We were part of the Office of External Affairs even though the head of the office reported directly to the Commissioner

VB: Was that Sharon Smith Holston at the time?

RM: Yes. Sharon Smith Holston. Before that, Carol Scheman was in that post. Carol was there when I came down to the FDA and then when she left, Sharon Smith Holston stepped in.

VB: So, since you were under the Associate Commissioner for External Affairs, were you -- was your first title director, and then the associate commissioner came later or did -- as the office was created?

RM: I was never Associate Commissioner.

VB: Always Director?

RM: Yes…reporting directly to the commissioner but also working with the Office of External Affairs but reporting directly to the Commissioner.

VB: Okay. So, did you have ideal staff in mind who you wanted to recruit or...?

RM: You know, I had some people who started working with me before there was an office and I worked collaboratively with different folks across the council. I worked closely with Mary Pendergast, for example, and with the Office of Constituent Health Affairs, e.g. with Grant Bagley, Stuart Nightingale. Bruce Burlington was from CDRH. Linda Carter was there, [I believe] she was from the Office of New Drugs. Mary Gross who was my right hand, and I brought her into the office right away. She was so great organizing all these different conferences. We had Jane Henney who was Deputy Commissioner for Operations. Catherine Lorraine who was in the Office of the Commissioner (Office of Policy). Dianne Murphy from CDER, Terry Toigo from the Office of Special Health Issues, Carl Peck and Roger Williams, both from CDER and both recognized the importance of analyzing data for women and men.

VB: Yes.

RM: Elyse Summers, who then joined the OWH and was terrific. She had forward looking ideas and was smart, organized (we later wrote a chapter together for a nursing textbook on the drug development and regulations). Mike Taylor, in the Office of the Commissioner and -- worked closely with David Kessler. He was supportive of an Office of Women's Health. I also worked closely with Terry Toigo, the head of the Office of AIDS and Special Health Issues. especially around the issue of women with HIV and clinical trials.

VB: She briefly was acting director of OWH later on, after Susan Wood left.

RM: And there was Janet Woodcock from CDER and Nancy Yeates from the Office of the Commissioner (Office of Policy). Creating this working group was my way of making this change come about because I knew it wasn't going to be easy. We had to demonstrate the scientific necessity of including women in clinical trials. This was essential for gaining support from Bob Temple and other physicians and scientists in CDER.

VB: Was it hard to convince him?

RM: Oh. (laughs) But, he was the smartest, one of the smartest people I ever knew and great to work with.

VB: And if you could convince him, then he could convince everybody else for you. (laughs)

RM: Exactly, right.

VB: And you obviously did. I mean the transcript for the conference on Gender Studies in Product Development, he comes out swinging, you know?

RM: Yes. I mean I love working with someone who'll give you a very tough argument. He'll make you hone your own argument and make a solid case, and that's exactly what he did. He was terrific, one of the smartest people I've ever known. I have a great deal of respect for Bob.

VB: You said you brought Mary and Elyse into the office. Audrey Sheppard came on pretty early.

RM: Audrey came through Bill Clinton's office. She had great ideas, and started talking about working with consumers and ultimately created the Take Time to Care program that continues through today. Important initiative

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RM: But, as we organized with our small staff, I focused on the issue that brought us to the creation of the Office of Women's Health, the issue of women in clinical trials that appeared in the *New England Journal of Medicine* in 1993 and foreshadowed the Office of Women's Health, what it would be responsible for and what it would do. At the very end of the article, I wrote a short paragraph on testing drugs on pregnant women. And one of the first things I was able to do was to have this conference on drugs in pregnancy.

VB: Which is about four months after November 1994. It was just very shortly after you officially opened the office.

VB: So, was Marietta Anthony already in your office?

RM: Yes. I recruited Marietta who was a clear and focused thinker.

VB: Was Rachel Berman in your office?

RM: No. Rachel worked in CDER. But she was on the Clinical Trials in Women Committee and always brought a clear approach to the issues we were grappling with.

VB: You did a lot of speaking in your new role, didn't you? You had to go all over the place.

RM: I did a lot of speaking because I felt that it was really important to shed light on what had been a silent issue for very long. And the fact that I didn't even know about it and physicians didn't know about it, nurses didn't know about it -- nobody knew about it… it was a well-kept secret that women weren't being included in clinical trials to the extent men were and in the early phases of drug development when you learn so much about safety, efficacy, pharmacokinetics and dosing. Nobody knew about it. And so I traveled and tried to spread the message about why it was so important to include women in all phases of clinical trials. Perhaps one of my most important outreach events was when I gave the keynote address to the Menopause Society. I remember the audience, medical leaders in the care of women, being astonished to learn that women weren't included in the early phases of clinical trials and even for Phase 3 trials that their numbers were not commensurate with the incidence of certain diseases in women, e.g. CVD.

VB: And you got a lot of press coverage too. I mean, if you just do like a random search for your name in newspapers --

RM: Oh, really? I guess I didn't pay that much attention to the press coverage

VB: Yeah. It was really effective.

RM: Here is one conference that I organized, and when I looked at it over the weekend, because I was still trying to find stuff for you, this I actually did with my husband.

VB: What jumps out at me is this is '93, and the title is Women's Health Across the Lifespan. So, the idea from the beginning was that you had to have as representative a group of women as possible, right?

RM: And that women are different from men in all stages of their life, different physiologically in several important ways including the way they manifest their diseases and which diseases are really important for them -- that wasn't talked about either. It wasn't just that women weren't in the clinical trials. It was an important fact, for example that heart disease is the no. 1 killer of women, that depression is a woman's disease in many cases, and the issue of our bones, how they are affected.

VB: Nutrition?

RM: Not talked about very much either and yet an important part of the women's health movement.

VB: One of my core questions in this process and as someone who is involved in women's health work from very early on, we had a really powerful movement for women's health. It started in the late '60s, early '70s, and it took at least 20 years, 25 years to get that knowledge and that experience and that force to protect women's health inside the federal government. And pinning down the contingencies and the turning points and how that happened I think is really important. For instance, with clinical trials, there is a conference. I think it came out of the Office of the Assistant Secretary for Health in 1985. I think you mentioned it earlier, right?

RM: Yeah.

VB: And subsequent to that, NIH started on a policy level encouraging, even requiring the involvement of more women in clinical trials, but it wasn't enough, right?

RM: It needed bold action to make it happen.

VB: To make it happen. And it seems like one of those factors was having women in Congress that insisted on change?

RM: The Women's Caucus was very important, very important and people like Barbara Mikulski, Pat Schroder from Colorado, Nita Lowey from NY.

VB: And having people in government. Certainly, your role as a special advisor was a critical turning point that allowed that to grow into an Office of Women's Health having connections throughout all of the HHS offices, right?

RM: Yes. Actually, the infrastructure almost was there to bring people together. There were meetings that had started to try and figure out how they could make more happen. So, that it was the right time and I think the breast implant issue that exploded soon after I arrived at the FDA brought women's health into focus. It also raised the bar in terms of how vocal women could be.

The other issue that was going on was the breast cancer movement, and that was strong. I have some great slides; I don't know if I could still find them. But breast cancer awareness was another thing that was happening in the '90s. There were different marches and organizations and they helped to bring into focus issues of quality related to mammography. And ultimately

that led to the Mammography Quality Standards Act championed by Senators Barbara A. Mikulski and Ted Kennedy who co-sponsored the bill. It was alarming to learn how many mammography centers around the country were operating without tight standards or oversight and as a result women were not always diagnosed early in their disease. The mammography centers didn't have rigorous standards that they had to comply with.

VB: And patients didn't have any way of knowing what standards they should be looking for or how to judge the quality of the facility.

RM: Do you know how exciting and important it was to see that every center had to have a little -- like a degree on the wall for women to see that they had met the Mammography Quality Standards Act?

VB: Um-hm. So, one of the things -- and I'm pretty sure this came out of your office, I don't know what year it was, but the hotline that women could call to find out about screening mammography facilities.

RM: That was out of CDRH.

VB: That was CDRH?

RM: Yes. But our office collaborated with CDRH – they were terrific to work with, e.g. Lillian Yen, Florence Hou. Our office worked closed with CDRH who implemented the hot line.it was something we recommended, but we didn't have the funds to do that. I had a very small budget when we started and used those funds to encourage research.

VB: So, research in women's health was the goal from the beginning, right?

RM: Oh, right. I should have this written down somewhere. I don't know recall exactly what my first budget was, but it was small, and we used it for to fund research focused on sex-specific medicine.

VB: Did you have particular projects that you were hoping people would pitch?

RM: Well, certainly, on better ways to get women into clinical trials and get statistically robust data. If you had very small numbers of women compared to men, what was the best way to analyze the data, so it would be valid? That was my statistics background coming into play because I knew that you couldn't just enroll women without first thinking through a statical analysis plan. If they were going to enroll these women, you wanted the data to be usable. Tracking, keeping close tabs on tracking, how we were doing with getting women into the

clinical trials for the new drug applications that were coming in. This was such a key issue. Then we were also grappling with the issue of women and HIV.

VB: And the concerns in the 1990s about HRT and also about ovarian cancer --

RM: And the Women's Health Initiative, the very big study that the NIH was about to undertake?

VB: Yes.

RM: One of the first tasks that David Kessler gave me was to work with the Reproductive Drugs Division that, at the time, was headed by a fellow named Sol Sobel who's the loveliest gentleman. Oh, he was so kind and nice, and he had a crackerjack exec sec by the name of Phil Korfman. He passed away last year – what a wonderful guy. So, one of the first tasks that David gave me was to help them fill the vacancies for the reproductive health advisory committee. This was tricky because David had been appointed under the Bush administration. When I first joined FDA in '91, George Bush Sr. was the president, so it was a Republican administration, abortion was a controversial issue. So, they needed to have committee members that were not abortion providers or abortion activists. One of the first things I did was to help populate that advisory committee because I knew a lot of the ob-gyns through my husband. I think my husband knew just about every academic ob-gyn in the country. Through that work to

organize the advisory committee I became a close partner with the Division of Reproductive Health Drugs, which turned out to be very important. They were staunch allies, great supporters, and terrific to work with. And with that division there never was a dull day. There were some other things going on within that division during my time, including changing the label on oral contraceptives. It used to be that you had to have a physical exam in order to get a prescription for an oral contraception. We got rid of that. Then, we had the Norplant issue. At that time, there were all these disasters with Norplant (a subcutaneous contraceptive patch) because physicians hadn't been trained on how to remove the rods. They only knew how to put them in; they didn't know how to remove them.

It's ironic too because Norplant was developed by the Population Council, which is dedicated to research and development. We license products we develop to companies, and whatever we get back in royalties goes back into our research. So, we just had a new contraceptive approved last year that I was very involved in. I ran all the phase 3 trials for a new contraceptive. It was hard work, but always interesting and exciting.

VB: What was it?

RM: It's called Annovera™. It's a contraceptive vaginal ring or system and one ring is good for one year.

VB: Wow. That's a game changer.

RM: It's a game changer, exactly. That's what the USAID said and why they funded us to do this work. So, we were funded by USAID, NIH, World Health Organization to do all the work.

VB: Did you work at all with Population Council when you were at FDA? When was it the founded?

RM: In the Fifties. It has a great history. I didn't know that eventually I would come to work at the Pop Council and was only indirectly involved with the Council [while I was at the FDA. Mary Pendergast and Donna Shalala came to the Population Council and asked them to conduct the clinical trials in RU-486, which they did.

VB: And am I correct in saying this, the Population Council has the patent for RU-486, no?

RM: No. It was owned by Roussel-Uclaf, but we ran the clinical trials under the request of the FDA. Can you imagine the FDA now doing something like that?

VB: No.

RM: It was really a revolutionary decade in the ’90s. We knew RU-486 was going to be very important especially in states were surgical abortions are not permitted. And if they overturn *Roe v. Wade*, it’s going to be really important. What’s interesting if you look through the panels in this program [referring to conference program], these are the topics that I thought were important to discuss. This is in 1994. It includes a panel on RU-486.

VB: So, I had asked you if research was part -- was on your agenda from the beginning with the Office of Women’s Health, what about outreach? Did you envision that it’s always going to be part of the mission of the Office of Women’s Health?

RM: Yes. And that was part of the way the mission was written from the very beginning. But at that time, the Office of Consumer Affairs was very much in existence, so we had to tread lightly on how much we did versus what the Office of Consumer Affairs did. But Audrey brought in this other way of positioning it with the Take Time to Care program and that was a great success.

VB: In fact, it was a great tactic for getting information to women and for appealing to their role as caretakers. And it’s grown so much over time. So, I guess in that sense, you were blessed with a very active community?

RM: Everyone was so happy to be able to focus on this because everyone in the office was a "feminist" and a woman's health activist but also totally focused on making sure that science and ethics were at the heart of everything that we did. Elyse Summers went on to lead the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP), one of the key groups that reviews IRBs. I was blessed with very capable people.

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VB: So, when OWH came into existence, you had already been working with different people throughout the agency on so many different issues. How did the rest of the agency perceive the Office of Women's Health? Did they know how to interface with it?

RM: I think there are always going to be the supporters and the naysayers and people who were a little reluctant to change. We had a retreat actually to iron out the development of an Office of Women's Health.

VB: With just the office or other agency leadership, as well?

RM: No. Leadership within the agency. We had a retreat on opening up an office.

VB: How did that go?

RM: Well, I think, for the most part, it was fine. There were a few people who were skeptical I remember one comment was made that, "Well, these issues are very important, but they probably can be ironed out and then the office will sunset." I think that's in the transcript somewhere because I heard from Marsha Henderson that she read about that somewhere.

VB: She told me that too.

RM: I still remember, that at the outset several thought the office could sunset.

VB: That it would deal with the clinical trials' guidelines and then it would serve its purpose?

RM: Fulfill its mission and that would be the end of it.

VB: Lucky for us that it wasn't.

RM: And I think that there are still some of that from what I hear in talking to different people occasionally that it may still be an issue.

VB: I'm sure there's always tension over who should play what role and how to share power. But I think there are a lot of things OWH has done that are genuinely appreciated. But one thing that I don't think was originally part of the vision is to provide training to the other centers on how to view approvals or policymaking through the women's health lens. I think there's a lot of recognized added value in that.

RM: We actually started going around to the different divisions to talk about the issue of analyzing data for women and making sure that women were in the clinical trials. I remember I personally went around and sometimes got darts thrown at me. There were a couple of divisions that were tough in that regard. Others were very open and easy to work; others were tough, but that was OK. It made me, it made us as an office realize how important it was to have the science behind us every step of the way and to make improvement is science the underpinnings of everything we did.

VB: Was CDRH enthusiastic about the partnership with OWH?

RM: CDRH was very good to work with.

VB: They had a lot of really hard issues to deal with in that time period. I would imagine they would've been grateful for support on women's health issues.

RM: Well, they had breast implants.

VB: Yeah, and they still do.

RM: And that was just really tough.

[Referring to conference program] We organized this Gender Effects on Product Development conference -- this was a very, very important program. There was a meeting 10 years later to talk about issues of drugs in pregnancy. Sandra Kweder gave opening remarks, and in those opening remarks, she refers to this conference. There were sessions on study design and analysis, hormonal influences on metabolism, bioequivalence trials.

VB: Why does it resonate for you as such an important conference?

RM: Because the issue of drugs on pregnant women is still not resolved. It took them more than 20 years to make any changes to the way drugs are categorized in pregnancies -- the A, B, C, D.

VB: And in the 2000s OWH started working on -- maybe you were working on it before then just the internet hadn't become fully useful yet -- were the pregnancy registries.

RM: We had some pregnancy registries. That was just beginning. In fact, after I left FDA and went to work for Pfizer, we started a pregnancy registry for sertraline (ZOLOFT). But, yes, it was in its infancy at that point.

VB: Was that something that came out of this conference?

RM: The registries? I can't remember. Recommendations, yes. [Esther Rome was a staunch advocate and actively supportive our work to change pregnancy labeling in favor of more information about what we did and didn't know about how drugs work in pregnancy. There was so little research with pregnant women, an area in great need of research and data. Vivian Pinn.

VB: Susan Wood was involved in this conference too. It says '94. I think she was still on the Hill at that point.

RM: She was on the Hill. She ran the Women's Caucus on the Hill. That's how I came to know Susan because I testified on the hill about eight times, including several testimonies to the Women's Caucus.

VB: In four years? That's a lot.

RM: And, of course, clinical trials is one of the topics that we would have been speaking about. I have on my CV the topics that I testified about on the Hill.

In 1994 I led OWH's early efforts to examine emergency off-label use of oral contraceptives, which ended up as Plan B. No pharmaceutical company would come forward to submit and application. Usually, a pharmaceutical company is dying to get their drug approved. Not in this case, so Mary Pendergast and I went out and actively sought applications.

VB: What do you attribute all the resistance to?

RM: Plan B? It's the whole issue of likening it to abortion.

VB: One thing I find so peculiar about the Plan B controversy is when the prescription NDA was originally approved, it didn't -- not to say it wasn't controversial, but it did not draw the same level of scrutiny as the OTC application. Do you have any insight into why?

RM: I think timing was an issue and the political environment. It was during the time that Clinton was in office.

VB: The OTC was 2005, so it was under Bush II. And the prescription approval I think was '98 or '99, late '90s, so it was under the Bill Clinton era.

RM: [Referring to pamphlet] "FDA: Making a Difference in Women's Health," I don't know what year this is. July 1994.

VB: Can I share something with you? I don't know if you have this in here. This is the *FDA Consumer* article from the fall of 1994 that discusses cardiovascular disease and the sex differences.

RM: Marianne Legato? I worked with Marianne. And Nanette Wenger. We had all these bright, talented women involved in the work we were doing and involved in publishing the special edition of *FDA Consumer* on this topic.

So, when I went to Pfizer -- and I didn't have to do marketing of a drugs -- they gave me a budget to promote women's health, which was great. And consistent with Pfizer's product portfolio the first thing I focused on was cardiovascular disease, the number one killer of women but little talked about (Pfizer had NORVASC and then they acquired LIPITOR). We also focused on mental health and depression (Pfizer had ZOLOFT) . and then arthritis -- all major medical challenges for women. So, I focused on serious diseases that affect women, which Pfizer was proud to promote… we developed educational materials for women and their health care providers that could be distributed nationally.

VB: Did you draw on your experience at FDA when you moved to Pfizer or any point since?

RM: Absolutely. Pfizer didn't really understand what women's health was. Like so many, they, too, thought women's health was reproductive health. They were not into contraception or any of those therapeutic areas at the time. So, I said, "think about heart disease and think about your number one product in Pfizer, NORVASC." so, they loved it and we developed all these educational materials for the health care providers and for their patients that the reps could take into doctors' offices. It was a real win-win for them and an effective way to get health information to women.

And then I partnered with WomenHeart, the first advocacy organization on heart disease in women, and we started "Heart Parties" in which we partnered with communities to raise awareness of heart disease in women. There would be a race and or a walk, and there would be a party afterward; we did it in Dallas, Boston, and then in Wisconsin, and everyone loved it

VB: And that was in the ’90s?

RM: That was after I went to Pfizer in 1997. I was at Pfizer from ’97 to 2005 and we had the heart parties somewhere in that timeframe.

VB: Did you work on anything between FDA and Pfizer?

RM: No, I left the end of 1996. I still remember leaving because my husband was not well. He was diagnosed with cancer, was receiving chemotherapy and I couldn’t continue commuting. When I started at FDA in September of ’91, my husband was also in Washington doing a Sabbatical as a Robert Wood Johnson health policy scholar. But he had to return to his work at Einstein Medical School by December of ’92, so by 1996 I had been commuting five years. It was hard for him to be alone when he was ill (our kids were out of the house by that time).

VB: And he was teaching?

RM: Yes, he was still doing his job. He never lost a day of work even though he was receiving chemo.

VB: He's the kind of person that thrives on his work?

RM: Yes.

VB: So, you left FDA in late '96. And Audrey was your deputy, I guess, at that point?

RM: Right.

VB: Where did you leave things, and what were you hoping for the office when you left?

RM: Well, I certainly hoped that they would continue the work on clinical trials. We needed to have a final regulation on the inclusion of women, which came out in '98 as part of the Food and Drug Administration Modernization Act. I had worked with Bob Temple on writing that. We laid the groundwork for focusing on clinical trials. And I was hopeful that office could continue to collaborate with other offices and Centers and focus on breast implants, contraception, and HIV.

VB: I recall that in 1993, before OWH was founded, you helped change the labeling on contraceptives to include the STD disclaimer.

RM: Based on my clinical nursing experience, I realized that many women and their partners were unclear about how various contraceptives worked and the protection they provided. We conducted a small study on what women thought about their contraceptives; many thought contraceptives like oral contraceptives protected them against STDs.

VB: Oh, that's scary.

RM: There was no controversy about that change, no one in the agency opposed it]. Working with them made the change. That was the advantage of the old Parklawn Building, I think. It was very "heimish" if you will. My office was just around the corner to the Division of Reproductive Health Drugs. We were in each other's offices all the time and had a very collegial relationship. It was easy to collaborate and come up with new ideas.

[01:00:00]

RM: With this idea, we just made it happen.

VB: There was so much advocacy work around condom use in the early ’90s. Do you think that partly led to the misconception, that if you use any birth control it would protect you against STDs?

RM: Yes. But we just wanted to make sure that people didn’t think that if they took a pill, they were going to also be protected against HIV or other STDs. We had a collection of all these novelty condoms. We had collected hundreds of condoms in the office -- they were unbelievable, but women were using them, not realizing that many of them didn’t provide any protection.

VB: Oh, that’s terrible.

VB: While you were at the FDA, did you miss interacting with patients?

RM: I did, and maybe that’s why I worked closely with the various consumer groups. But, you know, I had worked with patients my whole career, so it was okay. This was so exciting to me to really learn firsthand how governmental checks and balances really work. I mean there were always things going on, you had to be careful that you didn’t get lost in the fray. Another big thing I was involved in was starting a group with Randy Wykoff, who was the Director of the AIDS Coordination Staff. We wanted to look at whether or not spermicides might protect against HIV, and we were particularly interested in nonoxynol-9. So, we had this task force

comprised of people from the FDA and NIH. I remember being on vacation and taking some calls when that task force was holding meetings. And that led to the study of nonoxynol-9 (conducted by Carol Trapnell at Johns Hopkins) and whether or not it provided any protection, and what they found, of course, is that not only did it not provide protection but it was a risk for transmission of HIV.

VB: I didn't realize that. Why does it increase risk?

RM: It can create some small abrasions of the epithelium of the vagina, which is a portal of entry for the virus. And because we knew then that we needed to develop a spermicide or something that could protect women from HIV transmission in addition to condom use. While effective its use is sporadic.

In fact, one of the major areas of focus of work at the Population Council when I joined that organization in 2005 was microbicides, which is still going on. When I started working at the Population Council, they were conducting a phase 3 trial in South Africa with carrageenan (Carraguard) to protect against vaginal transmission. It was not successful; it didn't show efficacy, but part of the problem with the method was that not all women in the trial used the product despite claiming they had. Adherence in clinical trials continues to be a huge issue and is an area that I have continued to work on with clinical and social science colleagues.

VB: I'm just curious. You mentioned the folic acid research?

RM: Yes.

VB: That is one particularly interesting area where foods and drugs have this sort of murky, shared territory. And I noticed that one of the first studies you funded out of the Office of Women's Health had looked at listeriosis.

RM: But it had to do with pregnancy, and pregnancy was always something I always focused on based on my clinical nursing experience. Which is why I think I wanted to do this conference so early on the issue of drugs in pregnancy. But listeriosis -- especially with immigrant populations -- was an issue and that's why we funded research on it.

VB: So, I was saying before, what were your hopes for the Office of Women's Health when you departed. And you said certainly that they continue the work with clinical trials. Was there anything else?

RM: To continue to work across the centers. Because there are always going to be issues in the centers that have a women's health focus whether it's reviewing a new device for contraception, certainly the breast implants or devices for any part of the body where there are anatomical differences, even in size, musculature. Devices have a lot of issues, all of the various

types of equipment that are used for men and women, which traditionally have been tested primarily in men.

I'll just give you an example, and this wasn't at the time that I was there but... In 2009, my mother who was quite elderly at the time was diagnosed with lung cancer out of the blue. We thought she had bad kidney disease, which she did. But she was having some trouble breathing, and I had to race her to the hospital. They tapped her chest, and she was filled with fluid and when they analyzed the fluid, it was lung cancer. So, they had to put in a chest tube, and I remember they had to go in twice. The chest tubes that they had were so long and so big, and my mother was very thin. They had to keep cutting her chest tubes. They didn't have a chest tube for her body build because the chest tubes were all built for men. Something as simple as that, and this is a CDRH issue. So, just like the drugs weren't being tested in women, the devices weren't being tested in women. For me that experience watching my mother hit home to me more than anything else, why drugs, devices, biologics must all be tested with women as well as with men.

VB: I can't remember the year that OWH funded research on customizing artificial heart valve development for women.

RM: Yeah, I can't remember that either but that was --.

VB: Obviously a long time coming.

RM: So, that's why in the Office of Women's Health, not that the centers can't do it but the centers may not be focused on it. It's not only doing it, it's focusing around the doing, what needs to happen, including, how to get the message out to the various constituents.

VB: The agency, I think, is pretty good about being consistent in consumer messages, but if you have information for an entire group of constituents that spans different product areas, it does make sense to have one place --

RM: Right.

VB: -- especially if they're half the population. But I do also see the value in having advisors on women's health in the centers as well as a complement to that.

RM: Yes, absolutely. And maybe they'll feel more comfortable with an in-house group as opposed to going to the Office of the Commissioner.

VB: Yes, it's more direct, it's more -- informal perhaps isn't the right word, but also constant, right?

RM: Constant.

VB: Instead of just we have to have a special meeting or -- and then we can't just walk down the hall --

RM: I harken back to the relationship I had with the reproductive division in the Center for Drugs before we had an Office of Women's Health where we were neighbors, and we were constantly talking to each other. And so there was a lot that we were able to do together because of that.

VB: Yeah. That creates opportunities that you just wouldn't have otherwise.

So, since leaving FDA, have you followed the Office of Women's Health?

RM: Yes. I've kept in touch with all the subsequent directors. We have our own little network between Audrey and Susan and Marsha Henderson.

VB: Do you have any wishes for the Office of Women's Health now 25 years down the line?

RM: There are still some of the same issues today that we confronted back then. Look at breast implants for example and this finding about the lymphoma. By the way, this -- I don't know if you ever saw these. I wrote two papers based on letters that we received from consumers about their breast implants. This was published in 1993. I was busy. We took the letters, and together with Jane McCarthy and Grant Bagley from the Office of Constituent Health Affairs we published two papers, "A Qualitative Analysis of Self-Reported Experiences among Women Encountering Difficulties with their [*sic*] Implants," and "A Descriptive Analysis of Physical Complaints from Women with Silicone Breast Implants." We had received thousands of letters, at the Agency about breast implants from both satisfied women and dissatisfied women also wrote letters. Some of them also testified at FDA advisory committee hearings. We did a qualitative review of those letters and published the findings.

VB: I imagine that there was a much higher volume of patient contact with the FDA about ruptured implants or about the controversy about the implants than many other products.

RM: Yeah, because it got so much press.

VB: And it becomes such an emotional issue for women -- for some women who view it as such an important part of their recovery and for others who view it as a very dangerous practice that shouldn't be permitted, and nevertheless so intimate that it's just difficult to talk about. From the professional community, did you get a response about these kinds of publications?

RM: Oh yes. There were pros and cons from the professional community as well.

VB: I suppose that's to be expected. Well, in closing, is there anything from this time that when you think back about it, that really stands out, any things you're particularly proud of or things that you wish you could've done that there just wasn't time for or opportunity for?

RM: Well, I have to say, overall, I was very, very grateful for the opportunity… it was a once-in-a-lifetime opportunity. Maybe it was a sign of the times. We were able to, I think, accomplish quite a bit. It's never enough in terms of what more we could've done. The fact that we didn't really deal with the issue of drugs in pregnancy, but there are so many ethical questions associated with testing drugs in pregnancy. We had a task force with the NICHD that looked at the whole issue of informed consent for doing clinical trials in pregnant women. Who signs the informed consent? The mother? The mother and father? What do you do if there's no involved father?

So, I would say that I'm grateful for the things that we were able to accomplish, but it was just like opening the door and tiptoeing. I'm also grateful that the agency is continuing, to focus attention on the issues that are unique to women. But as with everything else, it is tied up with politics and we don't always have control over that. But I hope that the advocacy community remains strong and is always there backing the OWH but looking critically at what it is or is not doing. And, certainly, whatever I was able to do, it was not me alone. It was

wonderful support and guidance from colleagues like Mary Pendergast, and David Kessler was terrific. He pushed me but in the right direction. He had good instincts about what was right at that particular time.

VB: And of all of the accomplishments under his time as commissioner, the Office of Women's Health have lasted and grown and is now congressionally mandated --

VB: Well, I could keep talking to you all afternoon, but I know you have other things to do. So, thank you so much.

RM: I hope it was helpful.

VB: It's very helpful and a really important history that I'm really glad we were able to capture.

END OF INTERVIEW

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Rye, New York 10580
phone 917-670-5784 (mobile)
e-mail: rmerkatz@popcouncil.org; rmerkatz@gmail.com

EDUCATION	**DEGREE/YEAR**
Cornell University, Ithaca, NY Cornell University—The New York Hospital School of Nursing New York, NY	BS, RN - 1961
Frances Payne Bolton School of Nursing, Case Western Reserve University Cleveland, Ohio	MS - 1977
Adelphi University, School of Nursing Garden City, Long Island, NY	PhD - 1989

PROFESSIONAL EMPLOYMENT

Surgical Staff Nurse The New York Hospital, New York, NY	1961 – 1962 1965 - 1966
Camp Nurse Camp HES, Bear Mountain, New York	1966
Nurse Instructor The New York Hospital, Lying-In Division, New York, NY	1966 - 1970
Clinical Nurse Specialist (Maternal/Child Health) (Clinical Care & Staff Education/Parent Education &Counseling; The New York Hospital, Lying-In Division, New York, NY	1970 - 1973
Nurse Clinician	1976 - 1982
Postpartum Nursing; University Hospitals of Cleveland MacDonald House, Cleveland, Ohio	
Assistant Director of Nursing: Nurse Clinician-Maternal/Child & &Women's Health/Nurse Researcher The Jack D. Weiler Hospital of the AECOM: MMC Albert Einstein College of Medicine	1982 - 1990
Director of Nursing (Acting) The Jack D. Weiler Hospital of the Albert Einstein College of Medicine/ Montefiore Medical Center (MMC), New York, NY	1990 – 1991
Special Assistant to the Commissioner: Women's Health Issues	1991 – 1994

U.S. Food and Drug Administration—Department of
Health and Human Services, Washington, DC

Director, Office of Women's Health 1994 - 1996
U.S. Food and Drug Administration—Department of
Health and Human Services, Washington, DC
(Established the Office & Mission- ongoing today)*

Director/Team Leader, Pfizer Women's Health; 1997 – 2005
Pfizer Pharmaceuticals Group, Pfizer Inc, New York, NY

Project Director, Contraceptive Development, Population Council 2005 - 2007

Director, Clinical Development, Reproductive Health 2007 - Present
Population Council

ACADEMIC APPOINTMENTS

Clinical Instructor 1976 - 1979
Maternity Nursing-University Hospitals of Cleveland
Frances Payne Bolton School of Nursing, Case Western Reserve University

Assistant Clinical Professor 1979 - 1983
Frances Payne Bolton School of Nursing
Case Western Reserve University, Cleveland, Ohio

Adjunct Lecturer 1982 - 1986
Lehman College of the City University of New York

Clinical Assistant Professor 1989 - 1995
Department of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine

Clinical Associate Professor 1995 - Present
Department of Obstetrics & Gynecology and Women's Health
Department of Epidemiology and Social Medicine
Albert Einstein College of Medicine

Adjunct Professor, Division of Nursing 1997 - 2000
New York University

Clinical Professor 2015-Present
Department of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine

POLITICAL APPOINTMENTS 2001 - Present
Westchester County Board of Health

PROFESSIONAL SOCIETY MEMBERSHIPS (Current)
American Academy of Nursing

American Nurses Association (New York State Chapter)
Association of Women's Health, Obstetric, and Neonatal Nurses
Association of Reproductive Health Professionals
Sigma Theta Tau (Alpha Upsilon Chapter)

LICENSURE

New York Nursing Registration ID # 157030-1 Current
Ohio Nursing Registration ID # 21-13-4921
Washington, DC License ID # 58611

DISTINCTIONS

Sigma Theta Tau 1965
National Nursing Honorary Society

Helen Bunge Award for Nursing Research: 1977
Frances Payne Bolton School of Nursing
Case Western Reserve University

Award for Excellence in Nursing: 1977
Frances Payne Bolton School of Nursing
Case Western Reserve University

Certificate of Recognition for Contributions to the Community: 1982
Federation for Community Planning, Cleveland, Ohio

Bolton Award for the Professional Member Making an
Outstanding Contribution to the Community: 1982
Junior League of Cleveland, Ohio

FDA Commissioner's Special Citation for Contributions to the May, 1992
Scientific and Policy Issues Associated with Breast Implants

FDA Commissioner's Special Citation for Exceptional Skill and May, 1993
Commitment in Successfully Changing FDA Policy to Allow Women
of Childbearing Potential to Participate in Early Phase Drug Trials

Distinguished Alumnus Award: May, 1994
Cornell University-The New York Hospital School of Nursing

FDA Commissioner’s Special Group Citation May, 1995
for Outstanding Service to the National AIDS Drug
Development Task Force

FDA Commissioner’s Special Group Citation for
Establishing the Mammography Information Service
May, 1995

Fellow of the American Academy of Nursing November, 1995

FDA Commissioner's Special Citation for Outstanding December, 1995

Leadership and Vision in Establishing the Office of Women's Health

Distinguished Alumnus Award — May, 1996
Adelphi University; School of Nursing

FDA Commissioner's Special Citation for — January, 1997
Outstanding Contributions to the Women's Health
Program of the FDA

Athena Award — February, 1999
Partnership for Women's Health
Columbia University

Honoree, International Health Awareness Network — March, 1999

Career Achievement Award: Assoc of Women's Health, Obstetrics — June, 2002
& Neonatal Nursing

Best in Class, Top Scientific Research - Internationals Family Planning Research
Conference, International Conference on Family Planning, — November 15, 2013
Addis Ababa, Ethiopia; Sponsored by B & M Gates Foundation & Johns Hopkins
University School of Public Health

Case Western Reserve Univ. Graduation Speaker- Frances Payne Bolton School
of Nursing — December 5, 2014

RESEARCH/GRANT SUPPORT

Long-term Follow-up of High Risk Mothers, Infants and Families. — 1978 – 1981
The Robert Wood Johnson Foundation

The Effects of Frequency and Duration of Early Breast-Feeding on — 1980 - 1983
Development of Nipple Soreness, Milk Output, Infant Serum Bilirubin,
and Infant Well-Being on the Longevity of Nursing.
University Hospitals of Cleveland Fund

Doctoral Dissertation: The Influence of Maternal Attachment and the — 1989
Capacity for Empathy on Perception of Social Support among Pregnant
Minority Women.
Grant Support - Sigma Theta Tau

Co- Principal Investigator & Technical Coordinator:
Development of a new contraceptive vaginal ring with Nestorone® &
Ethinyl estradiol (Phase 3 trial) USAID Cooperative Agreement;
PO-A-00-04-00019- Population Council Product Development;
9/05 – 6/31/09
7/09-6/14

Acceptability of a Contraceptive Vaginal Ring: Supplementary study within
RO1 project **3RO1HD047764-02S2,** Assessing & Improving the Measurement

of Sexual Behavior; NIH/NICHD. Co-Investigator 9/05– 5/12

Co-Principle Investigator: Delivering Contraceptive Vaginal Rings: Annual Program Statement No. SOL-OAA-13-000024: Agreement No. USAID-0AA-A-13-00075 Family Planning & Reproductive Health to Address Unmet Need 10/13-9/18

ADDITIONAL CERTIFICATION

American Society for Psychoprophylaxis in Obstetrics 1969 - 1991
New York, NY

The National Certification Board of Diabetes Educators 1986 – 2000
Certified Diabetes Educator (CDE)

BOARD AFFILIATIONS

The National Certification Board of Diabetes Educators 1986 – 2000
Certified Diabetes Educator (CDE)

President's Council of Cornell Women- Cornell University 1995 – Present

Friends of the Institute of Nursing Research 1999 - 2005

Jacobs Institute of Women's Health 1999 – 2005

Westchester County Board of Health 2002- Present

New York Hall of Science 2004 – 2007

Scientific Advisory Committee- International Partnership for 2006- Present

Rosalind Franklin Society, Founding Board Member 2007- Present

International Partnership for Microbicides (IPM) Scientific Advisory Board 2009-Present
Chair- IPM/USAID Project Advisory Committee (PAC) 2014- Present

PROFESSIONAL & COMMUNITY ACTIVITIES AND AFFILIATIONS

Editor, Cornell Alumni News (School of Nursing) 1965 – 1968

Member, New York State Democratic Party 1965 – 1973
1992- Present

Committee to Recreate St. Catherine's Park, 1968 - 1973
NYC Steering and Planning Committee

Chairperson, Women's Program, American Congress on 1971
Fertility and Sterility, New York City

New York Junior League 1973

Cleveland Junior League	1973 - 1982
Western Reserve Historical Society, Docent	1973 - 1974
"Friends to New Mothers"; Proposer and Advisor to new program for Maternal and Infant Care Project of Cleveland	1974 - 1976
Mercer School Parent Teachers Association; Parent Aide Shaker Heights, Ohio	1976 - 1978
Editorial Advisory Board, The Female Patient.	1976 - 1978
Chairperson, Committee for Early Detection and Prevention of Child Abuse/Neglect; Federation for Community Planning Cleveland, Ohio	1977 - 1982
Chairperson, Healthy Baby Month, Sponsored by Cleveland Chapter, March of Dimes	1977
Committee for Children at Risk, Member under Federation for Community Planning, Cleveland, Ohio	1978 - 1982
Co-Chairperson, Institute on Children at Risk: The Home, School and Community, Cleveland, Ohio	1978
Coach "Crash Course in Childhood" developed by Dr. Ray Helfer, Cleveland, Ohio	1978 - 1979
Co-Chairperson, Parenting Disorders in Pediatric Settings Sponsored by Cleveland Regional Perinatal Network and Cleveland Council on Children at Risk	1979
Chairperson, Volunteer Program to Provide Support to New Mothers: Mac Donald House University Hospitals of Cleveland	1980 - 1982
New York City Steering Committee on Breast-Feeding New York State Department of Health	1983 - 1991
Nominating Committee, Rye Neck Board of Education	1985 - 1988
Bronx Community Child Abuse Task Force	1985 - 1991
Advisory Board Member, Prevention Intervention Research Center (PIRC), Albert Einstein College of Medicine Bronx Breast Feeding Project	1986 - 1991
Human Rights Commission Member, Rye, New York.	1986 -1991
Co-Chairperson, Bioethics Committee Weiler Division/Montefiore Medical Center.	1987 - 1991

Nurse Consultant American International Perinatal Health, Inc. .	1989
Education Chairperson, Mid Hudson Valley Region New York State Perinatal Association	1989 - 1991
Editorial Advisory Board, Obstetrics and Gynecology	1989 – 1995
Member, Women's Health Coordinating Committee, U.S. Public Health Service	1991 - 1997
Member, Surgeon General's Committee for Women and Children with AIDS; U.S. Public Health Service	1991 – 1997
Editorial Advisory Board, Journal of Women's Health	1992 - Present
Member, Consumer Education Committee, NAACOG.	1992 - 1993
Member, Breast Implant Research Task Force, US Public Health Service	1992
Member, DHHS Inter-Agency Working Group on Breast and Gynecologic Cancer, US Public Health Service.	1993 - Present
Invited Member, President's Council of Cornell Women; (Chair -Special Task Force on Health of Cornell Students)	1995 - Present 1999-2001
Contributing Member-National Action Plan on Breast Cancer US Public Health Service.	1993 - 1995
Member, Planning Group under National Plan on Breast Cancer to Implement a Comprehensive Plan to Address the Needs of Individuals Carrying Breast Cancer Susceptibility Gene(s), US Public Health Service	1994
Editorial Advisory Board, American Journal of Public Health.	1994 - 1995
Program Chair, FDA Regulated Products and Pregnant Women; Arlington, VA	11/7 – 8/1994
Member, Human Subject Regulation Drafting Committee To Revise Subpart B, CFR, Part 46 Additional DHHS Protections Pertaining to Research for Pregnant Women, Human Fetuses Member, Human Subject Regulation Drafting Committee; US DHHS	1994-1995
Board Member- Jacobs Institute of Women's Health	1995-2003
Board Member, Friends of the National Institute of Nursing Research- NIH	2002-2006
Program Co-Chair, FDA Regulated Products and Pregnant	11/7-8/1994

Women, US FDA, Crystal City, VA

Program Co-Chair, Gender Studies in Product Development: Scientific Issues and Approaches; US FDA, Rockville, MD — 11/6-7/1995

Invited Participant, "Beyond Hunt Valley: Research in Women's Health for the 21st Century, Scientific Meeting Sponsored by the Office of Research on Women's Health of the National Institutes of Health; Philadelphia, Pa., Santa Fe, NM, Bethesda, MD — 9/25-26/96

Volunteer, HIV Law Project, NYC — 1998 - 2003

Special Task Force on Nursing Shortage, City University of NY — 2001

Institute of Medicine Reviewer: Exploring the Biological Contributions To Health: Does Sex Matter? — 2001

Institute of Medicine Committee Member: New Frontiers in Contraception: A Blueprint for Action — 2003 - 2004

EINSTEIN AND POPULATION COUNCIL TEACHING ACTIVITIES

Conference Director: *Autumn in New York* — 11/14-15, 1993
"Women's Health Across the Lifespan"
Department of Obstetrics & Gynecology
Albert Einstein College of Medicine
Bronx, NY

Participant/Speaker: *Autumn in New York* — 11/15-16/2003
"A Commitment to Equity in Women's and Perinatal Health: Closing the Gaps"
Department of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine
Bronx, NY

Journey to Uganda- Grand Rounds Lecture* (sparked Departmental Interest among Faculty and students to embark upon teaching and service in selected SSA countries — 10/11/ 2005

Organizing Committee: *Autumn in New York* — 11/10-12/2006
"Women's Health: A Global Perspective In Honor of Allan Rosenfield, MD"
Department of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine
Bronx, NY

Director, Mentor — 2009-present
Population Council's Family Planning Teaching/Learning Program offered semi-annually to Selected Family Planning Fellows training under US Family Planning Fellowship Program
Mentored 10 Family Planning Fellows

Bixby Fellowship Mentor (Population Council) Mentor to Dr. Yongmei Huang 10/10-8/13
(International Peace Maternity and Child Health Hospital: Shanghai Institute of
Family Planning Technical Instruction

Program Committee: *Autumn in New York* 11/19/2013
"Local and Global Health Issues of Adolescent Girls"
Department of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine
Bronx, NY

Fellowship Director for Research 2014-present
Family Planning Fellowship
Department of Obstetrics and Gynecology & Women's Health
Albert Einstein College of Medicine (Assisted in preparation of Einstein fellowship application and site
Visit in 2014; Fellowship status awarded to Dept. of Obs and GYN & Women's Health
July 2014.

Mentored Dr. Carol Sales Vieira- FP fellowship at Population Council; Sept 2016-Jan 2018
Sponsored by Medical School of Ribeirao Preto, University of Sao Paulo, Brazil

ORIGINAL COMMUNICATIONS IN REVIEWED JOURNALS

1. Smith E, Veolitze M, **Merkatz R**. Social aspects of abortion counseling for patients undergoing elective abortion. ClinObstet Gynecol 1971 Mar; 14(1): 204-16**.**

2. **Merkatz R,** Smith E, Seitz R. Preoperative teaching for gynecologic patients. Am J Nurs 1974 June; 74(6) 1072-4.

3. **Merkatz RB**. Budd K. Merkatz IR. Psychological and social implications of scientific care for pregnant diabetic women. Sem in Perinatol 1978 October; 11(4):373-81.

4. DeCarvalho M. , Robertson S. Klaus M. **Merkatz RB.** The effects of frequency and duration of breast feeding on serum bilirubin, weight gain and milk output. Ped Res. 1981. 15. 530; doi 0.1203/00006450-198104001-00552

5. DeCarvalho M. Klaus MH. **Merkatz RB**. The effects of frequency of breast-feeding on serum bilirubin concentration. Am J Dis Child 1982 Aug; 136: (8):737-8.

6. Pittard WB. **Merkatz R.** Fletcher BD. Radioactive excretion in human milk following administration of technetium TC-99m macroaggregated albumin. Pediatrics, 1982 Aug; 70(2):231-4.

7. DeCarvalho M. Robertson S. **Merkatz RB.** Klaus MH. Milk intake and frequency of feeding in breast-fed infants. Early Hum Dev 1982 Nov; 7(2):155-63.

8. Anderson D. Williams F. **Merkatz RB.** Schulman P. Kerr D. Pittard W. Length of gestation and nutritional components of human milk. Am J Clin Nutr 1983 May; 37(5):810-14.

9. Langer O. Levy J. Brustman L. Anyaegbunam A. **Merkatz RB**. Divon M: Glycemic Control in GDM - How tight is tight enough: Sga vs lga. Am J Obstet Gynecol 1989 Sep; 161(3): 646-53.

10. **Merkatz RB** & Merkatz IR: The contribution of the nurse and the machine in home uterine monitoring systems. Am J Obstet Gynecol 1991 May; 164(5Pt1):1159-1162.

11. Mikhail MS. Freda MC. **Merkatz RB.** Polizzotto R. Mazloon E. Merkatz IR. The effect of fetal movement counting on maternal attachment to fetus. Am J Obstet Gynecol 1991 October; 165(4Pt1):998-991.

12. **Merkatz RB** & Couig MP. Helping America take its medicine. Am J Nurs 1992 June; 92(6):59-62.

13. **Merkatz RB**. Bagley GP. McCarthy EJ. A qualitative analysis of self reported experiences among women encountering difficulties with silicone breast implants. J Wom Health 1993 Summer; 2(2):105-9.

14. McCarthy EJ. **Merkatz RB**. Bagley GP. A descriptive analysis of physical complaints from women with silicone breast implants. J Wom Health 1993 Summer; 2(2): 111-15.

15. **Merkatz RB**. Temple R. Sobel S. Feiden K. Kessler DA. Women in clinical trials of new drugs and biologics: A change in FDA policy. N Engl J Med. 1993 July; 329(4):292-296.

16. Kessler DA. **Merkatz RB**. Shapiro R. A call for higher standards for breast implants. JAMA 1993 Dec 1; 270(21):2607-8.

17. **Merkatz RB**. FDA: Making a difference in women's health. J Am Med Wom Assoc 1994 July/Aug; 49(4)117-120.

18. **Merkatz RB**. White Junod S. Historical background of changes in FDA policy on the study and evaluation of drugs in women. Acad Med 1994 Sept; 69(9):703-707.

19. Sherman LA. Temple R. **Merkatz RB**. Women in clinical trials: An FDA perspective. Science. Aug 11, 1995; 269:793-5.

20. **Merkatz RB.** Inclusion of women in clinical trials: A Historical overview of scientific, ethical, and legal issues. JOGNN. 1998 Jan/Feb; 27(1): 001-7

21. **Merkatz RB.** Female Sexuality: Scientific Advances- Editorial. JWH. May 2002; 11(4): 331-3

22. **Merkatz RB.** FDA's Office of Women's Health- Will it Endure. JWH August 2007; 16(6):818-826.

23. **Merkatz RB,** Tokay B, Sitruk-Ware RL. Methods for female contraception: A model for innovation in drug delivery systems. Clin Pharmacology & Therapeutics. May 2009 85 (5): 553-7.

24. Huang YM, **Merkatz R,** Kang JZ, Roberts K, Hu XY, Di Donato F, Sitruk-Ware R, Cheng LN. Postpartum unintended pregnancy and contraception practice among rural-to-urban migrant women in Shanghai. Contraception. 2012 Dec; 86(6):731-8.

25. RamaRao S, Clark H, **Merkatz R**, Sussman H, Sitruk-Ware R. Progesterone vaginal ring: introducing a contraceptive to meet the needs of breastfeeding women. Contraception 2013 Nov; 88(5), 591-8). doi: 10.1016/j.contraception.2013.05.004. Epub 2013 May 16

26. Huang YM, **Merkatz R,** Zu, Zuu, Roberts K, F, Sitruk-Ware R, Cheng LN. The free perinatal/postpartum contraceptive services project for migrant women in Shanghai: Effects on the incidence of unintended pregnancy. Contraception 2014 June; 89 (6) 521-7.

27. **Merkatz RM,** Plagianos M**,** Hoskin E, M, Hewett P, Mensch B. Contraception**.** Acceptability of the Nestorone®/Ethinyl Estradiol Contraceptive Vaginal Ring; Development of a Model; Implications for Introduction. Contraception. 90 (5) 2014, 514–21.

28. Huang Y. Jensen JT, , Brache V, Cochon L, Williams A, Miranda MJ , Croxatto H, Kumar N, Sussman H, Hoskin E, Plagianos M, Roberts R, **Merkatz R.** Blithe D, Sitruk-Ware R.. A randomized study on pharmacodynamic effects of vaginal rings delivering the progesterone receptor modulator ulipristal acetate: research for a novel estrogen-free, method of contraception. Contraception. 90 (6) 2014, 559-622.

29. Brache V, **Merkatz R**, Kumar N, Jesam C, Sussman H, Hoskin E, Roberts K, Alami M, Taylor D, Jorge A, Croxatto H, Lorange E, Mishell DR, Sitruk-Ware R. A dose-finding, cross-over study to evaluate the effect of a Nestorone®/Estradiol transdermal gel delivery on ovulation suppression in normal ovulating women. CONTRACEPTION Epub 2015 May 29

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ABSTRACTS

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23 **Merkatz R**, Roy M. Plagianos M, Hazra A, Sales Vieira C, Rijo N, Sitruk Ware R. Reports of Acceptability by Women Using Novel Contraceptive Vagina. Rings in Diverse Settings. 15th ESC Congress, Budapest, Hungary, May 9-12 2018.

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25. Plagianos M, **Merkatz R,** Do women really tell us what they think of new contraceptives? What we can learn from various interviewing techniques.

26. Westhoff C, Darney P, Jensen JT, Bahamondes L, Apter L, **Merkatz RB.** Efficacy of the 1- Year Segesterone Acetate/Ethinyl Estradiol Contraceptive Vaginal System. American College of Obstetrics and Gynecology (**ACOG),** May 3-6, 2019, Nashville, TN.

27 **Merkatz RB**, Magnani M, Sussman H, Creasy GW, Sitruk-Ware R. Efficacy and Safety of a 1-Year Segesterone Acetate/Ethinyl Estradiol Contraceptive Vaginal System. American Academy of Nurse Practitioners (A**ANP),** Jun 18-23, 2019 Indianapolis, IN

28. **Merkatz RB**, Magnani M, Sussman H, Creasy GW, Sitruk-Ware R. Efficacy and Safety of a 1-Year Segesterone Acetate/Ethinyl Estradiol Contraceptive Vaginal System. Association of Women's Health, Obstetrical and Neonatal Nurses (AWHONN), Jun 8- 12, 2019, Atlanta, GA

29. Archer DF, Sitruk-Ware R, Mirkin S, Brache V, **Merkatz RB**. Low Systemic Levels of Segesterone Acetate are Required to Inhibit Ovulation in Women. Endocrine Society, Mar 23-26, 2019, New Orleans, LA

30. Archer DF, Thomas MA, Sitruk-Ware R, Liu J, Bernick B, Mirkin S, **Merkatz RB**, Kumar N, Blithe DL. A Novel 1-Year Contraceptive Vaginal System Delivering Segesterone Acetate and Ethinyl Estradiol: Effects on Lipids and other Hepatic Proteins. Endocrine Society, Mar 23-26, 2019, New Orleans, LA.

PRESENTATIONS: Historical Selections of Oral Presentations Prior to 1990

1. Preoperative Counseling of the Gynecologic Patient. The Nurses Association of the American College of Obstetrics and Gynecology, Annual Convention, New York City, 1972.

2. Predictors of Child Abuse. Case Western Reserve University Medical School, December 1977 sponsored by the Council on Children at Risk and the Cleveland Regional Perinatal Network. December, 1977.

3. Hospital Policies That Promote Breast-Feeding Success: A Research Approach. Bronx Lebanon Hospital, Department of Obstetrics, July 8, 1983.

4. The Nurses' Role in Supporting the Breast-Feeding Family During the Pregnancy Cycle. Lincoln Hospital, Department of Nursing, September 28, 1984.

5. Increasing the Incidence of Breast Feeding in the U.S.; National Conference of Child Health sponsored by Bureau Maternal/Child Health, Washington, DC, October 14, 1983.

6. Nursing Care Policies That Promote Successful Breast Feeding in the Hospital Setting. Mt. Sinai Hospital, Department of Obstetrical Nursing, New York, New York, April 25, 1984.

7. A Comprehensive Health Professional's Approach to Promoting Breast Feeding. New York City Conference sponsored by Steering Committee to Promote Breast Feeding New York, New York, June 4, 1984.

8. Mothering Behaviors and Child Development Outcomes: A Longitudinal Study Comparing High Risk and Low Risk Mothers. Research Day, Hospital of the Albert Einstein College of Medicine, Bronx, New York, June 14, 1984.

9. Medical Factors Associated with Preterm Birth. March of Dimes Annual Nursing Conference, New York City, March 6, 1987.

10. Psychological and Social Factors in the Management of Diabetes in Pregnancy: Critical Issues in Diabetes in Pregnancy, The Albert Einstein College of Medicine, Department of Obstetrics and Gynecology, November, 1987.

11. Nurses Working in Government. Guest Lecture in Honor of Nurse Recognition Week, Flushing Hospital, May 11, 1993.

Selected Oral Presentations/Teaching Lectures 1990-Present

12. The Effects of Maternal Attachment and the Capacity for Empathy on Social Support. The Society of Psychosomatic Obstetrics & Gynecology, New York City, March 29, 1990.

13. Avoiding Moral Distress in Caring for the Dying Oncology Patient. Oncology Nursing Society, Hudson Valley Chapter, February 7, 1990.

14. Utilizing the POPRAS Record; A Guide to Prenatal Care. New York City Hospitals Seminars for Perinatal Nurses, sponsored by the March of Dimes, New York Chapter, June 7, 1990.

15. Development of a Model for Social Support among Black and Hispanic Pregnant Women. Sigma Theta Tau, Alpha Upsilon Chapter, January, 1991.

16. A Women's Health Initiative at FDA. Washington, DC. Annual Meeting of FDA Public Affairs Specialists, October, 1991.

17. A Model for the Development of Social Support among Black and Hispanic Pregnant Women. Sigma Theta Tau International Conference, Orlando, Florida, November, 1991.

18. **Keynote Address:** Participation of Women with AIDS in Clinical Trials. Annual Meeting, Community Groups for Women and Aids, Washington DC. January, 1992.

19. Research Initiatives in Women's Health. University of Michigan School of Nursing, Ann Arbor, Michigan. March 19, 1992.

20. **Keynote Address:** The Challenge of Promoting Women's Health. Women's Health Conference, Texas Medical Center, Houston; Sponsored by FDA, USHHS, & Texas Agricultural Extension Service, March 20, 1992.

21. **Keynote Address:** An FDA Agenda for Women's Health. North American Menopause Society. Cleveland, Ohio, September 16, 1992.

22. **Keynote Address:** Women in Clinical Trials; An Overview. Keynote Address, Conference sponsored by USFDA and Food, Drug and Law Institute on Women in Clinical Trials of FDA-Regulated Products-Who Participates and Who Decides, Washington, DC, October 5, 1992.

23. FDA Approval of Depo-Provera. CBS Morning Show, October 30, 1992.

24. The Role of the FDA in Safeguarding Patient Care. Grand Rounds, Department of Obstetrics and Gynecology at the Albert Einstein College of Medicine, December 22, 1992.

25. FDA Calls for Changes in Contraceptive Labeling. CBS Morning Show, April 9, 1993.

26. Participation of Women in Clinical Trials of New Drugs. Pharmaceutical Manufacturers Association, Newark, NJ, April 16, 1993.

27. Nurses Working in Government. Guest Lecture in Honor of Nurse Recognition Week, Flushing Hospital, May 11, 1993.

28. Plenary Address: Women's Issues-Lessons Learned from the Breast Implant Story. Public Health Service, Commissioned Officers Association Annual Meeting, Scottsdale, AZ., May 24, 1993.

29. Women in Clinical Trials: The FDA's Historical Concern and Its Recent Developments. NIH Conference on Women and Minorities in Clinical Research, Georgetown University, Washington, DC, June 28, 1993.

30. FDA's New Policies on Women in Clinical Trials. Hearing on Recruitment and Retention of Women into Clinical Trials; Office for Research on Women's Health, NIH, Bethesda, MD, July 13, 1993.

31. The Mammography Quality Standards Act (MQSA): Consumer Concerns. FDA Conference, Implementing the MQSA of 1992: Roles in Improving Mammography Services, September 21, 1993, Reston, VA.

32. **Keynote Address:** Women's Health: An Historical Perspective. Keynote Address, Women's Health across the Lifespan, Annual Autumn in NY Conference sponsored by the Department of Obstetrics & Gynecology, Albert Einstein College of Medicine, November 14, 1993.

33. Participation of Women in Clinical Trials; Lecture to the Department of Epidemiology and Social Medicine; Albert Einstein College of Medicine; February 7, 1994.

34. Women's Health Comes of Age; FDA Seminar presented at the Annual Meeting of the American College of Obstetricians and Gynecologists, Orlando, FL. May 11, 1994.

35. Recent FDA and NIH Perspectives on Women's Participation/Access into Clinical Research vs. Scientific Objectives. Association of Clinical Pharmacology Units; 6th Annual Meeting, Chicago, Ill. October 7, 1994.

36. **Keynote Address:** Promoting Health in Women with Turner's Syndrome. Keynote Address; Annual Meeting, Turners Syndrome Society. San Diego, CA, October 9, 1994.

37. Testing FDA Medical Products in Pregnant Women: Is it Time to Change?

Introductory Address. Conference on FDA Regulated Products in Pregnant Women. Sponsored by the Office of Women's Health, US Food and Drug Administration, Crystal City, VA. November 7-8, 1994.

38. Eighteen Months since the New Gender Guideline. Speech to the Corporate Advisory Council of the Society for the Advancement of Women's Health Research, Washington, DC, January 19, 1995.

39. Women's Health: Its Role in the Women's Movement. Linnea Henderson Nursing Lectureship, Kent State University, Kent, Ohio, April 6, 1995.

40. Women and Drug Research Trials, Women's Wellness Conference to the New York State Legislature, sponsored by the American College of Obstetricians and Gynecologists, NY State, Albany, NY, May 22, 1995.

41. Women's Health at the FDA: A New Era- Speech to the Jacob's Institute of Women's Health, July 3, 1995.

42. Including Women in Clinical Trials. Luncheon Speech to Ohio Congress on Women's Health sponsored by Ohio Department of Health and Ohio State University. Columbus, Ohio, September 10, 1995.

43. Current Issues in Clinical Trials for Pharmaceuticals: 19th Annual Conference Regulatory Affairs Professional Society, Washington, DC, October 12, 1995.

44. Clinical Trials: Inclusion of Women. Sixth International Congress on Ethics in Medicine, New York Academy of Medicine, New York City, October 24, 1995.

45. Clinical Research and Products Liability Issues: Including Women with Childbearing Potential in Drug Trials. New York State Bar Association, New York City, October 30, 1995.

46. Historical Review of Women's Participation in Clinical Trials: Opening Remarks at FDA sponsored workshop on Gender Studies in Product Development: Scientific Issues and Approaches. Rockville, MD, November 6, 1995.

47. Inclusion of Women in Clinical Trials: New Developments Since the 1993 FDA Guideline; National Institutes of Health, Bethesda, MD, February 22, 1996.

48. Scientific Aspects of Including Women in Clinical Trials: Drugs Directorate of Canada, Ottawa, Canada, April 2, 1996.

49. Celebrating Nursing: Our Past, Present and Future: Montefiore Medical Center, Bronx, NY, May 9, 1996.

50. Women's Health Advances through Clinical Trials: Third Annual Women's Health Conference, Society for the Advancement of Women's Health Research, Washington, DC. June 18, 1996.

51. Women and HIV: Impact on Policies for Participation of Women in Clinical Trials. Duke University School of Law Conference on HIV Law & Policy: Ensuring Gender-Equitable Reform, Durham, NC, February 21, 1997.

52. Are any Drugs Safe for Use in Pregnancy? Annual March of Dimes Nursing Conference, New York City February 27, 1997.

53. Women's Health Comes of Age, US Public Health Service Nursing Research Conference, Bethesda, MD March 21, 1997.

54. Are any Drugs Safe for Use in Pregnancy: Status of Current Information, World Conference in Perinatology, Rome, Italy May 8-9, 1997.

55. Continuing Controversy on Mammography for Women Ages 40-49 Years, The National Council on Women's Health, Lenox Hill Hospital, New York, NY, June 12, 1997.

56. Cancers in Women: A Reassessment on Focus, 5th Annual Congress on Women's Health, Washington, DC. June 25, 1997.

57. The Art of Women's Health: Women's Healthcare and Wellness Conference, Washington, DC. September 10, 1997.

58. Recruitment and Retention of Minorities and Women in Cancer Clinical Trials, University of Illinois, Chicago, IL September 19, 1997.

59. Addressing Women's Health Issues in a Managed Care Environment; IPA Association of America, Washington, DC, October 20, 1997.

60. Women's Health Leadership Conference; Blue Cross and Blue Shield Association, Communicating Success to Women, Boston, MA, October 31, 1997.

61. Why Women's Health Matters, Women for Healthcare Education Reform and Equity (WHERE) First Anniversary Celebration, Seattle, WA, November 3, 1997.

62. Report to the Commission on Women-Commonwealth Foundation Conference, Washington, DC; November 12, 1998.

63. To Your Health, Madame, The New York Women's Agenda, May 15, 1998.

64. Heart Disease and Women, Washington Hospital Center, January 15, 1999.

65. The Changing Face of Women's Health, Introductory Remarks; Maryland Science Center, Baltimore; March, 1999.

66. From Seneca Falls to Women's Health, commemorating the 150th anniversary of the signing of the Declaration of Sentiments, Seneca Falls, NY, July, 1999.

67. **Keynote Speech**: Beijing +5 Conference on Women: "Health Issues for Women: A Global Perspective", United Nations Headquarters, NY; June 8, 2000.

68. Women's Health in the New Millennium: Focus on Mental Health; New York University Medical Center, Department of Psychiatry; September 17, 2000.

69. Developing Leadership for Women's Health: A Look at Changing Policies at the FDA; Society for Women's Health Research, Medical Health Advisory Board; Washington, DC, October 25, 2000.

70. History of Gender-Based Medicine and Future Directions - University of Kentucky Medical School Grand Rounds, April 17, 2001.

71. The Prime of Our Lives: An Innovative Women's Health Education Program; Dept. of Obs/Gyn & Women's Health Grand Rounds; Dec 3, 2002.

72. Women's Health-The Model Has Shifted; US Congressional Briefing Sponsored by the Jacobs Institute of Women's Health; May 13, 2004.

73. Journey to Uganda: Personal Reflections: Department of Ob/Gyn- Grand Rounds, Sept 20, 2005.

74. The Role of the FDA in Ensuring Safety of Drug Therapy: Grand Rounds, Dept. of Ob/Gyn, Lenox Hill Hospital, November, 9, 2005.

75. Presentations to the International Committee on Contraceptive Research (ICCR) (2005-2018-Supplement available on Request).

76. Development and Acceptability of the NES/EE CVR: A Year-Long, User Controlled Contraceptive Method. International Conference on Family Planning, Sponsored by the Bill & Melinda Gates Foundation. Uganda, Nov. 2009.

77. Phase III Investigators. Preliminary results from a phase III study of the nestorone®/ethinyl estradiol contraceptive vaginal ring: A new, long acting (one year) user controlled contraceptive method. 11th Congress of the European Society of Contraception and Reproductive Health. The Hague, May 2010.

78. A dose-finding, cross-over study to evaluate the effect of a transdermal Nestorone®- Estradiol (NES/E2) gel on ovulation suppression and assess acceptability in healthy ovulating women. 66th Annual Meeting of the American Society for Reproductive Medicine. Denver, CO, October 25, 2010.

79. Acceptability of the Nestorone®/Ethinyl Estradiol Contraceptive Vaginal. Ring. North American Forum on Family Planning, Washington, DC. October 24, 2011.

80. Translating Contraception Research to Product Delivery; Better semi long-acting methods: Acceptability of new contraceptives in development. International Conference on Family Planning. Dakar, Senegal, Nov 30, 2011.

81. A Phase II, Dose- Finding, Crossover Study to Evaluate the Effect of a Transdermal. Nestorone®/Estradiol (NES/E2 Gel on Ovulation Suppression and Assess Acceptability in Healthy Ovulating Women. International Conference on Family Planning, Sponsored by Sponsored by the Bill & Melinda Gates Foundation. Dakar, Senegal, Nov 30, 2011.

82. Family Planning for the Postpartum Lactating Mother. International Conference on Reproductive Health with Emphasis on Strategies for Family Planning and the 22nd Annual Meeting of the Indian Society for the Study of Reproduction & Fertility. February 19-21, 2012.

83. Efficacy, Safety & Acceptability of a New Contraceptive Vaginal Ring Delivering Nestorone® 150 µg & Ethinyl Estradiol 15µg daily: Results from a Multi-Center Open Label Phase 3 Clinical Trial. First global conference on contraception, reproductive & sexual health. Copenhagen, Denmark, May 22, 2013.

84. Plenary Session: An Acceptability Model for the Nestorone®/Ethinyl Estradiol Contraceptive Vaginal Ring. International Conference on Family Planning, Sponsored by the Bill & Melinda Gates Foundation. Addis Ababa, Ethiopia, Nov 15, 2013 (Awarded best in class scientific paper).

85. From Bench to Bedside: Public, Private, Regional and Donor Perspectives on the Challenges and Opportunities for Introducing New Contraceptives- A Preformed Panel: Donaldson R (Moderator) - 2013 International Conference on Family Planning. Ethiopia.

86. User controlled long acting reversible contraception: the pharmacokinetic profile of the Nestorone®/Ethinyl Estradiol Contraceptive Vaginal Ring. European Society for contraception. Lisbon, May 29-31, 2014.

87. Effects of a one- year reusable contraceptive vaginal ring on vaginal flora and vaginal infection: A prospective evaluation. European Society for Contraception. Lisbon, May 29-31, 2014.

89. Advancing Development of Multipurpose Prevention Technologies to Reduce Unintended Pregnancy and Acquisition of Sexually Transmitted Infection, ICFP- Kigali, Rwanda, Nov 2018

90. Discovery, Development, Delivery:A New Long-Acting Contraceptive Under a Woman's Control/ Grand Rounds, Albert Einstein College of Medicine, Montefiore Medical Center, Dec. 18, 2019.

U.S. CONGRESSIONAL TESTIMONIES AND BRIEFINGS

1. Breast Implant Update. Briefing before Committee on Energy and Commerce, US House of Representatives, October 24, 1991.

2. Breast Implant Update. Briefing before Women's Congressional Caucus, US Congress, October 31, 1991.

3. The Breast Implant Moratorium. Briefing before Energy and Commerce and Committee, US House of Representatives, January 6, 1992.

4. FDA Testimony on the Status of Women's Health. Before the Subcommittee on Regulation, Business Opportunities, and Technology: Committee on Small Business; US House of Representatives, May 8, 1992.

5. Women's Health Issues at FDA. Briefing before Subcommittee on Agriculture, Rural Development, Food & Drug Administration & Related Agencies, Committee on Appropriations, US House of Representatives, May 5, 1993.

6. Tamoxifen Update. Briefing for Congressional Staff on new information on Tamoxifen; Its use for treatment and prevention of breast cancer. U.S. House of Representatives, April 11, 1994.

7. Creation of the Office of Women's Health at FDA. Briefing for selected members of U.S. House of Representatives, November 16, 1994.

8. Creation of the Office of Women's Health at FDA. Briefing for selected members of U.S. Senate, November 17, 1994.

9. FDA Testimony on Breast Implants and Medical Devices. Before the Human Resources and Intergovernmental Affairs Subcommittee of the House Government Reform and Oversight Committee, U.S. House of Representatives, August 1, 1995.

10. FDA Office of Women's Health Update. Briefing for Selected House Members and Staff. May 23, 1996.

Speech Presented to The North American Menopause Society
Cleveland, Ohio
September 17, 1992

by
Ruth B. Merkatz, PhD, RN
Special Assistant to the Commissioner:
Women's Health Issues: USFDA

A FOOD AND DRUG ADMINISTRATION (FDA) AGENDA FOR WOMEN'S HEALTH: LEARNING FROM THE PAST TO PROMOTE AND SAFEGUARD THE FUTURE

It is a great honor for me to be with you today and to speak at this important meeting. It is especially rewarding to be in Cleveland where I spent nine professionally stimulating years during the seventies and early eighties at the Francis Payne Bolten School of Nursing and University Hospitals. Many of us during that period became embroiled in examining the impact of the Women's Movement on the Health Care of Women. Together with one of my most important mentors, the late Dr. Nancy Lytle, we published a book, Nursing of Women in the Age of Liberation. The bulk of the chapters focused on pregnancy and family planning, the major issues of change and upheaval at that time. We were concerned about quality of care, about women's voices being heard in the health care system, and about paying attention to the developmental needs of women and families. Menopause, however, was the subject of

just one chapter and only in relation to hysterectomy.

If we were to write that book today, there is no doubt that there would be an increased focus on menopause. You and I are part of the generation that witnessed major change in childbirth practices and a dramatic upheaval in the scientific and technologic expertise that is applied today in caring for pregnant women. This same incisive reevaluation process is now taking place in caring for women during menopause. It is no coincidence that this week, at the top of the NY Times non fiction best seller list is Gail Sheehy's book, The Silent Passage. This book is a journalist's investigation of the myths surrounding menopause and an attempt to deal with what is currently known and what is being debated about this normal developmental process in a woman's life. Unfortunately, we do not have enough scientific information to definitively answer many of the questions that arise with respect to this period of a woman's life, and especially about the desirability and longterm safety and efficacy of postmenopausal hormone replacement therapy. That is why the Women's Health Initiative (WHI), one of the largest studies ever to be initiated by the NIH is about to be launched. It will address questions such as what effect does

adding progestin to a regimen have on protection against cardiovascular disease, the leading cause of death in women? Who should be targeted for such therapy and what should the recommended dosage and regimens consist of? Should progestins be recommended for a woman who does not have a uterus? What is the relationship, if any, between estrogen only and estrogen with a progestin and the development of breast cancer, which today affects one woman in nine? What is the role of diet and lifestyle on development of breast cancer, cardiovascular disease, osteoporosis, and other medical problems. It will be many years, however, before these study questions can be answered, even though women want answers to these questions now in order to conduct their own risk/benefit analysis. They also want to know if there are other agents that can be used to prevent bone loss or stimulate new bone formation should they not choose to use HRT. Practitioners are in the same situation.

Let me share with you the current mood and goals at FDA, and what some of our experiences with Women's Health issues bring to the current debate about the potential widespread application of drug therapy for women during menopause. Since joining Dr. Kessler at FDA

one year ago as his Special Assistant for Women's Health, I have been heavily involved in FDA's decisions about silicone breast implants. Passions and fervor that have been expressed on all sides of this issue have generated enormous debate, both within and outside FDA. The decisions that had to be made had monumental public health consequences. As part of the team analyzing what our decisions should be, I examined similar controversial issues that have affected women's health and have directly involved FDA. I am eager to share some of my insights from that review with you today. For me, the story begins with Thalidomide.

Thalidomide came on the market in West Germany and Great Britain in the late 1950's, and became popular throughout Europe as a sedative and tranquilizer. Its chief attraction was thought to be its low level of toxicity, and for this reason it was thought to be safe for even pregnant women. In 1960, when the Merrill Richardson Company applied to FDA for permission to market the drug in the US, it was felt to be a fairly straightforward new drug application and was assigned to a new medical reviewer, Dr. Frances Kelsey. Despite the drug's reputation as being non toxic, Dr. Kelsey was concerned about the scarcity of information

concerning its absorption and distribution in the body. She wondered whether the low toxicity could be related to poor absorption in the human species, and requested further studies on the metabolism of the drug. Along with other reviewers at FDA, Dr. Kelsey was also concerned about the effects of the drug on the fetus. Despite pressure from the drug company, Dr. Kelsey recommended withholding approval until assurances about the teratogenic effects of the drug could be provided. Her concern was heightened by a report in the British Medical Journal which drew attention to possible neurological side effects with prolonged use of thalidomide. By May, 1961, attention had already been drawn in Germany to the sudden alarming increase of congenital limb deformities in newborn infants, and inquiries were underway to determine their cause. In November, 1961, Dr. Lenz from Hamburg announced his suspicion that thalidomide was the cause of the deformities. The same conclusion was reached by Dr. McBride in Australia. It is of interest to note that, in the course of these inquiries, several centers in the US were queried as to whether a similar increase in such anomalies had been noted. The FDA was not aware of these inquiries until the role of thalidomide in the phocomelia defects of infants had been established-

an example of inadequate scientific communication.

In Europe and Australia, over 5000 babies were born with the characteristic phocomelia deformities. In the US there were a few such babies because Merrell Richardson had distributed thalidomide as an experimental drug. Dr. Kelsey's reluctance to approve thalidomide for marketing unquestionably prevented more birth defects in this country. The thalidomide story and Dr. Kelsey's role in delaying its approval appeared in the Washington Post and inspired President John F. Kennedy to award her the US Medal of Honor.

The thalidomide event also unleashed public scrutiny of the entire drug approval process in this country. It aroused widespread support for stronger drug regulation and resulted in the Kefauver-Harris Drug Amendments of 1962 to ensure greater drug safety. These amendments strengthened the regulation of new drugs under investigation and provided for immediate withdrawal of drugs found to present an imminent hazard. In addition, companies had to include evidence of a drug's effectiveness as a prerequisite for marketing.

While the 1962 Drug Amendments required that drugs must be shown to be effective, they applied only to new drugs coming under

review for approval by FDA. Thus, some older drugs on the market were not initially subjected to the efficacy standard. Included in this category was DES, a drug familiar to all of you in this audience, I am sure. I merely remind you of the tragic legacy of in utero exposure to diethylstilbestrol which continues to unfold even now. A well known professor of Obstetrics and Gynecology recently recalled to me that the drug was prescribed in pregnancy by physicians such as he who genuinely believed it was helpful, and because there was nothing else to offer women at risk for pregnancy loss. It must be noted, however, that in the early 1950's, Dr. Dieckmann and his associates at the Chicago Lying-In Hospital conducted a double blind, prospective study using DES with pregnant women. They found no benefit in pregnancy outcomes among 840 women receiving DES compared with 806 women who received placebo. This study was presented in 1953 at the 76th annual meeting of the American Gynecological Society in Lake Placid. Despite the negative findings on efficacy in improving outcome, and even the suggestion that preterm birth was increased with use of DES, the drug continued to be prescribed during pregnancy until the 1970's. In 1971, when Drs. Herbst and Scully of Boston reported on the significant

linkage between in-utero exposure to DES and later development of adenocarcinoma in female offspring, its usage in pregnancy was finally stopped.

We have had other painful, recent lessons with respect to products prescribed for women. From the Dalkon Shield disaster, we again learned what can happen when enthusiasm for a product's potential benefit is not balanced against a careful and scrupulous examination of its risks, in this case a device. Before 1976, the FD&C Act did not require testing of devices prior to marketing as it did for drugs and vaccines. With no premarket clearance, a manufacturer could put on sale an untested, hazardous device and dangers might not be evident for decades. Only after a device had caused injury or death could the FDA go to court for seizure of specific devices or for an injunction to halt interstate sales. For the political science and history buffs in this audience during this election year, you may be interested to know that Presidents Kennedy, Johnson, and Nixon sent 3 consecutive annual messages to Capitol Hill urging premarketing clearance of medical devices for safety, efficacy, and reliability.

But the resulting 1976 Medical Device Amendments did not take care

of all devices. There were thousands already on the market that were grandfathered; they were allowed to stay on the market pending a decision from FDA about whether safety and effectiveness would have to be demonstrated. Included among these were silicone breast implants which had been introduced in the early 1960's. In 1982, FDA proposed that manufacturers of breast implants demonstrate product safety and efficacy. But as provided by the law, this proposal was followed by additional rulemaking, and it wasn't until 1991 that the companies actually submitted their data. The rest is history. Seven companies submitted applications, but only four of them were accepted for review by FDA. In November, 1991, FDA's outside advisory panel determined that the manufacturers had not provided sufficient data to demonstrate safety and efficacy. Under ordinary circumstances, this would have meant that these devices would be off the market. But the breast implant issue was not an ordinary circumstance. Not since the Saccharin debate of the late 1970's had FDA received the quantity of mail as it did in this case- more than 22,000 letters during this past year. The majority have come from women asking that silicone breast implants remain available, that women be given information about safety and the

right to choose what would go into their bodies. The same message came out in the public panel meeting. But we have also received quantities of mail and verbal testimony from women on the other side, women who have been harmed and believe that they have suffered a variety of illnesses as a result of these implants. As I analyzed these letters, several themes emerged from the latter group of women: 1) they had been given virtually no information about any potential problems that could arise from the implants; 2) those who had problems were generally put off by their physicians and told their problems could not possibly be related to their implants.

The FDA has been both praised and criticized for its decision to markedly restrict the use of silicone breast implants. Those who believe we did the right thing tell us that after much delay, FDA and Dr. Kessler acted with courage to demand that women receive information about these implants, and that manufacturers provide the evidence of safety that should have been accumulated during the preceding 30 years of unmonitored use.

Those who criticize FDA, such as the editorial staff of the NEJM, accuse FDA leadership of sexism in targeting a device used only by

women. To this argument, I, for one, say it would have been truly sexist to ignore a device used by women, particularly given some of the events of the past that I have reviewed today. The NEJM accuses FDA of coercion by insisting that women enroll in study protocols in order to obtain silicone breast implants. To this I can confidently reply with information from FDA's Breast Implant Information Service (our hotline) and the letters written by thousands of women with breast implants. They are pleading for the opportunity to be to enrolled in a registry and a data base so that they can be monitored closely and be informed periodically of future developments.

The agency has also been criticized for allowing implants to be used more readily by some women than by others. Women who need implants for medical reasons such as reconstruction following breast cancer surgery, congenital malformations, or trauma may have open availability to enter into research protocols and receive the implants. However, the number of women who desire implants for cosmetic augmentation purposes will be more restricted in gaining entry into protocols. As we at FDA debated the issues before us, it was clear that the indications for breast implant surgery were different between the two

groups. While these implants serve a cosmetic purpose in all cases and may provide important psychological benefits for both groups, women who choose reconstructive surgery do so as part of medical treatment for their disease. In many instances, and particularly in the case of women with breast cancer, availability of breast implants and reconstruction enables them to go forward with cancer treatments. Thus there was a public health need to allow the continued use of silicone breast implants under close supervision for women with a medical indication. In balancing the decision, we also considered that women choosing augmentation are generally younger than those requiring reconstruction. For these younger women, the potential risks became especially worrisome because of serious unanswered questions about the long range performance of silicone breast implants. Additional concern for younger women with healthy breasts included interference with critical breast cancer screening.

Regardless of this reasoning, critics still argue that women should be able to choose for themselves. Why should FDA presume to tell a given woman how much risk she may take to gain the appearance she desires? The answer to these dilemmas resides in the law and, more

fundamentally, in what FDA is all about. Congress established FDA to protect the health of the American consumer. The need for that protection is greatest when there is inadequate information about a product, when people are ill, or when they are in discomfort- either physically or psychologically.

In the course of the breast implant story, we at FDA learned of unpardonable marketing and advertising schemes, and of an insensitivity to the seriousness of a woman's decision to obtain silicone breast implants. We also learned that, in general, women were not given adequate information about these implants prior to giving consent. It goes without saying that such mistakes must not be permitted to recur in expanding menopausal therapies to women. Regardless of social class or ethnic background, women deserve suitable unbiased educational materials. These materials must be available and utilized with appropriate counselling and time for deliberation. Health care professionals have an obligation to ensure that companies be held accountable for the accuracy of direct to consumer advertising and for including an accurate representation of risks and benefits along with a favorable portrayal of postmenopausal women in the media. FDA will be

seeking your help in this effort.

For consumers, the silicone breast implant story provided the painful lesson that no device is completely free from risk, regardless of how long it has been used. The public often expects that a product regulated by FDA will be absolutely safe. But, of course, nothing in life is absolutely safe. Our goal with breast implants was not to assure absolute safety. It was to clarify and quantify the risks and determine whether they had been shown to be low enough to be acceptable, and then to be sure that those risks were adequately conveyed to physicians and patients.

It is the manufacturer's job to satisfactorily demonstrate that a product is safe and effective for marketing. Accordingly, it is not FDA's job to prove that the product is unsafe. However, no amount of premarket testing can catch all potential problems associated with the real-life use of medical products. It is at this point that professionals, attuned to the complexity of human biology, and the variability of individual responses must be alert in recognizing unanticipated events. This is particularly true for off label use of drugs. As new regimens of hormone replacement therapy and anti-bone resorptive agents are instituted, each of us must maintain a healthy vigil and there must be a

willingness to communicate both through the literature, and through reports to the FDA as the nation's designated regulatory body. I remind you once again of the key historic roles played by Dr. Lenz of Hamburg, Dr. Diekmann of Chicago, Drs. Herbst and Scully of Boston, and also of Dr. Frances Kelsey who is now in her late 70's, but still on the job in Washington.

Women, too, will be more alert and on guard in the 1990's than ever before in the past. Health care practitioners must appreciate the concerns, fears, and background experiences that perimenopausal women may bring to the doctor-nurse-patient relationship. Women of the post war and baby boom generations were the ones who stimulated major changes in childbirth practices. They were also the same women who witnessed the ramifications of the untoward historic medical events I have reminded you of today. It is the same generation of women who now seek care for problems of menopause at a point in time when concerns about cancer, heart disease, the spread of AIDS, and quality of life are paramount. FDA recognizes its special responsibility to this generation of women. It is an agency determined to strengthen its partnerships both with them and with the academic communities, health

professionals, and industries developing new concepts of care.

In cooperation with its sister agencies of the USPHS, FDA emphasizes Women's Health as a top research and public health priority. It intends to be very active in support of the evolving understanding of the physiologic and health needs of menopausal and aging women. Its professional staff and advisory committees will focus particular attention on the progress of research in prevention and treatment of heart disease; lung, breast, uterine, and other cancers afflicting women; osteoporosis; and AIDS which must include the prevention of the spread of AIDS even in post menopausal women. It will also focus on issues of Alzheimer's disease, a condition which is not only more prevalent in women, but is one which profoundly affects women who frequently are the caretakers of those who are afflicted. FDA also intends to further its educational role for women about nutrition, physical fitness, and life style in an effort to prevent some of the medical problems that afflict women as they mature. The Nutrition and Labeling Education Act of 1990 mandates that FDA provide clearer labeling of food content and the relationship of specific nutrients to the prevention of disease. This includes the role of calcium in prevention of osteoporosis, and excess dietary fat in the

etiology of cardiovascular disease.

FDA's role in food and drug labeling, drug advertising, and availability of objective health information is fundamental to its mission. The agency must simultaneously insist on appropriate consent procedures about new treatments so that women are empowered to participate in important decisions about their health care options. As we approach the twenty first century with eagerness and enthusiasm about our ability to provide the very best care for all citizens, it is important to incorporate the lessons of the past in ensuring the safest and most effective health care for women.

Thank you very much for the opportunity to share this message with you. I wish you well during this conference.

EXHIBIT 37

White House, Readout of White House Roundtable Meeting with Women's Rights and Reproductive Health Leaders (Sept. 3, 2021)

SEPTEMBER 03, 2021

Readout of White House Roundtable Meeting with Women's Rights and Reproductive Health Leaders

Today, Gender Policy Council Co-Chairs Jennifer Klein and Julissa Reynoso, White House Counsel Dana Remus and Deputy White House Counsel Danielle Conley, Director of the Office of Political Strategy and Outreach Emmy Ruiz, and Deputy Director of the Domestic Policy Council Christen Linke Young hosted a roundtable with women's rights and reproductive health leaders to discuss the Supreme Court's ruling on Texas' SB8. The meeting followed the unprecedented assault on constitutional rights under *Roe v. Wade* and underscored the President's commitment to ensuring that every person in this country has access to reproductive health care. President Biden made clear in his statement earlier this week that this law will significantly impair access to care, particularly for communities of color and individuals with low incomes and Vice President Harris reiterated in her statement the Administration's commitment to use every lever to defend that right to safe and legal abortion and to strengthen that right.

During the meeting, women's rights leaders shared the impact of the ruling—what Fatima Goss Graves, President and CEO of the National Women's Law Center, called "a legal and public health emergency"—on those directly impacted in local communities across the state of Texas. Leaders shared recommendations for steps the federal government can take to ensure that all people in the U.S.,

including in Texas, have access to safe and legal abortions as protected by Roe and highlighted connections to racial equity, gender-based violence, and the maternal health crisis in the U.S.

Senior White House officials expressed gratitude for the leadership and advocacy of the reproductive health and rights community, especially during a time where women's health is under attack in states across the country. National leaders support an ecosystem of local affiliates, providers, and community-based organizations—many led by women of color—on the frontlines of protecting reproductive rights and health.

White House officials also underscored the Biden-Harris Administration's urgent commitment to protecting and advancing reproductive health and rights, as exemplified by the launch of a whole-of-government effort—led by the Gender Policy Council and Office of the White House Counsel—to respond to the law. Earlier this week, the President tasked the Department of Health and Human Services and the Justice Department to explore what steps the federal government can take to ensure access to safe and legal abortion. These efforts build on the President's earlier commitments to a government-wide approach to advancing gender equity and equality, including women's reproductive health care.

Women's rights and reproductive health leaders that participated in today's roundtable included:

- Alexis McGill Johnson, President and CEO, Planned Parenthood Federation of America
- Brigitte Amiri, Deputy Director at the ACLU's Reproductive Freedom Project, American Civil Liberties Union

- Fatima Goss Graves, President and CEO, National Women's Law Center
- Jamie Mason, President, Catholics for Choice
- Jocelyn Frye, Senior Fellow, Women's Initiative, Center for American Progress
- Marcela Howell, President and CEO, In Our Own Voice: National Black Women's Reproductive Agenda
- Nancy Northup, President and CEO, Center for Reproductive Rights
- Shaina Goodman, Director of Policy for Reproductive Health and Rights, National Partnership for Women and Families
- Sheila Katz, CEO, National Council of Jewish Women
- Silvia Henriquez, Co-President, All* Above All
- Sung Yeon Choimorrow, Executive Director, National Asian Pacific American Women's Forum

EXHIBIT 38

White House, Press Briefing by Press Secretary Jen Psaki and Deputy National Security Advisor for Cyber and Emerging Technologies Anne Neuberger, September 2, 2021
(Sept. 2, 2021)

SEPTEMBER 02, 2021

Press Briefing by Press Secretary Jen Psaki and Deputy National Security Advisor for Cyber and Emerging Technologies Anne Neuberger, September 2, 2021

James S. Brady Press Briefing Room

2:07 P.M. EDT

MS. PSAKI: So we have another special guest today — a return visitor — Deputy National Security Advisor Anne Neuberger, who is going to speak to you briefly about cyberthreats. She only has time for just a very few questions because she has to run off to a meeting. I will always be the bad cop.

With that, come on up. And then we'll, of course, do a full briefing.

MS. NEUBERGER: Good afternoon, everyone. So, we want to take a moment to encourage organizations to be on guard for malicious cyberactivity in advance of the holiday weekend.

To be clear, we have no specific threat information or information regarding attacks this weekend, but what we do have is history. And in the past, over holiday weekends, attackers have sometimes focused on security operation

centers that may be understaffed or a sense that there are fewer key personnel on duty as they may be on vacation. And indeed, a long weekend can sometimes make attackers feel they have extra time to navigate in a network before they are detected.

So, as a long weekend comes, we want to raise awareness. And this need for awareness is particularly for critical infrastructure owners and operators who operate critical services for Americans.

As part of the administration's ongoing efforts to secure our — America's defenses against cybercrime and ransomware, on Tuesday, the FBI and DHS's CISA released an advisory outlining specific steps that organizations and individuals can take to really increase their defenses and be safe online.

You can find this on CISA's one-stop shop for information: StopRansomware.gov. And we encourage you to please visit the site, read the advisory, and take those critical steps.

Organizations and individuals should be on alert now because criminals sometimes lay in their steps in advance and begin their planning.

Now, I want to walk through a few specific things you can do right now to protect against possible attacks and to ensure that you can recover quickly in the event that an organization is compromised.

Specifically, I'd like to call on executives to please bring together your leadership teams and run through this set of activities to ensure that your organizations are as secure as they need to be before the holiday weekend:

First, update and patch all software. We continuously see attackers compromising organizations based on vulnerabilities that are known, for which patches are available.

Second, ensure that individuals have strong passwords in place. And indeed, for key personnel, encourage them to change their passwords now.

Third, implement multifactor authentication, particularly for key personnel and IT staff. Multifactor authentication is something more than a password. It could be a biometric, like a fingerprint. It could be a code that comes off software.

Last week, President Biden hosted key executives from technology companies as part of his efforts to really secure America online. And a number of those executives pointed to multifactor authentication as preventing 80 to 90 percent of cyberattacks. Indeed, because it is such a helpful way to address cyber vulnerabilities, it's one of the five things President Biden mandated be rolled out across the federal government quickly as part of his executive order in May.

Fourth, review your incident response plan and do a drill against it to ensure that, if a compromise occurs, you're ready to react and respond quickly.

And finally, ensure that you have up-to-date backups and that they're segregated from a network so that they're not accessible to an attacker.

There are a couple of other good practices to do. Security teams should proactively hunt on a network. It's kind of like a digital version of walking the beat. Look for any initial signs of compromise or anything unusual on a network.

And everyone should be extra vigilant for phishing emails and clicking on links that may be new or something that looks unusual.

I want to repeat that we have no information about any specific threats or attacks, so the purpose of this is really to raise awareness before a holiday weekend, given the history of increased criminal cyberactivity during holiday weekends.

As always, CISA, FBI, and other U.S. government partners are positioned to support any organization that needs it. Please visit StopRansomware.gov and follow the practices that you see.

Taking a step back for a moment, the Biden administration is committed to addressing cyber threats to the country. And indeed, as I mentioned, last week, President Biden hosted executives from technology companies, education firms, critical infrastructure, and others to focus on addressing the root causes of cyber. The technology companies, in particularly, announced a set of commitments online to address some of the root causes of technology vulnerabilities and improve security of their products.

Thank you. Wishing you a safe and enjoyable holiday weekend.

MS. PSAKI: Steve.

Q It's been more than two months since the President's meeting with President Putin. Have the Russians done anything to crack down on ransomware attackers?

MS. NEUBERGER: Thank you for the question. The discussions with the Russians continue. As President Biden

noted, he's looking for action with regard to addressing cyberactivity. And we continue to see — to look for that.

That being said, we also need to look at our own activity — and it's the reason for this today — to ensure that we're doing everything we can to lock our digital doors and ensure that our networks and our organizations are as safe as they need to be online.

MS. PSAKI: Jacqui.

Q Have you guys determined who is responsible for the attack on the State Department a couple of weeks ago?

MS. NEUBERGER: I won't address specific incidents here. We're certainly looking at that. And we're also focused on, as I noted, the rollout of the five particular technologies across the federal government so we can confidently reduce the risk of such continued attacks.

Those are on a tight timeline. So far, both CISA and Commerce's NIST have met every single timeline, and those key technologies are scheduled to be rolled out within six months of the President's executive order last May. So we're really tracking October and November to ensure that we've modernized our defenses across the federal government.

Q Do you believe that the patches that need to have been done have happened across agencies?

MS. NEUBERGER: That work continues. As I noted in a prior discussion, there's a great deal of work to modernize our federal notwork [sic] — networks. They were not where they needed to be.

And that's one of the reasons that the President mandated such aggressive — we believe achievable, but aggressive —

steps to bring them up to where they need to be to meet the level of the attackers' focus on those networks.

MS. PSAKI: Jen.

Q Some of my colleagues at Bloomberg reported today about identifying some of the Chinese state-sponsored hackers who are behind an alleged NSA — co-opting an alleged NSA backdoor in products from Juniper Networks, which has obviously been known about for quite a few years. What are the administration's policies around the use of backdoors? And what are the guidelines, if any, about NSA's ability to insert backdoors into U.S. tech companies' products?

MS. NEUBERGER: As you know, that's been — as you noted, that's been an old story that's been reported, and I think we've continuously noted that there isn't substantiation for it.

Focusing on supply chain for a moment: The supply chain and the — the need to ensure that software is as secure as possible is something that's absolutely a priority of this administration.

I think you saw, in the President's executive order, he mandated putting in place certain steps to ensure secure supply chains for products, and those are rolling out.

Indeed, as well, I think you saw several of the announcements that came out of the summit last week.

So, we're absolutely committed to working with technology companies to ensure that their products are as secure as needed to face the attacks of today.

MS. PSAKI: We'll do Monica, and then right in the back, and then we'll have to wrap it up.

Q So, there was a spike in ransomware attacks earlier in the summer. That seems to have slowed down slightly. To what do you attribute that?

And then you did mention there wasn't something specific that caused you to come and bring out this morning. But in terms of Labor Day, is there anything different about it that you would like to highlight, given we haven't seen these kinds of warnings before the Fourth of July or anything else more recently?

MS. NEUBERGER: Two really good questions. First, we've noted the decrease in ransomware. And we think it's an important step in — in reducing the risk to Americans. There could be a host of reasons for it. So, we're noting that trend, and we hope that that trend continues.

And with regard to the change in why we're here today, I think it reflects the administration's focus on cyber threats and the recognition that we play a role in all of that.

Yes, there are attackers, but they're leveraging vulnerabilities across the networks that we have. We continue to see successful attacks occurring against vulnerabilities for which there are patches, so we want to use the opportunity of this pressroom and the attention that it gets to ask Americans, to ask organizations to do the steps they need to do to be safe online, even as the government focuses on its efforts — and you've heard our counter ransomware strategy, working with countries around the world, focusing on the illicit use of cryptocurrency, and pursuing and disrupting ransomware networks around the world.

So, it's — this really represents the focus we're putting on this issue and the need — and the highlight we're saying to Americans to do what they need to do, in partnership with the government, to be safe online.

MS. PSAKI: Last one, in the back.

Q If you're a small company just trying to check yourself when it comes to ransomware attacks, what is the weakest link attackers will try to exploit? Just a small company — mom-and-pop shop — you're worried about getting an attack.

MS. NEUBERGER: Really great question. I would say two things. One is: Make sure your leadership and IT staff have deployed multifactor authentication and have a strong password.

Q So the password (inaudible)?

MS. NEUBERGER: Really, a strong password.

Q Okay.

MS. NEUBERGER: And then, of course, patching the software that's most important.

Q Thank you.

MS. PSAKI: Go ahead. Last one.

Q I wanted to ask what you and your team are doing heading into the weekend — whether it's here at the White House, through NSC, or at CISA. Do you have certain staff on call this weekend? Do you have certain preparations that you're making on your end in addition to the advice you're giving to the public?

MS. NEUBERGER: Great question. So, first, we pulled together the intelligence community to ensure that we were tracking any and all threats, and to ensure that they're highly alert for anything related to that.

Second, we, of course, brought together agencies across the government, including key ones like FBI and CISA, to ensure that they were fully postured and fully prepared to be on staff and noting any early signs of any incidents so we could rapidly jump on them and respond to them.

And, finally, is this: calling on Americans, organizations to do the steps they need to do to be as safe as possible in advance of what may be an increased threat, as we've seen in history — for the reasons I noted — during the holiday weekend.

MS. PSAKI: Thank you so much.

MS. NEUBERGER: Thank you.

MS. PSAKI: We will see you again, I'm certain.

MS. NEUBERGER: Thank you, Jen.

MS. PSAKI: Thank you for taking the time.

Okay, a couple of things for you at the top. Obviously, the President spoke to our ongoing work to help the people in the Gulf Coast and also in the Northeast and also out West as we're going through a range of natural disasters across the country.

I just wanted to call out a few things:

In Louisiana, Disaster Survivor Assistance teams arrived today to support cooling stations in the city of New Orleans

and St. John the Baptist Parish, where heat advisories are in effect and many residents remain without power.

FEMA also announced today a new policy, this morning, to reduce barriers that have long prevented many disaster survivors, particularly Black Americans, from receiving disaster assistance by expanding the types of legal documentation for homeowners and renters to prove ownership or occupancy. This has been a big barrier in the past, and it was something we worked hard to address proactively.

Also, finally, to help disaster survivors — and I've talked about this a bit, but just to give you an update — register for federal assistance, mobile emergency response support assets are deployed to support Louisiana and Mississippi.

Now, as of today, roughly 50,000 households in Louisiana have already received a one-time payment of $500 from FEMA to support critical needs. And as the President noted, FEMA has awarded more than $77 million to help disaster survivors.

Also this week, as part of our efforts to engage with communities that are hesitant about COVID-19 vaccines, White House Senior Policy Advisor for COVID-19 Equity Dr. Cameron Webb has held community confidence visits to encourage vaccinations in cities across the South, including Columbia, Jacksonville, Columbus, and Mobile.

The community confidence visits aim to take a systematic approach to community conversations about COVID-19 and the vaccines that focus on the interrelatedness between COVID-19 and longstanding social determinants of health, including housing, education, mental health, and food insecurity.

We've been really encouraged by how receptive people have been to these conversations and, more broadly, encouraged that more people continue to get vaccinated, including nearly 2 million in the past — to date — people in the past two days — a strong start to the month.

And I know there's a COVID briefing that starts in about 40 minutes, and you can learn more there.

Go ahead, Josh.

Q Wonderful. Thanks, Jen. Two subject areas, both legal. With regard to the Texas abortion law, President Biden has a Supreme Court Commission, with a report due by October 6th. Did the President or anyone in the administration reach out to members of the commission in the wake of what happened? And does the President have any new thoughts on the structure of the Court?

MS. PSAKI: Well, first, I would say you're correct that there is ongoing work that the Court Commission is doing. Their work is — and just to remind you all of what their focus is — there's about 30 members of this Court Commission. They're from diverse backgrounds and diverse views. And they're going to examine a range of questions about the future of the Court, including term limits, including court expansion, and the — and in addition — and several additional topics.

We have not — not to my awareness have we reached out to the commission. It's important they do their work on the timeline that was designated and that they examine, from a broad and diverse viewpoint, all of these questions. But the President looks forward to reviewing their work when it's completed.

Q And the President doesn't have any new thoughts on the structure of the Court?

MS. PSAKI: He's waiting for the conclusion of this report — looks forward to reviewing it, seeing where they come out.

Q And then secondly, on the new pharma bankruptcy, does the administration believe the settlement gave sufficient justice to the victims of the opioid crisis?

MS. PSAKI: It's a great question, Josh. I want to speak to our team and see if we can get you a more specific comment on that.

Go ahead.

Q On the Texas law, what avenues are available to you in the short term for reacting to this law? We saw the President's statement. He directed the Gender Policy Council to do some things. What — what do you envision happening here?

MS. PSAKI: Well, Steve, that's exactly what the President directed his team to look into — to be able to answer that question. Obviously, we're under — we're about 12 hours, or less than that, since this ruling.

And what the President made clear in his statement this morning is that the impact of last night's decision should be immediate and requires an immediate process.

So, yes, he's asked the Gender Policy Council because he feels it's important for there to be a point of — point of contact — or a point person, I should say, at a senior level in the White House.

But most importantly, he's also directed them to work with the legal team here at the White House, the Department of

Justice, the Health — the Department of Health and Human Services to determine what, if any, steps can be taken here to protect a woman's right to choose and access to healthcare for women in Texas.

Q Were you surprised by this ruling?

MS. PSAKI: We can never predict rulings, I will say, Steve. We certainly know the makeup of the court. But again, we try to stay out of the business of making predictions.

Q And just one thing on Afghanistan: Do you see any possibility for a limited easing of the freeze in Afghan assets to prevent the collapse of that country's banking sector?

MS. PSAKI: Well, I would say, first — and let me give you just kind of an overview of, kind of, what some of the considerations and good questions are.

Q It's part of the economic leverage you have over them, right?

MS. PSAKI: Yeah. Yes. But no one should assess that we are considering — currently considering an easing of sanctions on the Taliban. That is not under — that is not actively being discussed or pursued.

We have not reduced sanctions pressure on the Taliban leaders or the significant restrictions on their access to the international financial system. And we will judge — and we want to make clear — this very clear: We are going to judge the Taliban by their actions and we will stay in close coordination with the international community on any steps that we take moving forward.

Now, at the same time, we also want to ensure there is assistance to the Afghan people — humanitarian assistance

and other assistance — to keep them afloat and make sure they have — we provide that from the international community at this point in time.

So there have been steps that have been taken in coordin- — including issuing an OFAC license that allows this humanitarian assistance to go through. That, of course, is not through the Taliban; that is through outside organizations. And that's something we're working to be big contributors to.

Go ahead, Jeff.

Q Back to the commission for one second. The President obviously served for a long time as Chairman of the Judiciary Committee; he's been in this town longer than most anyone. What is he looking for from a commission to offer him that he would not have for this? And what do you say to critics who say he's simply punting this to them to avoid making a yes-or-no decision if he thinks the Court should or should not be expanded?

MS. PSAKI: Well, I would say to critics — or we would say to critics: Yes, the President has a long history of working on judicial issues as the former Chairman of the Judiciary Committee, and he takes the role of institutions in our nation's history, including the Supreme Court, quite seriously.

That's one of the reasons why this court was put together and construction in the way it — I mean, this commission, I should say — was put together and constructed in the way it was, which is with a diverse set of viewpoints, a diverse set of expertise.

And he asked them to look at a broad set of questions, wanted to give them time to do that work and come out of that with some — with some viewpoints. But he wants to leave them space to do exactly that.

And I think the fact that he named a commission with a diverse set of viewpoints reflects his strong, you know, commitment to preserving institutions, but also taking a fresh look at things that need to change if needed.

Q Is he misleading supporters of "expanding the Court," though, by allowing his commission to do its work? I mean, the reality is: This would take a legislative change. It's something he couldn't change on his own. Why doesn't he just come out and say how difficult this would be?

MS. PSAKI: Well, I think it's clear it's difficult. But the President's view on the expansion of courts has not changed. He also wants this group — this commission to take a close look at a range of issues, not just court expansion, which is an important question for them exam- — to examine, but term limits and a range of questions that are — the commission is looking at.

I will also note, though, Jeff, that in the President's statement today, he also made very clear — and in pretty strong terms — his viewpoints on the ruling of the Supreme Court in this case. And rulings like that do raise concerns — not just for the President, but for people out there in the country — about how the Court is operating.

And I'll just note what he said, you know: " For the majority to do this without a hearing, without the benefit of an opinion from a court below, and without due consideration of the issues, insults the rule of law and...rights of all Americans to seek redress from our courts."

That is, of course, of concern not just to him, but it should be to all Americans who watched the ruling this morning.

Q On Afghanistan, really quickly, if I can: Are there updates on the 100 to 200 Americans who — American citizens who work in the country or are still in the country? Do you believe they still are? Or what's the latest on the diplomatic mission?

MS. PSAKI: Well, I know my colleague at the State Department is briefing right about now and will be — give a more in-depth update on this.

But what he said yesterday, and I will just echo, is it closer to 100. We're in close touch from the State Department, from our diplomatic officials, with all of these individuals, working in close coordination with them to determine how they can leave the country, if they've left the country.

There have been reports, as I think many of you have seen or reported yourself, about charter flights. If I can just make a — speak to that for a moment, because I know it's been a popular question.

We — there have been some confusion about this. We don't — do not have personnel on the ground, nor do we have air assets in the country to — and we don't control the airspace. So, anyone who's suggesting we are preventing these flights, that's not accurate. We don't — we couldn't prevent a charter flight from taking off.

But what is important for people to understand is where we have some concern. And that is the fact that we're — we do not have reliable means to confirm the basic details of charter flights, including who may be organizing them, the number of American citizens, and other priorities groups on

board, the accuracy of the rest of the manifest and where the plane may land, what security protocols are taking in — they're taking into place.

So, just to kind of give you an example here, these charter flights are landing on U.S. military bases, and we have to be very careful. And I think it's understandable we have concern about flights that — where we don't have that level of information and understanding about the manifests, what the protocols are that are taking — that are underway.

There's also a question — there are active — there continue to be active ISIS-K threats, and there's also a question of where these flights go, where they land. We know ISIS-K has a keen interest in attacks against aviation targets and our personnel on the ground in our airport — in our military bases. And these are among the risks that we take into account.

Go ahead.

Q Just a few here. Most of them Texas-related questions I'm going to ask.

MS. PSAKI: Sure.

Q I'm just — we're curious: What advice would the President give to a woman in Texas right now who wants or needs to get an abortion at this point?

MS. PSAKI: What the — what the President would convey to any woman who is trying to get an abortion, seek an abortion, be able to — to employ her constitutional right to — to seek healthcare, and healthcare that is enshrined in and allowed by federal law — what he would convey to

them? I don't think he's going to be giving medical advice, A; that's not the role of any president, he would say.

But I would say he would convey to them: "I have asked my team — I've asked my team to use every lever at their disposal to ensure you have this right, to ensure you have access, to ensure that you can have the ability to — to seek medical care in the way that every woman should have the right to across the country." And he has made that a priority.

Q And this request of DOJ and HHS for "what more can we do," is the understanding or the expectation that they will actually come back with specific ideas? Or is it possible that they determine there really isn't much beyond making sure somebody takes this to the Supreme Court? Because the federal government can't be subject to a civil suit in Texas, but there are other things, potentially, the federal government would be able to do.

MS. PSAKI: The President has every hope, expectation that the leaders of agencies across the government who have capacity will seek every way they can, every means they can to protect a woman's right to choose in Texas.

I can't preview for you. I don't know yet what they will come back with.

Go ahead.

Q Thanks, Jen. On the Texas law, has the President been in touch with Speaker Pelosi and Majority Leader Schumer in the past two days about their efforts to pass legislation protecting abortion rights?

MS. PSAKI: He does intend to talk with them about this. I — so I can't — I can't tell you exactly when that will be, but he

has every intention to do that.

I will note that Speaker Pelosi also put out a statement about the intention to bring up the codification of Roe up for a vote, which is something the President certainly supports and would be eager to sign into law.

Q Okay. And one more. Does the administration have a message for industry and private businesses that have operations in Texas? Would the President and the White House support a boycott of sorts against Texas?

MS. PSAKI: That's not a call we're making from here. What our effort and what the focus of the federal government is, is to look for every resource, every lever at our disposal to ensure women in Texas have the ability to seek healthcare.

Q And following up on the Texas law, why does the President support abortion when his own Catholic faith teaches abortion is morally wrong?

MS. PSAKI: Well, he believes that it's a woman's right, it's a woman's body, and it's her choice.

Q Why does the President — who does he believe, then, should look out for the unborn child?

MS. PSAKI: He believes that it's up to a woman to make those decisions and up to a woman to make those decisions with her doctor.

I know you've never faced those choices, nor have you ever been pregnant. But for women out there who have faced those choices —

Q Well —

MS. PSAKI: — this is an incredibly difficult thing. The President believes their rights should be respected.

Q And what's his message to —

MS. PSAKI: Go ahead.

I think we've got to move on.

Q — pro-life groups that support this law without (inaudible) —

MS. PSAKI: I think we have to move on. You've had plenty of time today.

Q I know you like to be a wise guy and throw some — (inaudible.)

MS. PSAKI: Go ahead.

Q How many green card holders and SIV applicants remain in Afghanistan?

MS. PSAKI: Let me give you — well, let me give you, first — and I'll get to your question, but it reminds me I wanted to give you guys an update on one piece that was asked yesterday, which is how many people have come into the country. And this is something that DHS will be providing regular updates on, but just to give you an understanding of the breakdown, and then I will come back to your question, Jacqui, I promise.

First, between August 17th and August 31st, of the breakdown of people who have come into the country: 31,170 — -107, I'm sorry — people have arrived in the United States as a part of Operation Allies Welcome; 4,446 are U.S. citizens, 14 percent of them; 2,785, or 9 percent, are U.S.

lawful permanent residents; 23,876, or 77 percent — this is the statistic I gave yesterday, which I then later butchered in the briefing — are other Afghans at risk, including SIV and other visa holders, SIV applicants, p-1 and p-2 referrals, and others. Note that this group includes a small number of third-country nationals that were also evacuated and processed.

We will give updates on that. That's obviously the data as of just a couple of days ago.

In terms of your question — which is a very good one, Jacqui — in terms of how many people are in the country now, there are people who are eligible, and we may not even know they're eligible yet. Right? It is very hard to define those numbers. That is something that certainly the State Department, in coordination with the Department of Homeland Security, are going to be assessing what we think the population is and how we can work with this population to ensure that we help individuals who want to leave and want to depart the country to depart.

Some of those people may be eligible for a range of our programs — SIV programs, p-1/p-2 programs. Some of them may not, but they still want — may want to depart the country.

Now, as I noted yesterday, and I've noted several times, everybody who wants to leave Afghanistan and come to the United States will not be able to and will not be eligible, and we don't want to set the expectation that will be the case. But what we want to do is try to assess and try to do extensive outreach through — outreach through diplomatic channels to see how many people there are, what programs they might be eligible for.

Q Thank you. And then I wanted to get to the Taliban and questions of whether it's keeping its promise for amnesty.

There was some reporting from the BBC — some color from that story. Since the Taliban came to power, one man said they haven't stopped killing. A few days ago, this person said they killed 12 members of special forces in Kandahar, 3 soldiers in Jalalabad as well. The Taliban took them out of their homes and shot them.

Given this kind of reporting that we're hearing, is it possible that our reliance on the Taliban to keep their word, in terms of our evacuation, is misplaced — with going back on things like the amnesty promise?

MS. PSAKI: Well, first, I don't have any confirmation of those details. I'm not questioning the BBC's reporting. I just don't have any confirmation of them from the U.S. government. I would certainly point you to the Department of Defense and others who might have additional details.

But what I would note here, Jacqui, is no one is saying, from the federal government — no one — the President, the Secretary of Defense, no one from the intelligence community — that the Taliban are good actors. Right? We are not saying that. That is one of the reasons we are being so clear that we are not rushing to recognition. We will be watching clearly. We have a range of leverage at our disposal, including access to the global marketplace.

And, of course, we will be assessing. It's, of course, based on how they treat individuals in the country, how they treat women, whether they let people who want to leave the country leave. All of those are factors that we will be assessing.

But I don't have any confirmation of that specific reporting.

Go ahead.

Q Jen, yesterday, you said you were going to check on the specifics. So, just to be clear, the President does support the Women's Health Protection Act?

MS. PSAKI: We are looking at a range of options in Congress, including that — the Women's Health Protection Act — but I don't have an assessment at this point in time about that piece of legislation.

Q Got it. And will there be a point person for this whole-of-government approach, like with voting rights or with immigration? And if not, why not?

MS. PSAKI: The President has conveyed clearly in his statement he'd ask the Gender Policy Council co-chairs to oversee this effort.

Q And what's the timeline on that policy council?

MS. PSAKI: In what — I'm not —

Q In terms of when they might — will they have a deadline to get back to him or when they may produce a report.

MS. PSAKI: Well, I wouldn't look at it as producing a report. They are going to be coordinating all of the leverage and all of the efforts and policy options across the government. And they — the President asked — wants them to act as quickly as possible. So, it's not a means of "100 days and then we'll get a report." It's, "Let's see what our options are, and let's act on them."

Go ahead.

Q If I could just try to drill down on that: The President did say an immediate response is required. I know you said you're not in a position to preview any, but what does the White House see as its — as the federal responsibility here? I mean, you're talking about the possibility of involving the Justice Department, HHS. In Oklahoma, there are clinics that are saying, "You know, okay, we are offering the service. Come here." Is that something that the federal government could do: provide transportation for women outside the state of Texas?

MS. PSAKI: These are all great questions. And I would note that it wasn't just the Department of Justice that the President referenced in his statement, on purpose, right? Because the Department of Health and Human Services has a range of resources, funding, programs that they can look at and potentially deploy.

And, yes, it is urgent. The President wants them to look at these programs now and come back and see what's possible. But it has been less than a day here, and I just want the experts and the policy experts to be able to assess what's possible, and then we will get back to you and make sure you all know exactly what our options look like.

Go ahead.

Q Thanks so much. There are some concerns about the recent drone strikes and the possibility of more. Some groups, like the ACLU, as well as some former Obama officials, feel this is an indicator that the forever wars are not over if drone strikes continue. Can you address those concerns and speak to whether these drone strikes mean an extension of the war?

MS. PSAKI: The strikes that killed ISIS-K terrorists?

Q And the possibility of more. I mean, President Biden yesterday said that this is not over.

MS. PSAKI: Well, if anybody wants to convey they don't think that we should kill ISIS-K terrorists and kill the people who killed 13 members of our military, then the President is happy to have that debate.

Go ahead.

Q Can I ask —

MS. PSAKI: Yeah.

Q — another question on refugees? Thank you.

Some groups are anticipating about 50,000 Afghans coming to the United States. Can you — is that an estimate that you're able to confirm? And is there anything more that you can share on what status they will arrive? Will most of them have humanitarian parole — SIVs, P1/P2s?

And how will that — those numbers be applied to the refugee cap? Will they be part of the 125,000 that's been committed to, or in addition?

MS. PSAKI: Sure. These are all really good questions that are being discussed by the team as we speak. But let me try to answer what I can answer at this point in time.

So, right now, the U.S. military bases — they confirmed, about two days ago, that they had about 20,000 people. That may have — number may have gone down now, so I would certainly encourage you to ask them for an updated number if that's of interest. They are working towards space for about 50,000.

Now, there are people who come to this country — American citizens and others — who have family members who may not go to those military base — U.S. citizens, of course — who may not go to those bases. And those bases are meant to be temporary regardless.

In terms of what classification — so, as you know, there are different classifications people have come into the country under from Afghanistan: the SIV — the Special Immigrant Visa Program; P1, P2 programs. Some have come in through parolee programs.

And, yes, we are having discussions about, over the long term, what this looks like. Right now, refugees who come in as refugee status would be under the refugee cap, but beyond that, I have to let the policy process see itself through. It's a good question.

Go ahead.

Q On the 125,000, do you know that? I apologize.

MS. PSAKI: Oh, sorry, about whether — say that one more time. What was the question?

Q The 125,000 —

MS. PSAKI: Yeah.

Q — will it be in addition to the committed refugee cap of 125,000, or will it be just the 50,000 — or whatever the number is? Does it fall with —

MS. PSAKI: Well, 50,000 — a lot of those people are Special Immigrant Visa applicants — right? — or through other programs. So that wouldn't be under a refugee cap.

Go ahead.

Q Thank you. Reproductive rights activists have noted that President Biden seems reluctant to use the word — the specific word "abortion," although he did use it in his statement today, in the statement you put out yesterday. Can you explain his seeming reluctance to use that word? And was it a deliberate messaging strategy or choice to use it this week in relation to the Texas law?

MS. PSAKI: I have to say, as somebody who strongly supports a woman's right to choose — myself; as somebody who spent time working with groups like Planned Parenthood, amazing groups like that — that I think the most important value people should look at is what the President does in his actions and what he fights for.

And I don't think I'm going to have any other assessment beyond that.

Go ahead.

Q The President said today — talking about the hurricane — that the climate crisis is here, and then he went on to talk about the wildfires and —

MS. PSAKI: Yeah.

Q — the flooding. Is anything in the recent — that recent string of weather events changed his view on how aggressive the administration needs to be on carbon reduction in its policy?

MS. PSAKI: Well, I think it's reaffirmed, as you heard the President reference today, his commitment to getting his Build Back Better agenda passed — which has a huge — huge focus on addressing the climate crisis and taking a

number of steps, including creating more — investing in resiliency for infrastructure, as you know; also setting ambitious goals and taking policy steps to reach those.

So, I think it really reaffirms more the policies he's already proposed that will take huge steps forward in helping to address the climate crisis. I'd note that also even Senator — Senator Cassidy fro- — also noted the need to invest in infrastructure and how these recent events reiterate that.

Q And on the Build Back Better, would the President sign a version of that passed by the House and Senate that does not fully fund his carbon reduction agenda?

MS. PSAKI: Well, I'm not going to negotiate from here, obviously, but the President put those proposals in the package because he feels they are vitally important to addressing the climate crisis. And the climate crisis is one of four crises he's identified from the beginning as being central to the issues he's going to address as President.

I will say that, you know, as people look to the next couple of weeks of the very expansive legislative agenda that we are going to all be undertaking together, what the President is quite focused on is, yes, of course, steps — the investments that will help cut costs for the American people in a range of ways, whether it's the Child Tax Credit, making childcare less expensive, making college more affordable.

But he is equally as focused on the tax — the — making wealthiest Americans and corporations pay more because he thinks that's fair, and he thinks that's — that is how we can deliver on equality in this country. And that can also pay for a lot of these important policy initiatives.

Go ahead.

Q Are there any more details about the President's trip to Louisiana tomorrow?

MS. PSAKI: Sure. They are still being finalized, which is not out of the norm, but let me tell you what I know at this point in time.

So, the President will travel to New Orleans to survey storm damage from the hurricane. He'll meet with state and local leaders. I would expect that will include the governor and the mayor from impacted communities. And beyond that, we're still finalizing all the details, which we'll hopefully have more later tonight on.

Q And, on the Texas abortion law, how worried — or is the administration worried at all that this will enable other state legislatures to pass similar bills?

MS. PSAKI: Of course, we're worried. Of course, we're worried that other states where there is — where there is a movement and an effort to prevent women from having access to healthcare will copycat the steps by the Texas — that happened in Texas. Now, that is one of the reasons why the President thinks it's so urgent and why he has asked his team to act as quickly as possible to see what our options are.

Go ahead.

Q Thanks, Jen. On Afghanistan, the Taliban says China will be their main partner and, kind of, financial lifeline. Does that weaken America's leverage over the group to change its behavior, especially given the geographic closeness between China and Afghanistan?

MS. PSAKI: Well, I would first say that — as the President has said many times, so let me repeat — there are few countries that wanted us to stay in Afghanistan more than China and Russia, because it would have tied up our own resources and tied up our own U.S. military and tied up our own financial assets and options.

What the — our leverage over the Taliban is, is a range of of — of things. I mean, one is, of course, access to the global marketplace, which is not just China; it is a range of money that is in the Federal — that is in the New York Federal Reserve, that — that is — was the Afghan government's money that they currently don't have access to. It is working with a coalition of 100 countries around the world that have signed this statement on what their expectations are of the Taliban. It's working with the U.N. Security Council.

So, the world is united in what they expect the Taliban to do, which is allow people who want to depart the country to depart, and China has to decide where they are in that effort.

MS. PSAKI: Go ahead.

Q Just to the eviction moratorium — or lack thereof of an eviction moratorium: I'm curious what specifically the administration is doing to help those states who seem to be having issues doling out these billions of dollars —

MS. PSAKI: Yeah.

Q — available for renters and landlords beyond the — you know, telling them to speed it up.

MS. PSAKI: Well, I promise you we're not just telling them to speed it up. We are telling them to speed it up, but we are

not stopping there.

One of the steps we've taken — and we've outlined — we've announced a few steps over the course of the last few weeks — is working to cut bureaucratic red tape from here. So that includes making it easier for landlords and tenants to apply for this assistance and ensuring that that is not an incredibly difficult process.

We've also worked with individual states to determine what are the holdup in their processes. And some of the bureaucratic steps in places where we've eased the red tape has expedited the funding going out in states, so we've seen successes on that front.

What's important to note here is that the funding exists in states across the country to essentially do the federal eviction moratorium, even though the Supreme Court has ruled as they ruled — because states can do it on an individual basis.

So, what we're really including states to — what we're really encouraging states to do is put in place eviction moratoriums statewide, or take any steps they can sta- — take across the state to make it harder for people to kick tenants out of their homes during this time.

And we can get you a rundown of that too. I'm looking for all the pieces.

Go ahead.

Q Thank you. A Taliban spokesman told an Australian news network that the 41 Australians who died in the war in Afghanistan died in vain.

During this time, the Australian government found out about the withdrawal date change through media reporting. We weren't included on the list from Secretary of State Antony Blinken of countries called on the final day — August 31. Does the Taliban have a point?

MS. PSAKI: I'm not sure I understand your question.

Q We have sacrificed a lot for this alliance and — including the lives of 41 Australians — and we've been left, seemingly, out of the loop during this withdrawal process. There hasn't been high-level communication with the Australian government during this time. So —

MS. PSAKI: I don't think that's true. I don't think that we have not engaged with the Australian government. We have worked with our partners around the world to evacuate individuals from a range of countries around the world who need evacuating from the country.

I would say — and the President would say, if he were standing here — those 41 Australians did not die in vain, and we are incredibly grateful for their partnership. We're incredibly grateful for their support over the course of a 20-year war. And Australia remains a pivotal partner to the United States.

But I would be very shocked if we had not been in touch with and engaged with — so what I was asking you for clarification on was question about the 31st and a call on the 31st. I'm not sure what that would be a reference to.

Q Sure. That would be on the speech that Antony Blinken, the Secretary of State, gave at the withdrawal — at the end of the —

MS. PSAKI: Yeah.

Q — conflict — the last flight. He listed through all these different countries that he called at the end of that, and Australia wasn't on the list.

MS. PSAKI: I can certainly ask the State Department when their most recent diplomatic conversations were with Australian leaders, but I know that we are in close touch, in close coordination, and that Australia is an incredibly vital partner, not just in — over the last several years in the war in Afghanistan, but a range — on a range of important global issues.

Go ahead.

Q Thanks, Jen. I wanted to follow up on Jeff's question. We know that commission is not tasked with providing specific recommendations to the President out of that review, and he's already said that he is not a fan of court packing. So, realistically, what kind of changes can we expect to come once that review is complete? Is the President committed to addressing the court system in a significant way?

MS. PSAKI: Well, the President wants to take a look at what the court reform group advises on. And, yes, they're not coming out with, "These are the seven steps that we are recommending." It's a diverse group with diverse opinions, and he felt that was important, given this is a vital institution in our nation's history.

So, I can't predict for you; I don't — we — I don't know where he's going to land. I'm going to leave the space for the President to determine that.

Go ahead, in the back.

Q A couple of follow-ups. First, I wanted to ask about the answer that you gave to Franco about the ongoing drone strikes in Afghanistan, because the President talked about, in his recent remarks, that this was kind of a new chapter. And you've talked from the podium there about sort of meeting these threats now where they are outside of Afghanistan.

MS. PSAKI: Yeah.

Q So, if these drone strikes do continue, the concern from the international community is these are extrajudicial killings, there are civilian casualties often. I mean, how is this sort of the new era? It seems almost like business as usual.

MS. PSAKI: Well, I think it's — the context of the President's remarks was not "Drone strikes are the new era." It is "We need to meet threats where they are and ensure we're taking steps to address them in coordination with the global community, of course."

I will say that the United States takes the threat of civilian casualties incredibly seriously. We do everything we can to prevent civilian casualties; that will continue.

I know there have been very good questions about the strike over the — that happened over the weekend, which — and there is an investigation into that. There's been a range of reporting, but the investigation needs to play out and conclude before we speak to that.

But I would say what the President is referencing is there are a range of countries around the world we don't have a military presence on the ground but we can still prevent terrorist groups from metastasizing and posing threats to

not just the United States but to our partners and countries around the world. And there's a range of tools and tactics. So, that's what he was conveying.

Q Jen, may I follow up?

MS. PSAKI: Go ahead.

Q Just one last question — oh, sorry.

MS. PSAKI: Oh, go ahead.

Q Apologies. One more follow-up —

MS. PSAKI: Sure.

Q — on Steve Holland's question this time. You kind of updated us on how you're sort of encouraging the international leaders to get the money flowing into Afghanistan again.

MS. PSAKI: Yeah.

Q And as these aid groups are warning of a humanitarian crisis, given the fact — and this is, again, referencing the President's remarks — there's been $2 trillion spent there, what's being done to ensure that all this money that's spent, whether it was in the past or in the future, is actually getting to the people that need it and not just corporations that have profited off of people's misery for so long?

MS. PSAKI: Absolutely. One, I would say he signed this OFAC license because he wants humanitarian groups that we know we can rely on to be able to have access to provide this assistance. And that was a step we took to ensure that.

One of the pieces we've talked about a bit in here is the importance of getting airports functioning — right? — not just at HKIA, but in regional airports, because that's how this humanitarian assistance is going to be delivered to people across Afghanistan.

So, that's another area where he's quite focused, and the Secretary of State and our government is quite focused.

Q May I follow up, Jen?

Q Thanks, Jen.

Q Two more foreign questions. First of all, on Afghanistan, what is the administration's position on the National Resistance Front led by Ahmad Massoud? And is the U.S. talking to or assisting them in — or in any way supporting them in reaching their goals?

MS. PSAKI: I don't have anything to read out in terms of engagements with them. I'd point you to the State Department.

Q Secondly, as you know, Climate Envoy Kerry is in China right now to talk about climate change.

MS. PSAKI: Mm-hmm.

Q China's Foreign Minister has said, quote, if the U.S. want progress on climate — forgive me, sorry, quote starts here —

MS. PSAKI: Yeah.

Q — "Stop regarding China as a threat and as an adversary." End quote. Does the administration see China as an adversary in this regard? And are you willing to meet them in the middle to make progress on climate change?

MS. PSAKI: Well, the United States sees China as a country where we have disagreements, and we also have areas where we can work together. And that's what complicated diplomatic relationships look like. And certainly, our relationship with China falls into that category.

Thanks, everyone, so much.

Q Jen — Jen, on drone strikes, there was a —

MS. PSAKI: I don't think I'm going to have anything new to what I already — already answered on that. But we'll see you all tomorrow.

Thanks, everyone.

Q Have a good trip.

MS. PSAKI: Thank you.

2:53 P.M. EDT

EXHIBIT 39

Ian Millhiser,
It sure sounds like Roe v. Wade is doomed,
Vox (Dec. 1, 2021)

Vox

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POLITICS

It sure sounds like Roe v. Wade is doomed

Republican presidents have said for years that they would appoint justices who will overrule Roe. They've probably succeeded.

by **Ian Millhiser**
Dec 1, 2021, 2:10 PM EST



Abortion rights advocates and anti-abortion protesters demonstrate in front of the US Supreme Court on December 1, as the court heard arguments in a case from Mississippi, where a 2018 law would ban abortions after 15 weeks of

pregnancy, well before viability. Andrew Harnik/AP



Ian Millhiser is a senior correspondent at Vox, where he focuses on the Supreme Court, the Constitution, and the decline of liberal democracy in the United States. He received a JD from Duke University and is the author of two books on the Supreme Court.

Midway through arguments in a case that could end with the Supreme Court abolishing the constitutional right to an abortion, Justice Sonia Sotomayor asked a pointed question about the Court's future: "Will this institution survive the stench that this creates in the public perception, that the Constitution and its reading are just political acts?

There are early signs Sotomayor is correct that the public is turning against the Court as the Court turns against *Roe v. Wade*. But during Wednesday's oral arguments in *Dobbs v. Jackson Women's Health Organization*, all six of the Court's Republican appointees appeared eager to push ahead anyway and overrule at least some key parts of the Court's prior decisions protecting abortion.

The justices were asked to consider a Mississippi law that prohibits nearly all abortions after 15 weeks of pregnancy, a law that violates the Court's decision in *Planned Parenthood v. Casey* (1992) that pregnant people have a right to terminate their pregnancy up until the point when the fetus is "viable," meaning it can live outside the womb. A majority of the Court appeared very likely to overrule this part of *Casey*.

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At least four justices seemed inclined to go even further, eliminating the right to an abortion altogether. And though Justice Amy Coney Barrett played her cards a little closer to her chest than her colleagues, it seems more likely than not that she will join them. In other words, there could be a majority for overturning *Roe*.

And even if the Court does not explicitly overrule *Roe*, it could easily announce a new legal standard that renders *Roe* an empty husk. A decision like that might leave *Roe* nominally alive, but that would also leave states free to restrict access to abortions to the point they're nonexistent in the state, or come up with other creative ways to effectively ban them.

It is still possible the Court will surprise the myriad of legal analysts predicting the end of a constitutional right to an abortion. In 1992, when the Court heard *Casey,* even Justice Harry Blackmun, the author of *Roe*, expected his landmark opinion to be overruled. Instead, *Casey* weakened, but didn't overrule, *Roe.*

But after Wednesday's oral arguments, no one should bet *Roe* will receive another stay of execution. The two political parties are too well-sorted on questions of abortion rights, the Republican Party has grown too sophisticated in picking judges who will hew to the GOP's policy preferences, and a majority of the sitting justices were exceedingly skeptical of *Roe* at Wednesday's argument.

The two issues at stake in *Dobbs*

Casey laid out a two-part framework governing the right to an abortion. The first part is that "a State may not prohibit any woman from making the ultimate decision to terminate her pregnancy before viability," which occurs around the 24th week of pregnancy.

Casey also held that states may, under certain circumstances, regulate abortion. But such regulations may not impose an "undue burden" on the right to terminate a pregnancy — meaning states cannot enact a law "if its purpose or effect is to place substantial obstacles in the path of a woman seeking an abortion before the fetus attains viability."

The Court initially asked the parties in *Dobbs* to write briefs on only the first of these two holdings, whether "all pre-viability prohibitions on elective abortions are

unconstitutional" — a clear signal that at least some members of the Court want to overrule *Casey*'s viability holding.

Indeed, all six of the Court's Republican appointees appeared eager to overrule that holding. That includes Chief Justice John Roberts, the most cautious member of the Court's conservative majority. Roberts asked Julie Rikelman, one of the lawyers struggling to defend *Roe* from a hostile Court, "Why is 15 weeks not enough time" for someone to decide whether to terminate their pregnancy?

While Mississippi styles its law as a 15-week ban, that clock starts to tick on "the first day of the last menstrual period of the pregnant woman." So, in practice, the law functions more like a 13-week abortion ban.

But Mississippi wound up going much further in its brief, asking the Court to overrule *Roe* and *Casey* altogether. If the Court agrees *Roe* should be overruled, it could do so explicitly, or it could reinterpret the "undue burden" standard so it no longer imposes meaningful limits on abortion regulations.

Roberts largely focused his questions on *Casey*'s viability line. He appeared less interested in the question of whether to overrule *Casey*'s second holding, that abortion regulations are invalid if they impose an undue burden on the right to terminate a pregnancy — at least for now.

But a majority of the Court did not appear to share Roberts's relatively incrementalist approach. At least four, and most likely five, of the Court's remaining conservatives seemed ready to toss out *Roe* and *Casey* in their entirety.

The Court's right flank sounded quite emboldened

There's been a lot of commentary lately arguing that we have a 3-3-3 Supreme Court — three justices on the far right, three on the left, and three somewhere in between. That characterization of the Court is superficially accurate but also somewhat misleading. While it is true that Roberts, Barrett, and Justice Brett Kavanaugh are often more cautious than their three most conservative colleagues, the three justices in the middle are still very far to the right.

The three most conservative justices — Justices Clarence Thomas, Samuel Alito, and Neil Gorsuch — played their typical role of insisting the Court should give conservatives everything they are asking for in *Dobbs*, and without any delay. Thomas, at one point, compared *Roe* to *Lochner v. New York* (1905), an infamous decision striking down pro-labor legislation, and which is widely taught in law schools as an example of how judges should never, ever behave.

Similarly, Alito seemed to compare *Roe* to *Plessy v. Ferguson* (1896), the equally infamous pro-segregation decision.

Gorsuch, meanwhile, spent much of his question time arguing that *Casey*'s undue burden standard is "difficult to administer" and should be abandoned. He even tried to get Rikelman to admit that, if the Court overrules *Casey*'s viability line, it must also scrap the undue burden test — a result that would effectively eliminate the constitutional right to an abortion.

In the past, Kavanaugh has sometimes pushed for more incremental attacks on *Roe.* In *June Medical Services v. Gee* (2019), for example, he argued in favor of placing complicated procedural barriers in the way of abortion plaintiffs that would make it difficult for them to bring their cases to federal court or to receive a meaningful remedy.

But on Wednesday, Kavanaugh seemed no less eager to overrule *Roe* than Thomas, Alito, or Gorsuch. At one point, Kavanaugh rattled off a long list of landmark — and largely celebrated — Supreme Court decisions, including its school integration decision in *Brown v. Board of Education* (1954), its first one person/one vote decision in *Baker v. Carr* (1962), and its marriage equality decision in *Obergefell v. Hodges* (2015), which all overruled previous decisions.

The clear implication was that if the Court could overrule precedent in those cases, why can't it overrule *Roe*?

That leaves Barrett, who often implies at oral argument that she might take a more centrist approach than her most conservative colleagues, but who also votes with the Court's right flank much more often than not. Though Barrett's questions were less revealing than Kavanaugh's, they left little doubt that she disagrees with essential parts of *Roe* and *Casey.*

Among other things, Barrett repeatedly brought up so-called "safe haven" laws, which allow someone who recently gave birth to immediately give up their child for adoption (Barrett herself is the adoptive mother of two children). "Both *Roe* and *Casey* emphasized the burdens of parenting," she noted, before asking why safe haven laws don't "take care of that problem?"

In one particularly remarkable moment, Barrett appeared to argue that being forced to carry and birth a child is no big deal. "It doesn't seem to me to follow that pregnancy and parenthood are all part of the same burden," she said. "It seems to me that the choice, more focused, would be between, say, the ability to get an abortion at 23 weeks or the state requiring the woman to go 15, 16 weeks more" before terminating their parental rights after giving birth.

Barrett, in other words, appeared quite determined to erase *Casey*'s viability rule. And, while she was less explicit about whether she would eliminate *Casey*'s undue burden standard, the tone of her questioning was extremely dismissive of both *Roe* and *Casey*.

So the right to an abortion is in deep trouble. At the least, the Court appears very likely to overrule *Casey*'s viability standard — and there's a good chance it will go all the way to overruling *Roe* entirely.

I will conclude by reiterating a point I've made several times before; that the most important question in *Dobbs* is not whether the Court writes the magic words "*Roe v. Wade* is overruled."

Dobbs is almost certain to announce a new legal standard governing abortion rights that is far less protective of those rights than *Roe* or *Casey*. The Court might explicitly overrule *Roe.* It might leave some small part of the right to an abortion — such as the undue burden standard — in place for at least a little while. Or it might announce a completely new legal rule that makes it functionally impossible for abortion plaintiffs to protect their rights, even if some hollow shell of *Roe* remains nominally on the books.

It now appears more likely than not that the Court will either explicitly overrule *Roe* or eliminate it in a more backhanded way. Either of these outcomes would mean the end of the constitutional right to an abortion.

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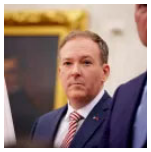
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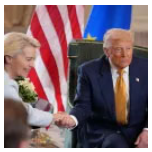


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EXHIBIT 40

White House,
Remarks by President Biden Before Meeting with His Task Force on Reproductive Healthcare Access
(Jan. 22, 2024)

JANUARY 22, 2024

Remarks by President Biden Before Meeting With His Task Force on Reproductive Healthcare Access

State Dining Room

2:44 P.M. EST

THE PRESIDENT: Well, good afternoon, folks.

Doctor, thank you for sharing your story. And I'm sure there's others like it many doctors across America have had to contemplate.

Fifty-one years ago today, in Roe v. Wade, the Supreme Court recognized a woman's constitutional right to choose — constitutional right to choose — the right to make a deeply personal decision with her doctor, free from the interference of politicians.

I believe Roe v. Wade was right. I'm not supporting — we didn't — they didn't support abortion on demand. It was Roe v. Wade. Roe v. Wade was the decision. And a majority of Americans agree.

But then, a year and a half ago, this — this Supreme Court — this Supreme Court made an extreme decision, overturning Roe with their Dobbs decision, to rip away a constitutional right from the American people, which had never been done before — a fundamental right ripped away — important to so

many Americans, a right that is vital to a country founded on the idea of freedom.

I said on the — on that day that Roe was overturned, the health and lives of women in this nation would now be at risk. And that has unfortunately proven to be true. They have been at risk. It made them at risk — put them at risk.

Today, in 2024 in America, women are turned away from emergency rooms, forced to travel hundreds of miles to get basic healthcare in another state that may have a different rule, forced to go to court to plead for help.

Thanks to [Think of] the mothers of two in Texas — a mother of two in Texas, who was pregnant with her third child. From her doctor, she received the news no one wants to hear: The life of the child and her own life were at risk if she continued her pregnancy. But instead of being able to receive care from her doctor, she was blocked by the State of Texas Attorney General and the State Supreme Court.

Think about that. As she and her family were going through the frightening, heartbreaking ordeal, she had to fight extreme politicians in the court. They turned a deeply private and painful matter into a public matter.

She ultimately had to leave the state to get the help she needed to protect herself and her ability to have more children in the future.

The cruelty is astounding — an affront to a woman's dignity, being told by extreme politicians to wait, to get sicker and sicker to the point where her life may be in danger before you can get the care you need.

That cruel reality is the result of extreme Republicans who, for years, have made it their mission to end the Roe v. Wade decision.

Since Roe was overturned, in 21 states, abortion bans are now in effect, many with no exception for rape or incest.

We have doctors — we have doctors with us today who are on the frontlines of this crisis. And they can attest to the consequences that these extreme laws are having on doctors and on their ability to care for their patients.

Some doctors are feeling their — fleeing their home states because of laws that would send them to prison for providing evidence-based healthcare.

In states like Texas, doctors can get a life sentence — a life sentence for providing the care they were trained to provide. It's outrageous. It's simply outrageous.

And, frankly, this is just the beginning.

My congressional Republican friends are going to even further — further extremes to undermine a woman's rights to threaten — and threatening the lives of women.

Three different Republican members in the United States Congress have proposed three different additional national bans to criminalize healthcare in every state. Let me tell you what they are.

One is a zero-week ban with absolutely no exceptions — a zero-week with absolutely no exceptions. The second is a six-week ban. The penalty for violating it is jail. The third is a 15-week ban. The penalty is a five-year prison sentence.

That means even if you live in a state where the extremist Republicans are not running the show, your right to choose, your right to privacy would still be at risk if this law was passed — any of these were passed nationally.

And the extreme right is trying to limit all women in America from getting a safe and effective medication, approved by the Federal Drug Administration over 20 years ago based on the FDA's independent expert judgment. They're trying to block women from getting this medication even in states where abortion is legal.

And on top of all of that, if you live in a state where you cannot get this care you need and you make a plan to travel to a state where you can get the medicine [medical care], Republicans official [Republican officials] are trying to stop that as well.

And get this, in Alabama — as my mother would say, "God love them" — the Attorney General is threatening to prosecute people who help family members travel to another state — who help family members travel to another state.

Folks, this is what it looks like when the right to privacy is under attack. These extreme laws have no place — no place in the United States of America.

You know, the American people know these laws are wrong. The vast majority of Americans believe the right to choose is fundamental.

Since the Court overturned Roe v. Wade, every single time abortion has been on the ballot — and, by the way, a lot of people don't really understand. The Court said that it's up to the states to decide whether or not abortions are valid.

So, it says that if the cou- — if the state comes along and wants to say, "No, no, it's valid in my state — Roe v. Wade is valid in my state," it's allowed.

Well, guess what? Every single time that decision had been put before the people of a state — on the ballot in Ohio, Kansas, Michigan, Kentucky — voters have voted to protect reproductive rights. But we need these protections in every state, because your family [ability] to have access to healthcare should not depend on your ZIP code. It should not depend on your ZIP code.

As I've made clear, we have to do what the Supreme Court decision in Dobbs would allow, and that is: Congress must codify Roe v. Wade for all the states in America.

Stop playing politics with the women's lives and freedom. Let doctors do their job.

Let me say it again: Pass laws restoring the protections of Roe v. Wade for women in every state. That's what can be done under this co- — on the — even under the Dobbs decision. But under this Court, that is going to be constitutional if we pass it nationwide.

That's what I'm working for. I'm working for that law. And when they send me that law, I'm going to sign it immediately and restore that right. Until then, my administration is going to keep working to protect women in the wake of the Supreme Court's extreme decision.

That's why I created a task force to ensure we are doing everything we can to support women.

I've signed executive orders and my administration has taken action to ensure that women get the care they need in

medical emergencies, to protect a woman's right to travel to get healthcare, to protect a woman's right to receive healthcare free from discrimination, and to protect her privacy.

The idea that a woman should have to carry a fetus after she has been raped or a victim of incest is just — I think it's just cruel. To me, it's outrageous.

The idea that a woman who receives competent medical advice that the fetus she's carrying wouldn't live and will impact on her ability to have children in the future and still gets [can't get] medical care — can't get medical — it's ridiculous.

I could go on, but I'm already taking too much time.

I want to thank the Vice President of the United States, Kamala Harris, for her leadership on this important issue as she travels the country in her fight for freedom.

I'd also like to thank the Gender Policy Advisor — my Gender Policy Advisor, Jen Klein. Jen — where's Jen sitting? There you are, Jen. Thank you. And Secretary Becerra, who's sitting right next to her, for their leadership on this task force.

And I want to thank all the members of my Cabinet here today, including the Attorney General for leading efforts and the — at the Department of Justice to protect reproductive rights in court, and Secretary McDonough for leading the important work being done at the VA.

I know that folks across America are worried about what they're seeing happening to women all across America. I hear about it everywhere I go.

My message is: We're fighting hard to reinstate your rights and the rights to protect women and families and doctors who care for those women.

And we need the American people to keep making their voices heard so congr- — so congressional Republicans finally get the message that these laws do not represent the United States of America.

Your voice will have a final say. This is not over.

With that, I'm going to sit down, and we're going to get to work.

Thank you all for being here. And let's get this done. It's important.

Thank you. (Applause.)

2:54 P.M. EST

EXHIBIT 41

White House,
Remarks by President Biden on the Supreme Court's
Decision on Affirmative Action
(June 29, 2023)

JUNE 29, 2023

Remarks by President Biden on the Supreme Court's Decision on Affirmative Action

Roosevelt Room

12:48 P.M. EDT

THE PRESIDENT: Good afternoon, folks. Sorry to keep you waiting a few minutes.

Forty-five years — for forty-five years, the United States Supreme Court has recognized a college's freedom to decide how — how to build diverse student bodies and to meet their responsibility of opening doors of opportunity for every single American.

In case after case, including recently, just as a few years ago in 2016, the Court has affirmed and reaffirmed this view: that colleges could use race not as a determinative factor for admission, but as one of the factors among many in deciding who to admit from a quali- — from a qualified — already qualified pool of applicants.

Today, the Court once again walked away from decades of precedent and make — as the dissent has made clear.

The dissent states that today's decision, quote, "rolls back decades of precedent and momentous progress." End of quote.

I agree with that statement from the dissents — from the dissent.

The Court has effectively ended affirmative action in college admissions. And I strongly — strongly disagree with the Court's decision.

Because affirmative action is so misunderstood, I want to be clear — make sure everybody is clear about what the law has been and what it has not been, until today.

Many people wrongly believe that affirmative action allows unqualified students — unqualified students — to be admitted ahead of qualified students. This is not — this is not how college admissions work.

Rather, colleges set out standards for admission, and every student — every student has to meet those standards.

Then, and only then, after first meeting the qualifications required by the school, do colleges look at other factors in addition to their grades, such as race.

The way it works in practice is this: Colleges first establish a qualified pool of candidates based on meeting certain grade, test scores, and other criteria.

Then, and only then — then, and only then, and it's from this pool of applicants — all of whom have already met the school's standards -- that the class is chosen, after weighing a wide range of factors, among them being race.

You know, I've always believed that one of the greatest strengths of America — and you're tired of hearing me say it — is our diversity, but I believe that.

If you have any doubt about this, just look at the United States military, the finest fighting force in the history of the world. It's been a model of diversity. And it's not only been our — made our nation better, stronger, but safer.

And I believe the same is true for our schools. I've always believed that the promise of America is big enough for everyone to succeed and that every generation of Americans, we have benefitted by opening the doors of opportunity just a little bit wider to include those who have been left behind.

I believe our colleges are stronger when they are racially diverse. Our nation is stronger because we use what we — because we are tapping into the full range of talent in this nation.

I also believe that while talent, creativity, and hard work are everywhere across this country, not equal opportunity. It is not everywhere across this country.

We cannot let this decision be the last word. I want to emphasize: We cannot let this decision be the last word.

While the Court can render a decision, it cannot change what America stands for.

America is an idea — an idea unique in the world. An idea of hope and opportunity, of possibilities, of giving everyone a fair shot, of leaving no one behind. We have never fully lived up to it, but we've never walked away from it either. We will not walk away from it now.

We should never allow the country to walk away from the dream upon which it was founded: that opportunity is for everyone, not just a few.

We need a new path forward — a path consistent with a law that protects diversity and expands opportunity.

So, today I want to offer some guidance to our nation's colleges as they review their admissions systems after today's decision — guidance that is consistent with today's decision.

They should not abandon — let me say this again: They should not abandon their commitment to ensure student bodies of diverse backgrounds and experience that reflect all of America.

What I propose for consideration is a new standard, where colleges take into account the adversity a student has overcome when selecting among qualified applicants.

Let's be clear: Under this new standard, just as was true under the earlier standard, students first have to be qualified applicants. They need the GPA and test scores to meet the school's standards.

Once that test is met, then adversity should be considered, including — including its lack — a student's lack of financial means, because we know too few students of low-income families, whether in big cities or rural communities, are getting an opportunity to go to college.

When the poor kid — when a poor kid — may be the first in their family to go to college — gets the same grades and test scores as a wealthy kid whose whole family has gone to the most elite colleges in the country and whose path has been a lot easier, well, the kid who faced tougher challenges has demonstrated more grit, more determination. And that should be a factor that colleges should take into account in admissions. And many still do.

It also means examining where the student grew up and went to high school.

It means understanding the particular hardships that each individual student has faced in life, including racial discrimination that individuals have faced in their own lives.

The Court says, quote, "[N]othing in this opinion should be construed as prohibiting universities from considering an application's [applicant's] discussion of how race [has] affected his or her life," but it's — it's through — but "be it through discrimination [or] inspiration or otherwise."

Because the truth is — we all know it: Discrimination still exists in America. Discrimination still exists in America. Discrimination still exists in America.

Today's decision does not change that. It's a simple fact.

If a student has — has overcome — had to overcome adversity on their path to education, a college should recognize and value that.

Our nation's colleges and universities should be engines of expanding opportunity through upward mobility. But today, too often that's not the case.

The statistics — one statistic: Students from the top 1 percent of family incomes in America are 77 times more likely to get into an elite college than one from the bottom 20 percent of family incomes. Seventy-seven ti- — percent great- — greater opportunity.

Today, for too many schools, the only people who benefit from the system are the wealthy and the well-connected.

The odds have been stacked against working people for much too long.

We need a higher education system that works for everyone, from App- — from Appalachia to Atlanta and to far beyond.

We can and must do better, and we will.

Today, I'm directing the Department of Education to analyze what practices help build a more inclusive and diverse student bodies and what practices hold that back, practices like legacy admissions and other systems that expand privilege instead of opportunity.

Colleges and universities should continue their commitment to support, retain, and graduate diverse students and classes.

You know, and companies — companies who are already realizing the value in diversity should not use this decision as an excuse to turn away from diversity either.

We can't go backwards.

You know, I know today's Court decision is a severe disappointment to so many people, including me, but we cannot let the decision be a permanent setback for the country.

We need to keep an open door of opportunities. We need to remember that diversity is our strength. We have to find a way forward.

We need to remember that the promise of America is big enough for everyone to succeed.

You know, that's the work of my administration, and I'm always going to fight for that.

And I want to thank you all.

And I know you've been told I have a helicopter out there waiting to go up to do an interview in New York. I'll be talking to more about this in a live interview.

But thank you very much. And we're going to have plenty of time to talk about this. But we're not going to let this break us.

Thank you.

Q President Biden, the Congressional Black Caucus said the Supreme Court has "thrown into question its own legitimacy." Is this a rogue Court?

THE PRESIDENT: This is not a normal Court.

Q Should there be term limits for the justices, sir?

12:57 P.M. EDT

EXHIBIT 42

White House,
FACT SHEET: President Biden to Sign Executive Order Protecting Access to Reproductive Health Care Services
(July 8, 2022)

JULY 08, 2022

FACT SHEET: President Biden to Sign Executive Order Protecting Access to Reproductive Health Care Services

Two weeks ago, the Supreme Court issued a decision that overturned *Roe v. Wade* and eliminated a woman's Constitutional right to choose. This decision expressly took away a right from the American people that it had recognized for nearly 50 years – a woman's right to make her own reproductive health care decisions, free from government interference. Fundamental rights – to privacy, autonomy, freedom, and equality – have been denied to millions of women across the country, with grave implications for their health, lives, and wellbeing. This ruling will disproportionately affect women of color, low-income women, and rural women.

President Biden has made clear that the only way to secure a woman's right to choose is for Congress to restore the protections of *Roe* as federal law. Until then, he has committed to doing everything in his power to defend reproductive rights and protect access to safe and legal abortion.

Today, President Biden will sign an Executive Order Protecting Access to Reproductive Health Care Services. This Executive Order builds on the actions his Administration has already taken to defend reproductive rights by:

- Safeguarding access to reproductive health care services, including abortion and contraception;
- Protecting the privacy of patients and their access to accurate information;
- Promoting the safety and security of patients, providers, and clinics; and
- Coordinating the implementation of Federal efforts to protect reproductive rights and access to health care.

SAFEGUARDING ACCESS TO REPRODUCTIVE HEALTH CARE SERVICES

The President has directed the Secretary of Health and Human Services (HHS) to take the following actions and submit a report to him within 30 days on efforts to:

- **Protect Access to Medication Abortion.** HHS will take additional action to protect and expand access to abortion care, including access to medication that the FDA approved as safe and effective over twenty years ago. These actions will build on the steps the Secretary of HHS has already taken at the President's direction following the decision to ensure that medication abortion is as widely accessible as possible.
- **Ensure Emergency Medical Care.** HHS will take steps to ensure all patients – including pregnant women and those experiencing pregnancy loss – have access to the full rights and protections for emergency medical care afforded under the law, including by considering updates to current guidance that clarify physician responsibilities and protections under the Emergency Medical Treatment and Labor Act (EMTALA).

- **Protect Access to Contraception.** HHS will take additional actions to expand access to the full range of reproductive health services, including family planning services and providers, such as access to emergency contraception and long-acting reversible contraception like intrauterine devices (IUDs). In all fifty states and the District of Columbia, the Affordable Care Act guarantees coverage of women's preventive services, including free birth control and contraceptive counseling, for individuals and covered dependents. The Secretary of HHS has already directed the Centers for Medicare and Medicaid Services to take every legally available step to ensure patient access to family planning care and to protect family planning providers.

- **Launch Outreach and Public Education Efforts.** HHS will increase outreach and public education efforts regarding access to reproductive health care services—including abortion—to ensure that Americans have access to reliable and accurate information about their rights and access to care.

- **Convene Volunteer Lawyers.** The Attorney General and the White House Counsel will convene private pro bono attorneys, bar associations, and public interest organizations to encourage robust legal representation of patients, providers, and third parties lawfully seeking or offering reproductive health care services throughout the country. Such representation could include protecting the right to travel out of state to seek medical care. Immediately following the Supreme Court decision, the President announced his Administration's position that Americans must remain free to travel safely to another state to seek the care they need, as the Attorney General made clear in his statement, and his commitment to fighting any attack by a state or local official who attempts to interfere with women exercising this right.

PROTECTING PATIENT PRIVACY AND ACCESS TO ACCURATE INFORMATION

The President's Executive Order takes additional steps to protect patient privacy, including by addressing the transfer and sales of sensitive health-related data, combatting digital surveillance related to reproductive health care services, and protecting people seeking reproductive health care from inaccurate information, fraudulent schemes, or deceptive practices. The Executive Order will:

- **Protect Consumers from Privacy Violations and Fraudulent and Deceptive Practices.** The President has asked the Chair of the Federal Trade Commission to consider taking steps to protect consumers' privacy when seeking information about and provision of reproductive health care services. The President also has directed the Secretary of HHS, in consultation with the Attorney General and Chair of the FTC, to consider options to address deceptive or fraudulent practices, including online, and protect access to accurate information.
- **Protect Sensitive Health Information.** HHS will consider additional actions, including under the Health Insurance Portability and Accountability Act (HIPAA), to better protect sensitive information related to reproductive health care. The Secretary of HHS has already directed the HHS Office for Civil Rights to take initial steps to ensure patient privacy and nondiscrimination of patients, as well as providers who provide reproductive health care, including by:
    - Issuing new guidance to address how the HIPAA Privacy Rule protects the privacy of individuals' protected health information, including information related to reproductive health care. The guidance helps ensure doctors and other medical providers and

health plans know that, with limited exceptions, they are not required – and in many cases, are not permitted – to disclose patients' private information, including to law enforcement.

- Issuing a how-to guide for consumers on steps they can take to make sure they're protecting their personal data on mobile apps.

PROMOTING SAFETY AND SECURITY

The Executive Order addresses the heightened risk related to seeking and providing reproductive health care and will:

- **Protect Patients, Providers, and Clinics.** The Administration will ensure the safety of patients, providers, and third parties, and to protect the security of other entities that are providing, dispensing, or delivering reproductive health care services. This charge includes efforts to protect mobile clinics, which have been deployed to borders to offer care for out-of-state patients.

COORDINATING IMPLEMENTATION EFFORTS

To ensure the Federal government takes a swift and coordinated approach to addressing reproductive rights and protecting access to reproductive health care, the President's Executive Order will:

- **Establish an Interagency Task Force.** The President has directed HHS and the White House Gender Policy Council to establish and lead an interagency Task Force on Reproductive Health Care Access, responsible for coordinating Federal interagency policymaking and program development. This Task Force will also include the Attorney General. In addition, the Attorney General

will provide technical assistance to states affording legal protection to out-of-state patients as well as providers who offer legal reproductive health care.

EXECUTIVE ORDER BUILDS ON ADMINISTRATION'S ACTIONS TO PROTECT ACCESS TO REPRODUCTIVE HEALTH CARE

In addition to the actions announced today, the Biden-Harris Administration has taken the following steps to protect access to reproductive health care and defend reproductive rights in the wake of the Supreme Court decision in *Dobbs*. On the day of the decision, the President strongly denounced the decision as an affront to women's fundamental rights and the right to choose In addition to action mentioned above, the Biden-Harris Administration is:

- **Supporting Providers and Clinics.** The Secretary of HHS directed all HHS agencies to ensure that all HHS-funded providers and clinics have appropriate training and resources to handle family planning needs, and announced nearly $3 million in new funding to bolster training and technical assistance for the nationwide network of Title X family planning providers.
- **Promoting Access to Accurate Information.** On the day of the Supreme Court's decision, HHS launched ReproductiveRights.gov, which provides timely and accurate information about reproductive rights and access to reproductive health care. This includes know-your-rights information for patients and providers and promoting awareness of and access to family planning services, as well as guidance for how to file a patient privacy or nondiscrimination complaint with its Office for Civil Rights.

- **Providing Leave for Federal Workers Traveling for Medical Care.** The Office of Personnel Management issued guidance affirming that paid sick leave can be taken to cover absences for travel to obtain reproductive health care.

- **Protecting Access to Reproductive Health Care Services for Service members, DoD Civilians, and Military Families.** The Department of Defense (DoD) issued a memo to the Force, DoD civilians and military families on ensuring access to essential women's health care services. The memo reiterates that the Department will continue to provide seamless access to reproductive healthcare for military and civilian patients, as permitted by federal law. Military providers will continue to fulfill their duty to care for Service members, military dependents and civilian personnel who require pregnancy termination in the cases of rape, incest, or to protect the life of the mother.

For up-to-date information on your right to access reproductive health care, visit www.reproductiverights.gov

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EXHIBIT 43

White House,
Remarks by President Biden on the Supreme Court
Decision to Overturn *Roe v. Wade*
(June 24, 2022)

JUNE 24, 2022

Remarks by President Biden on the Supreme Court Decision to Overturn Roe v. Wade

Cross Hall

12:37 P.M. EDT

THE PRESIDENT: Today is a — it's not hyperbole to suggest a very solemn moment. Today, the Supreme Court of the United States expressly took away a constitutional right from the American people that it had already recognized.

They didn't limit it. They simply took it away. That's never been done to a right so important to so many Americans.

But they did it. And it's a sad day for the Court and for the country.

Fifty years ago, Roe v. Wade was decided and has been the law of the land since then.

This landmark case protected a woman's right to choose, her right to make intensely personal decisions with her doctor, free from the inter- — from interference of politics.

It reaffirmed basic principles of equality that women have the power to control their own destiny. And it reinforced the fundamental right of privacy the right of each of us to choose how to live our lives.

Now, with Roe gone, let's be very clear: The health and life of women in this nation are now at risk.

As Chairman and Ranking Member of the Senate Judiciary Committee, as Vice President and now as President of the United States, I've studied this case carefully. I've overseen more Supreme Court confirmations than anyone today, where this case was always discussed.

I believe Roe v. Wade was the correct decision as a matter of constitutional law, an application of the fundamental right to privacy and liberty in matters of family and personal autonomy.

It was a decision on a complex matter that drew a careful balance between a woman's right to choose earlier in her pregnancy and the state's ability to regulate later in her pregnancy. A decision with broad national consensus that most Americans of faiths and backgrounds found acceptable and that had been the law of the land for most of the lifetime of Americans today.

And it was a constitutional principle upheld by justices appointed by Democrat and Republican Presidents alike.

Roe v. Wade was a 7 to 2 decision written by a justice appointed by a Republican President, Richard Nixon. In the five decades that followed Roe v. Wade, justices appointed by Republican Presidents from Eisenhower, Nixon, Reagan, George ~~W.~~ [H.W.] Bush were among the justices who voted to uphold the principles set forth in Roe v. Wade.

It was three justices named by one President — Donald Trump — who were the core of today's decision to upend the scales of justice and eliminate a fundamental right for women in this country.

Make no mistake: This decision is the culmination of a deliberate effort over decades to upset the balance of our law. It's a realization of an extreme ideology and a tragic error by the Supreme Court, in my view.

The Court has done what it has never done before: expressly take away a constitutional right that is so fundamental to so many Americans that had already been recognized.

The Court's decision to do so will have real and immediate consequences. State laws banning abortion are automatically taking effect today, jeopardizing the health of millions of women, some without exceptions.

So extreme that women could be punished for protecting their health.

So extreme that women and girls who are forced to bear their rapist's child of the child of consequence.

It's a — it just — it just stuns me.

So extreme that doctors will be criminalized for fulfilling their duty to care.

Imagine having a young woman having to ch- carry the child of incest as a consequence of incest. No option.

Too often the case that poor women are going to be hit the hardest. It's cruel.

In fact, the Court laid out state laws criminalizing abortion that go back to the 1800s as rationale the Court literally taking America back 150 years.

This a sad day for the country, in my view, but it doesn't mean the fight is over.

Let me be very clear and unambiguous: The only way we can secure a woman's right to choose and the balance that existed is for Congress to restore the protections of Roe v. Wade as federal law.

No executive action from the President can do that. And if Congress, as it appears, lacks the vote — votes to do that now, voters need to make their voices heard.

This fall, we must elect more senators and representatives who will codify a woman's right to choose into federal law once again, elect more state leaders to protect this right at the local level.

We need to restore the protections of Roe as law of the land. We need to elect officials who will do that.

This fall, Roe is on the ballot. Personal freedoms are on the ballot. The right to privacy, liberty, equality, they're all on the ballot.

Until then, I will do all in my power to protect a woman's right in states where they will face the consequences of today's decision.

While the Court's decision casts a dark shadow over a large swath of the land, many states in this country still recognize a woman's right to choose.

So if a woman lives in a state that restricts abortion, the Supreme Court's decision does not prevent her from traveling from her home state to the state that allows it. It does not prevent a doctor in that state in that state from treating her.

As the Attorney General has made clear, women must remain free to travel safely to another state to seek the care they need. And my administration will defend that bedrock right.

If any state or local official, high or low, tries to interfere with a woman's ex- — exercising her basic right to travel, I will do everything in my power to fight that deeply un-American attack.

My administration will also protect a woman's access to medications that are approved by the Food and Drug Administration — the FDA — like contraception, which is essential for preventative healthcare; mifepristone, which the FDA approved 20 years ago to safely end early pregnancies and is commonly used to treat miscarriages.

Some states are saying that they'll try to ban or severely restrict access to these medications.

But extremist governors and state legislators who are looking to block the mail or search a person's medicine cabinet or control a woman's actions by tracking data on her apps she uses are wrong and extreme and out of touch with the majority of Americans.

The American Medical Association and the American College of Obstetricians and Gynecologists wrote to me and Vice President Harris stressing that these laws are not based on are not based on evidence and asking us to act to protect access to care. They say by limiting access to these medicines, maternal mortality will climb in America. That's what they say.

Today, I'm directing the Department of Health and Human Services to take steps to ensure that these critical medications are available to the fullest extent possible and that politicians cannot interfere in the decisions that should be made between a woman and her doctor. And my administration will remain vigilant as the implications of this decision play out.

I've warned about how this decision risks the broader right to privacy for everyone. That's because Roe recognized the fundamental right to privacy that has served as the basis for so many more rights that we have come to take we've come to take for granted that are ingrained in the fabric of this country: the right to make the best decisions for your health; the right to use birth control — a married couple — in the privacy of their bedroom, for God's sake; the right to marry the person you love.

Now, Justice Thomas said as much today. He explicitly called to reconsider the right of marriage equality, the right of couples to make their choices on contraception. This is an extreme and dangerous path the Court is now taking us on.

Let me close with two points.

First, I call on everyone, no matter how deeply they care about this decision, to keep all protests peaceful. Peaceful, peaceful, peaceful. No intimidation. Violence is never acceptable. Threats and intimidation are not speech. We must stand against violence in any form regardless of your rationale.

Second, I know so many of us are frustrated and disillusioned that the Court has taken something away that's so fundamental. I know so many women are now going to face incredibly difficult situations. I hear you. I support you. I stand with you.

The consequences and the consensus of the American people core principles of equality, liberty, dignity, and the stability of the rule of law — demand that Roe should not have been overturned.

With this decision, the conservative majority of the Supreme Court shows how extreme it is, how far removed they are from the majority of this country. They have made the United States an outlier among developed nations in the world. But this decision must not be the final word.

My administration will use all of its appropriate lawful powers. But Congress must act. And with your vote, you can act. You can have the final word. This is not over.

Thank you very much. I'll have more to say on this in weeks to come. Thank you.

12:49 P.M. EDT

EXHIBIT 44

Exec. Order No. 14076, Protecting Access to Reproductive Healthcare Services, 87 Fed. Reg. 42053 (July 8, 2022)

Presidential Documents

Executive Order 14076 of July 8, 2022

Protecting Access to Reproductive Healthcare Services

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. *Policy.* Nearly 50 years ago, *Roe* v. *Wade,* 410 U.S. 113 (1973), articulated the United States Constitution's protection of women's fundamental right to make reproductive healthcare decisions. These deeply private decisions should not be subject to government interference. Yet today, fundamental rights—to privacy, autonomy, freedom, and equality—have been denied to millions of women across the country.

Eliminating the right recognized in *Roe* has already had and will continue to have devastating implications for women's health and public health more broadly. Access to reproductive healthcare services is now threatened for millions of Americans, and especially for those who live in States that are banning or severely restricting abortion care. Women's health clinics are being forced to close—including clinics that offer other preventive healthcare services such as contraception—leaving many communities without access to critical reproductive healthcare services. Women seeking abortion care—especially those in low-income, rural, and other underserved communities—now have to travel to jurisdictions where services remain legal notwithstanding the cost or risks.

In the face of this health crisis, the Federal Government is taking action to protect healthcare service delivery and promote access to critical reproductive healthcare services, including abortion. It remains the policy of my Administration to support women's right to choose and to protect and defend reproductive rights. Doing so is essential to justice, equality, and our health, safety, and progress as a Nation.

Sec. 2. *Definitions.* (a) The term ''agency'' means any authority of the United States that is an ''agency'' under 44 U.S.C. 3502(1), other than one considered to be an independent regulatory agency, as defined in 44 U.S.C. 3502(5).

(b) The term ''reproductive healthcare services'' means medical, surgical, counseling, or referral services relating to the human reproductive system, including services relating to pregnancy or the termination of a pregnancy.

Sec. 3. *Protecting Access to Reproductive Healthcare Services.* (a) Within 30 days of the date of this order, the Secretary of Health and Human Services shall submit a report to the President:

(i) identifying potential actions:

(A) to protect and expand access to abortion care, including medication abortion; and

(B) to otherwise protect and expand access to the full range of reproductive healthcare services, including actions to enhance family planning services such as access to emergency contraception;

(ii) identifying ways to increase outreach and education about access to reproductive healthcare services, including by launching a public awareness initiative to provide timely and accurate information about such access, which shall:

(A) share information about how to obtain free or reduced cost reproductive healthcare services through Health Resources and Services Administration-Funded Health Centers, Title X clinics, and other providers; and

(B) include promoting awareness of and access to the full range of contraceptive services, as well as know-your-rights information for those seeking or providing reproductive healthcare services; and

(iii) identifying steps to ensure that all patients—including pregnant women and those experiencing pregnancy loss, such as miscarriages and ectopic pregnancies—receive the full protections for emergency medical care afforded under the law, including by considering updates to current guidance on obligations specific to emergency conditions and stabilizing care under the Emergency Medical Treatment and Labor Act, 42 U.S.C. 1395dd, and providing data from the Department of Health and Human Services concerning implementation of these efforts.

(b) To promote access to reproductive healthcare services, the Attorney General and the Counsel to the President shall convene a meeting of private pro bono attorneys, bar associations, and public interest organizations in order to encourage lawyers to represent and assist patients, providers, and third parties lawfully seeking these services throughout the country.

Sec. 4. *Protecting Privacy, Safety, and Security.* (a) To address potential heightened safety and security risks related to the provision of reproductive healthcare services, the Attorney General and the Secretary of Homeland Security shall consider actions, as appropriate and consistent with applicable law, to ensure the safety of patients, providers, and third parties, and to protect the security of clinics (including mobile clinics), pharmacies, and other entities providing, dispensing, or delivering reproductive and related healthcare services.

(b) To address the potential threat to patient privacy caused by the transfer and sale of sensitive health-related data and by digital surveillance related to reproductive healthcare services, and to protect people seeking reproductive health services from fraudulent schemes or deceptive practices:

(i) The Chair of the Federal Trade Commission (FTC) is encouraged to consider actions, as appropriate and consistent with applicable law (including the Federal Trade Commission Act, 15 U.S.C. 41 *et seq.*), to protect consumers' privacy when seeking information about and provision of reproductive healthcare services.

(ii) The Secretary of Health and Human Services shall consider actions, including providing guidance under the Health Insurance Portability and Accountability Act, Public Law 104–191, 110 Stat. 1936 (1996) as amended by Public Law 111–5, 123 Stat. 115 (2009), and any other statutes as appropriate, to strengthen the protection of sensitive information related to reproductive healthcare services and bolster patient-provider confidentiality.

(iii) The Secretary of Health and Human Services shall, in consultation with the Attorney General, consider actions to educate consumers on how best to protect their health privacy and limit the collection and sharing of their sensitive health-related information.

(iv) The Secretary of Health and Human Services shall, in consultation with the Attorney General and the Chair of the FTC, consider options to address deceptive or fraudulent practices related to reproductive healthcare services, including online, and to protect access to accurate information.

Sec. 5. *Coordinating Implementation Efforts.* (a) The Secretary of Health and Human Services and the Director of the Gender Policy Council shall establish and co-chair an Interagency Task Force on Reproductive Healthcare Access (Task Force). Additional members shall include the Attorney General and the heads of other agencies as determined by the Secretary of Health and Human Services and the Director of the Gender Policy Council. The Task Force shall work to identify and coordinate activities to protect and strengthen access to essential reproductive healthcare services. In addition, the Task Force shall coordinate Federal interagency policymaking, program development, and outreach efforts to address barriers that individuals and entities may face in seeking and providing reproductive healthcare services.

The Department of Health and Human Services shall provide funding and administrative support as may be necessary for the performance and functions of the Task Force.

(b) The Attorney General shall provide technical assistance, as appropriate and consistent with applicable law, concerning Federal constitutional protections to States seeking to afford legal protection to out-of-State patients and providers who offer legal reproductive healthcare.

Sec. 6. *General Provisions.* (a) Nothing in this order shall be construed to impair or otherwise affect:

(i) the authority granted by law to an executive department or agency, or the head thereof; or

(ii) the functions of the Director of the Office of Management and Budget relating to budgetary, administrative, or legislative proposals.

(b) This order shall be implemented consistent with applicable law and subject to the availability of appropriations.

(c) This order is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity by any party against the United States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.



THE WHITE HOUSE,
July 8, 2022.

[FR Doc. 2022–15138
Filed 7–12–22; 11:15 am]
Billing code 3395–F2–P

EXHIBIT 45

Exec. Order No. 14079, Securing Access to Reproductive and Other Healthcare Services, 87 Fed. Reg. 49505 (Aug. 3, 2022)

Federal Register
Vol. 87, No. 154
Thursday, August 11, 2022

Presidential Documents

Title 3—

The President

Executive Order 14079 of August 3, 2022

Securing Access to Reproductive and Other Healthcare Services

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. *Policy*. On July 8, 2022, following a decision by the Supreme Court to overrule *Roe* v. *Wade*, 410 U.S. 113 (1973), I signed Executive Order 14076 (Protecting Access to Reproductive Healthcare Services). As that order recognized, eliminating the right recognized in Roe has had and will continue to have devastating implications for women's health and public health more broadly.

Following that order, the Department of Health and Human Services (HHS) has taken critical steps to address those effects. These steps include clarifying the obligation of hospitals and providers under the Emergency Medical Treatment and Labor Act, 42 U.S.C. 1395dd, to provide to patients presenting at an emergency department with an emergency medical condition stabilizing care, including an abortion, if that care is necessary to stabilize their emergency medical condition, and issuing guidance to the Nation's retail pharmacies on their obligations under Federal civil rights laws—including section 504 of the Rehabilitation Act, 29 U.S.C. 794, and section 1557 of the Affordable Care Act, 42 U.S.C. 18116—to ensure equal access to comprehensive reproductive and other healthcare services, including for women who are experiencing miscarriages.

However, the continued advancement of restrictive abortion laws in States across the country has created legal uncertainty and disparate access to reproductive healthcare services depending on where a person lives, putting patients, providers, and third parties at risk and fueling confusion for hospitals and healthcare providers, including pharmacies. There have been numerous reports of women denied health- and life-saving emergency care, as providers fearful of legal reprisal delay necessary treatment for patients until their conditions worsen to dangerous levels. There are also reports of women of reproductive age being denied prescription medication at pharmacies—including medication that is used to treat stomach ulcers, lupus, arthritis, and cancer—due to concerns that these medications, some of which can be used in medication abortions, could be used to terminate a pregnancy. Reportedly, a healthcare provider, citing a State law restricting abortion, even temporarily stopped providing emergency contraception.

As it remains the policy of my Administration to support women's access to reproductive healthcare services, including their ability to travel to seek abortion care in States where it is legal, I am directing my Administration to take further action to protect access to reproductive healthcare services and to address the crisis facing women's health and public health more broadly.

Sec. 2. *Definition*. The term ''reproductive healthcare services'' means medical, surgical, counseling, or referral services relating to the human reproductive system, including services relating to pregnancy or the termination of a pregnancy.

Sec. 3. *Advancing the Ability to Obtain Reproductive Healthcare Services*. In furtherance of the policy set forth in section 1 of this order, the Secretary of HHS shall consider actions to advance access to reproductive healthcare

services, including, to the extent permitted by Federal law, through Medicaid for patients traveling across State lines for medical care.

Sec. 4. *Promoting Compliance with Non-Discrimination Law in Obtaining Medical Care*. In furtherance of the policy set forth in section 1 of this order, and to ensure that individuals are not denied necessary healthcare on the basis of any ground protected by Federal law, including current pregnancy, past pregnancy, potential or intended pregnancy, or other medical conditions, the Secretary of HHS shall consider all appropriate actions to advance the prompt understanding of and compliance with Federal non-discrimination laws by healthcare providers that receive Federal financial assistance. Such actions may include:

(a) providing technical assistance for healthcare providers that have questions concerning their obligations under Federal non-discrimination laws;

(b) convening healthcare providers to provide information on their obligations under Federal non-discrimination laws and the potential consequences of non-compliance; and

(c) issuing additional guidance, or taking other action as appropriate, in response to any complaints or other reports of non-compliance with Federal non-discrimination laws.

Sec. 5. *Data Collection*. The Secretary of HHS shall evaluate the adequacy of research, data collection, and data analysis and interpretation efforts at the National Institutes of Health, the Centers for Disease Control and Prevention, and other relevant HHS components in accurately measuring the effect of access to reproductive healthcare on maternal health outcomes and other health outcomes. Following that evaluation, the Secretary shall take appropriate actions to improve those efforts.

Sec. 6. *General Provisions*. (a) Nothing in this order shall be construed to impair or otherwise affect:

(i) the authority granted by law to an executive department or agency, or the head thereof; or

(ii) the functions of the Director of the Office of Management and Budget relating to budgetary, administrative, or legislative proposals.

(b) This order shall be implemented consistent with applicable law and subject to the availability of appropriations.

(c) This order is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity by any party against the United States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.



THE WHITE HOUSE,
August 3, 2022.

[FR Doc. 2022–17420
Filed 8–10–22; 8:45 am]
Billing code 3395–F2–P

EXHIBIT 46

Presidential Memorandum, Further Efforts
To Protect Access to Reproductive
Healthcare Services,
88 Fed. Reg. 4895 (Jan. 22, 2023)

Presidential Documents

Memorandum of January 22, 2023

Further Efforts To Protect Access to Reproductive Healthcare Services

Memorandum for the Attorney General[,] the Secretary of Health and Human Services[, and] the Secretary of Homeland Security

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. *Policy.* Since 2000, the medication mifepristone has been approved by the Food and Drug Administration (FDA) for use in the United States as a safe and effective method to end early pregnancy.

The Food and Drug Administration Amendments Act of 2007 (Public Law 110–85) requires the FDA, working with drug manufacturers, to specify conditions for the use of certain drugs after considering six congressionally mandated factors. The Act sets forth a detailed administrative process to develop such conditions for use, known collectively as the Risk Evaluation and Mitigation Strategies (REMS), for individual drugs. Mifepristone has long had a REMS specifying the conditions for its use.

On January 3, 2023, the FDA, after an independent and comprehensive review of the risks and benefits of the drug, modified the REMS for mifepristone. The FDA took evidence-based action that supports access to mifepristone by helping ensure that healthcare providers and patients can continue to use telehealth to prescribe and receive mifepristone by mail after the end of the COVID–19 public health emergency. During the COVID–19 public health emergency, the FDA stopped enforcing a prior requirement that mifepristone be dispensed in person, and the FDA's January 2023 REMS permanently removed the in-person dispensing requirement. Additionally, pharmacies can now choose to become certified to dispense mifepristone to patients. These changes seek to reduce the burden on the healthcare delivery system while ensuring the benefits of the medication outweigh the risks. These changes also help ensure that patients can access mifepristone similarly to how they would access other prescribed medications.

In the wake of the new REMS for mifepristone, there have been reports of efforts to suppress access to medication abortion. Some State officials have announced that they will impose restrictions to limit access to this evidence-based, safe, and effective medication. In a letter to the FDA, for example, 22 State Attorneys General threatened to enforce State laws that purport to interfere with access to mifepristone. In Florida, the Governor recently said that major pharmacy chains in the State will not offer mifepristone. Florida health officials issued guidance discouraging pharmacies from dispensing mifepristone, claiming that State law limits where abortion medication can be provided to hospitals, clinics, or physician offices. These actions have stoked confusion, sowed fear, and may prevent patients from accessing safe and effective FDA-approved medication.

At the same time, those who provide reproductive healthcare continue to face heightened safety concerns. There are reports that some have vowed to make people uncomfortable entering pharmacies that dispense mifepristone.

In Executive Order 14076 of July 8, 2022 (Protecting Access to Reproductive Healthcare Services), I directed the Secretary of Health and Human Services

(HHS) to identify potential actions to protect and expand access to abortion care, including medication abortion. In that order, I directed the Attorney General and the Secretary of Homeland Security to consider actions, as appropriate and consistent with applicable law, that would protect the safety and security of patients, providers, and third parties, and that would protect the security of pharmacies and other entities providing, dispensing, or delivering reproductive and related healthcare services.

Since the issuance of Executive Order 14076, my Administration has taken steps to clarify the protections available to those who seek reproductive health services. The Department of Justice announced the formation of a Reproductive Rights Task Force, which, among other things, is focused on evaluating and monitoring State and local legislation, regulation, and enforcement actions that threaten to infringe on Federal legal protections relating to the provision or pursuit of reproductive care. HHS has published a report detailing its efforts to protect access to reproductive healthcare, including abortion care; protect patients' privacy and promote access to accurate information about reproductive healthcare services; and ensure that patients receive appropriate medical treatment under the law. Furthermore, HHS has continued taking action to help ensure non-discrimination in healthcare service delivery, including with respect to reproductive healthcare services and pharmacy access.

My Administration remains committed to supporting safe access to mifepristone, consistent with applicable law, and defending women's fundamental freedoms. Defending and protecting reproductive rights is essential to our Nation's health, safety, and progress. It is the policy of my Administration to protect against threats to the liberty and autonomy of those who live in this country.

Sec. 2. *Continuing to Protect Access to FDA-Approved Medication.* In light of recent developments and consistent with Executive Order 14076, within 60 days of the date of this memorandum:

(a) The Secretary of HHS, in consultation with the Attorney General and the Secretary of Homeland Security, shall consider:

(i) issuing guidance for patients seeking legal access to mifepristone, as well as for providers and entities, including pharmacies, that provide reproductive healthcare and seek to legally prescribe and provide mifepristone; and

(ii) any further actions, as appropriate and consistent with applicable law, to educate individuals on their ability to seek legal reproductive care, free from threats or violence.

(b) The Attorney General, the Secretary of Homeland Security, and the Secretary of HHS shall, as appropriate, provide the Interagency Task Force on Reproductive Healthcare Access, established in Executive Order 14076, with information concerning:

(i) potential barriers faced by patients seeking legal access to mifepristone or other reproductive healthcare, as well as by providers and entities, including pharmacies, that provide reproductive healthcare in providing mifepristone or other reproductive healthcare, and any recommendations for addressing these barriers; and

(ii) whether any additional institutional resources may be necessary to address these barriers.

Sec. 3. *General Provisions.* (a) Nothing in this memorandum shall be construed to impair or otherwise affect:

(i) the authority granted by law to an executive department or agency, or the head thereof; or

(ii) the functions of the Director of the Office of Management and Budget relating to budgetary, administrative, or legislative proposals.

(b) This memorandum shall be implemented consistent with applicable law and subject to the availability of appropriations.

(c) This memorandum is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity by any party against the United States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.

(d) The Attorney General is authorized and directed to publish this memorandum in the *Federal Register*.



THE WHITE HOUSE,
Washington, January 22, 2023

[FR Doc. 2023–01691
Filed 1–25–23; 8:45 am]
Billing code 4410–19–P

EXHIBIT 47

White House,
FACT SHEET: President Biden Announces Actions In Light of Today's Supreme Court Decision on *Dobbs v. Jackson Women's Health Organization*
(June 24, 2022)

JUNE 24, 2022

FACT SHEET: President Biden Announces Actions In Light of Today's Supreme Court Decision on Dobbs v. Jackson Women's Health Organization

Today, President Biden announced actions that his Administration is taking to protect women who will face the grave consequences of today's Supreme Court decision. This decision expressly took away a Constitutional right from the American people that it had recognized for nearly 50 years – a woman's right to choose, free from government interference.

This decision will have devastating consequences in the lives of women around the country.

The President made clear that the only way to secure a woman's right to choose is for Congress to restore the protections of Roe as federal law. Until then, he has announced two actions the Administration is taking to protect women.

Protecting the Right to Seek Medical Care

As the Attorney General made clear, women must remain free to travel safely to another state to seek the care they need.

A person has the right to travel between states for whatever reason they want – it is no one else's business – especially the government's. If a woman lives in a state that restricts abortion, the Supreme Court's

decision does not prevent her from traveling from her home to a state that allows it.

If any state or local official tries to interfere with women exercising this basic right, the Biden Administration will fight that deeply un-American attack.

Protecting Access to Medication

The President directed the Secretary of Health and Human Services to protect women's access to critical medications for reproductive health care that are approved by the Food and Drug Administration—including essential preventive health care like contraception and medication abortion.

More than 20 years ago, the FDA approved mifepristone to safely end an early pregnancy; this drug is also commonly used to treat miscarriages. The American Medical Association and the American College of Obstetricians and Gynecologists wrote to President Biden and Vice President Harris, asking the federal government to protect access to this care. In the face of threats from state officials saying they will try to ban or severely restrict access to medication for reproductive health care, the President directed the Secretary of Health and Human Services to identify all ways to ensure that mifepristone is as widely accessible as possible in light of the FDA's determination that the drug is safe and effective including when prescribed through telehealth and sent by mail.

***

EXHIBIT 48

Press Release, HHS,
HHS Secretary Becerra's Statement on Supreme Court Ruling in *Dobbs v. Jackson Women's Health Organization*
(June 24, 2022)

An official website of the United States government Here's how you know

U.S. Department of Health and Human Services
Enhancing the health and well-being of all Americans
</replay-web-page/w/id-aae9c8b5e5f5/mp_/https://www.hhs.gov/>

MENU

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FOR IMMEDIATE RELEASE
June 24, 2022

Contact: HHS Press Office
202-690-6343
media@hhs.gov

HHS Secretary Becerra's Statement on Supreme Court Ruling in Dobbs v. Jackson Women's Health Organization

Today, U.S. Department of Health and Human Services Secretary Xavier Becerra released the following after the Supreme Court's decision to overturn Roe v. Wade:

"Today's decision is unconscionable. Abortion is a basic and essential part of health care – and patients must have the right to make decisions about their health care and autonomy over their own bodies. For decades, both as a member of Congress and as California's Attorney General, I have stood with people around the country to fight for reproductive freedom for everyone, no matter who you are, where you live or how much you make. At the Department of Health and Human Services, we stand unwavering in our commitment to ensure every American has access to health care and the ability to make decisions about health care -- including the right to safe and legal abortion, such as medication abortion that has been approved by the FDA for over 20 years. I have directed every part of my Department to do any and everything we can here. As I have said before, we will double down and use every lever we have to protect access to abortion care. To everyone in this fight: we are with you."

###

Note: All HHS press releases, fact sheets and other news materials are available at https://www.hhs.gov/news </replay-web-page/w/id-aae9c8b5e5f5/mp_/https://www.hhs.gov/news>.
Like HHS on Facebook </replay-web-page/w/id-aae9c8b5e5f5/mp_/https://www.hhs.gov/disclaimer.html>, follow HHS on Twitter @HHSgov <https://rejouer.perma.cc/replay-web-page/w/id-aae9c8b5e5f5/mp_/https://twitter.com/#!/hhsgov> </replay-web-page/w/id-aae9c8b5e5f5/mp_/https://www.hhs.gov/disclaimer.html>, and sign up for HHS Email Updates <https://rejouer.perma.cc/replay-web-page/w/id-aae9c8b5e5f5/mp_/https://cloud.connect.hhs.gov/subscriptioncenter>.
Last revised: June 24, 2022

EXHIBIT 49

Press Release, HHS,
Remarks by Secretary Xavier Becerra at the Press Conference in Response to President Biden's Directive following Overturning of *Roe v. Wade*
(June 28, 2022)

Remarks by Secretary Xavier Becerra at the Press Conference in Response to President Biden's Directive following Overturning of Roe v. Wade

Xavier Becerra
June 28, 2022
Hubert H. Humphrey Building
Washington, D.C.

As Prepared for Delivery

On Friday, June 24th, five Americans decided to use the vast power bestowed upon them by our democracy and our Constitution to unconscionably put at risk the life and health of millions of their fellow Americans. They chose to unconscionably limit Americans' established freedom and autonomy to control their own body — decisions usually made in consultation with their doctor, not a politician. And they chose to unconscionably strip away the fundamental health care protections that every American of child-bearing age has known all their lives.

Friday's Supreme Court decision was despicable, but it was also predictable. HHS has been preparing for this for some time. That's why, earlier this year, we launched our HHS Reproductive Access Task Force to plan for every action necessary to protect women's access to reproductive health care.

There is no magic bullet. But if there is something we can do, we will find it and we will do it at HHS. Indeed, that was the instruction I received from the President of the United States.

Last Friday, President Biden announced the actions he is taking to ensure medication abortion is available to the fullest extent possible and that women can travel safely from states where abortion is banned to states where abortion is legal. Here is how HHS will support these issues:

- First, HHS will take steps to increase access to medication abortion.

  - Federal law requires our programs to provide medication abortion in limited circumstances, including life of the woman, rape, or incest.

- Now more than ever it is imperative that all federally-supported programs and services are complying and providing this under the law.

- Second, I am directing the Office for Civil Rights within HHS to ensure patient privacy and nondiscrimination for patients seeking reproductive health care, as well as for providers who offer reproductive health care.

- Third, I am directing the Department to examine its authority under the Emergency Medical Treatment Act (EMTALA) to ensure that clinical judgment of doctors and hospitals is supported in treating pregnant patients, including those experiencing pregnancy loss or complications, and reaffirming that abortion care can be appropriate to stabilize patients.

- Fourth, I am directing all agencies in my Department to work to ensure that all providers – from doctors to pharmacists -- and clinics have appropriate training and resources to handle family planning needs, including administering patient referrals for care, and helping patients navigate this new reality.

- Fifth, I am directing the Centers for Medicare and Medicaid Services (CMS) to take every legally available step to protect family planning care, including emergency contraceptives and long acting reversable contraceptives, such as IUDs. Health care is a matter to be decided by patients and their providers, not politicians. As part of these efforts, we will make clear that family planning providers are able to participate in the Medicaid program. These clinics provide safe care and have a vast expertise in providing reproductive health care.

Let me now tell you a little more about why I think medication abortion is so critical.

- Medication abortion has been approved by the FDA for years and is safe for patients.

- It is the gold standard for care when someone who’s pregnant experiences a miscarriage, which is all too real for many expectant mothers across the country.

- The Supreme Court’s decision will result in worsened health outcomes and death for some patients. Working to increase access to this drug is a national imperative and in the public interest.

- We will continue to support the FDA and its rigorous scientific review for these safe and effective drugs.

- We will also work with the Attorney General and the Justice Department as they work to ensure that states may not ban medication abortion, based on a disagreement with the FDA’s expert judgment about the drug’s safety and efficacy.

- And we will issue guidance to providers to ensure they receive accurate and robust information on medication abortion.

The HHS Reproductive Access Task Force will report to me on additional impactful ways to ensure appropriate information about, access to, and coverage for sexual and reproductive health care – as well as coordinate with other federal agencies.

I was at a Planned Parenthood clinic in St. Louis, Missouri, on Friday morning when the Supreme Court overturned Roe v. Wade. I saw in real time the impact of this unconscionable decision. The Clinic Director had to almost immediately start turning away patients as the state's ban went into effect. This clinic has stopped providing safe and legal abortion care. People in the room were visibly shaken, there were tears and an unshakeable sense of sadness.

After my visit to the clinic in St. Louis, I traveled across the state line to another clinic in Fairview Heights, Illinois – a state that, unlike Missouri, still had lawful abortion care. There, I visited a site that helps patients get care by providing assistance – ranging from helping patients find appointments to paying for their travel expenses –and abortion care. It was shocking that, in the United States of America, a short drive can make such a dire and draconian difference in health care outcomes. I saw restrictions that leave women and families on unequal footing and widen maternal health disparities.

The impact was visible and real.

This is a critical moment in history. How we respond will speak to how we view the rights, dignity and wellbeing of women everywhere. This is a moment of crisis in health care. We will leave no stone unturned. All options are on the table. We will do everything within the legal limit of the law to reach patients and support providers.

I know we are all tired and our hearts are broken by this loss of rights and dignity. But now is the time for us to continue on for the many people across the country who live in banned abortion states, who lack voices that represent them.

I stand with you and I have your back.

HHS Headquarters

U.S. Department of Health & Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201
Toll Free Call Center: 1-877-696-6775

EXHIBIT 50

Center for Drug Evaluation and Research, Application Number: 020687Orig1s025 Summary Review
(Jan. 3, 2023)
("FDA 2023 Summary Review")

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s025

SUMMARY REVIEW

[redacted] and [redacted]

Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 091178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequences 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022 (sequences 24 and 92 respectively), December 9, 2022 (sequences 25 and 93 respectively) and December 16, 2022 (sequences 26 and 95 respectively). This supplement is on a 180-Day clock.
Targeted Action Date	December 19, 2022
[redacted] #	2022-1169
Reviewer Names	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	January 3, 2023
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS
Name of Sponsor	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

TABLE OF CONTENTS

EXECUTIVE SUMMARY 3
1. Introduction 4
2. Background 4
2.1. Product Information and REMS Information 4
2.2. Regulatory History 6
3. Review of Proposed REMS Modification 8
3.1. REMS Goal 8
3.2. REMS Document 8
3.3. REMS Requirements 9
3.3.1. Addition and Removal of ETASU 9
3.3.2. REMS Participant Requirements and Materials 9
3.3.2.1. Prescriber Requirements 9
3.3.2.2. Patient Requirements 11
3.3.2.3. Pharmacy Requirements 12
3.3.2.4. Distributor Requirements 15
3.3.3. REMS Sponsor Requirements 15
3.3.3.1. Sponsor Requirements to Support Prescriber Certification 15
3.3.3.2. Sponsor Requirements to Support Pharmacy Certification 16
3.3.3.3. Sponsor Implementation Requirements 16
3.4. REMS Assessment Timetable 16
4. Supporting Document 17
5. REMS Assessment Plan 17
6. Discussion 19
7. Conclusions and Recommendations 21
8. References 21
9. Appendices 22

EXECUTIVE SUMMARY

This is a review of the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178. The Sponsors submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, and amended their submissions on October 19, 2022 (Danco), October 20, 2022 (GBP), November 30, 2022 (both), December 9, 2022 (both) and December 16, 2022 (both).

The Mifepristone REMS Program was originally approved on April 11, 2019, to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021.[a] The Mifepristone REMS Program consists of elements to assure safe use (ETASU) A, C and D, an implementation system, and a timetable for submission of assessments of the REMS.

The Sponsors submitted the proposed modification to the REMS in response to the Agency's REMS Modification Notification letters dated December 16, 2021, which required removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") and the addition of certification of pharmacies that dispense the drug.

In addition, the following were addressed during the course of the review:

- revisions to the REMS goal to align with the updated REMS requirements.
- replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms*, *Patient Agreement Form*, and *Pharmacy Agreement Forms*).

The review team finds the proposed modification to the Mifepristone REMS Program last submitted on December 16, 2022, to be acceptable and recommends approval of the REMS modification. The proposed REMS modification includes changes to the REMS goal, additional REMS requirements for prescribers to incorporate dispensing from certified pharmacies and new REMS requirements for pharmacy certification.

The proposed goal of the modified REMS for mifepristone 200 mg is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

[a] The May 14, 2021 REMS modification approved the inclusion of gender neutral language in the Patient Agreement Form as well as corresponding minor changes to the REMS document to be consistent with the changes made to the Patient Agreement Form.

The timetable for submission of assessments of the REMS was modified to one year from the date of the approval of the modified REMS and annually thereafter. The assessment plan was revised to align with the changes to the REMS and capture additional metrics for drug utilization and REMS operations.

The modified REMS includes ETASU A, B and D, an implementation system, and a timetable for submission of assessments of the REMS. Mifepristone will no longer be required to be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement" for brevity) and will be able to be dispensed from certified pharmacies.

1. Introduction

This review evaluates the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Sponsors initially submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, in response to the Agency's REMS Modification Notification letters issued on December 16, 2021, to Danco and GBP, requiring the following modification to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement")
- addition of certification of pharmacies that dispense the drug

Per the Agency's December 16, 2021, REMS Modification Notification letters, the proposed REMS was required to include the following ETASU to mitigate the risk of serious complications associated with mifepristone, including at least the following:

- healthcare providers have particular experience or training, or are specially certified
- pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- the drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS was also required to include an implementation system and timetable for submission of assessments.

2. Background

2.1. Product Information and REMS Information

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

the risk of serious complications associated with mifepristone when used for medical abortion.[c] Mifeprex was deemed to have in effect an approved REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and the Mifeprex REMS was approved on June 8, 2011.

On March 29, 2016, FDA approved an efficacy supplement for Mifeprex, which included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol, as well as a modification of the gestational age up to which Mifeprex has been shown to be safe and effective and a modification to the process for follow-up after administration of the drug. FDA also approved modification to the Mifeprex REMS that reflected the changes approved in the efficacy supplement.[1-5] On April 11, 2019, FDA approved ANDA 091178 and the Mifepristone REMS Program.[6-7] The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 091178. The goal of the approved Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber (under ETASU C).
c) Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

The Mifepristone REMS Program was last modified and approved in 2021 to revise the *Patient Agreement Form* to include gender-neutral language; however, the goal of the Mifepristone REMS Program has not changed since the initial approval in 2019.

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and agree to follow the guidelines for use of mifepristone. Under ETASU C, in the Mifepristone REMS Program as approved prior to today's action, mifepristone was required to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The approved Mifepristone REMS Program includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 public health emergency (PHE) regarding the in-person dispensing requirement in the Mifepristone REMS Program. Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form*, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020, to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.[8]

[c] Mifepristone is also approved in approximately 80 other countries. https://gynuity.org/assets/resources/biblio_ref_lst_mife_en.pdf

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

2.2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 04/11/2019: Approval of the Mifepristone REMS Program, a single, shared system REMS that includes NDA 020687 and ANDA 091178.
- 04/12/2021: The Agency issued a General Advice letter to both the NDA and ANDA Applicants, explaining that FDA intended to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form.
- 05/07/2021: The Agency stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with section 505-1 of the FD&C Act.
- 12/16/2021: The Agency completed its review of the Mifepristone REMS Program and determined, among other things, that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification.[9]
- 12/16/2021: REMS Modification Notification letters were sent to both Sponsors stating that the approved Mifepristone REMS Program must be modified to minimize the burden on the healthcare system of complying with the REMS and ensure that the benefits of the drug outweigh the risks.
- 04/08/2022: Final written responses to a Type A meeting request were provided to Danco, the point of contact for the Mifepristone REMS Program. The questions pertained to the 12/16/2021 REMS Modification Notification letter requirements.
- 04/13/2022: The Sponsors requested an extension to 6/30/2022, to submit a proposed REMS modification in response to the Agency's 12/16/2021 REMS Modification Notification letters.
- 04/15/2022: The Agency granted the Sponsors' request for an extension to submit a proposed REMS modification and conveyed that the modification must be submitted no later than 06/30/2022.[10]
- 06/22/2022: Danco and GBP submitted a proposed REMS modification to their respective applications in response to the 12/16/2021 REMS Modification Notification letters.
- 07/22/2022: An Information Request was sent to the Sponsors requesting clarification of the proposed prescriber and dispenser requirements and additional rationale to support their proposal.
- 08/26/2022: Sponsors submitted responses to 07/22/2022 Information Request.
- 09/19/2022: Teleconference was held between Agency and Sponsors where the Agency communicated the REMS requirements that are necessary to support the addition of pharmacy

certification. The Agency proposed focusing on the pharmacy settings where a closed system[d] REMS could be implemented using the existing email and facsimile based system, (b) (4) , as the best strategy for an approvable modification by the goal date.

- 09/22/2022: An Information Request was sent to Sponsors requesting confirmation that the Sponsors agree with the pharmacy distribution approach outlined in the 09/19/2022 teleconference so that the Agency's feedback could be appropriately tailored.
- 09/23/2022: The Sponsors confirmed via email that they were willing to pursue (b) (4) , as discussed in the 09/19/2022 teleconference. The Sponsors also requested a teleconference to discuss the current modification (b) (4) .
- 09/27/2022: Comments from the 09/19/2022 teleconference sent to Sponsors with additional comments and requests regarding what will be necessary for pharmacy certification.
- 09/29/2022: An Information request was sent to the Sponsors asking for agenda items, questions, and a request to walk through their proposed system for pharmacy certification, including dispensing through mail-order or specialty pharmacies, at the 10/06/2022 scheduled teleconference.
- 10/04/2022: Sponsors emailed that they will focus the 10/06/2022 teleconference on the 09/27/2022 Agency comments and their mail order and specialty pharmacy distribution model.
- 10/06/2022: Teleconference was held between Agency and Sponsors where Sponsors outlined their proposal for pharmacy certification, including dispensing through mail order and specialty pharmacies, as well as their concerns with certain requirements and general timelines.
- 10/19/2022: Danco submitted a REMS amendment to their pending sNDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/20/2022: GBP submitted a REMS amendment to their pending sANDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/25/2022: Teleconference was held between Agency and Sponsors to discuss the *Patient Agreement Form* and timing related to shipping a mifepristone prescription from a certified pharmacy to the patient.
- 11/23/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document, submitted on 10/19/2022 (Danco) and 10/20/2022 (GBP).
- 11/30/2022: Danco and GBP submitted REMS amendments, which included the REMS Document, to their respective pending supplemental applications.
- 12/01/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document.
- 12/05/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document submitted on 11/30/2022 and discussed at the teleconference on 12/01/2022, and REMS materials submitted to their applications on 10/19/2022 and 10/20/2022.

[d] "Closed system" in this case refers to a system where prescribers, pharmacies, and distributors are certified or authorized in the REMS and the certification of the stakeholder must be verified prior to distribution or dispensing, as per the REMS.

- 12/07/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document and REMS materials the Agency sent to the Sponsors on 12/05/22.
- 12/08/2022: Danco and GBP submitted REMS amendments, including the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form, Patient Agreement Form* and REMS Supporting Document, to their respective pending applications.
- 12/09/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS assessment plan.
- 12/14/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form*, and REMS Supporting Document.
- 12/15/2022: Two teleconferences were held between Agency and Sponsors to discuss the proposed REMS Document and REMS materials the Agency sent to the Sponsors on 12/14/22.
- 12/16/2022: Sponsors submitted a REMS amendment to their respective applications.

3. Review of Proposed REMS Modification

(b) (6) has discussed the Sponsors' proposed modification with the review team, which includes members of the (b) (6) and the (b) (6) ; hereafter referred to as the review team. This review includes their input and concurrence with the analysis and proposed changes to the Mifepristone REMS Program.

3.1. REMS Goal

The Sponsors proposed modification to the goal for the Mifepristone REMS Program to add that mifepristone can also be dispensed from certified pharmacies on prescriptions issued by certified prescribers. The proposed REMS goal is:

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

Reviewer Comment: *We agree with the Sponsors' proposal.*

3.2. REMS Document

The proposed REMS Document is not in the format as outlined in the 2017 Draft Guidance for Industry, Format and Content of a REMS Document.[11]

Reviewer Comment: *To avoid the misperception that this REMS modification is making major changes to the REMS document that go beyond our December 16, 2021, determination that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification, CDER staff and management discussed whether to change the format of the REMS document to that described in the 2017 draft guidance.*[11] *After internal discussion, CDER staff and management aligned not to transition the REMS document at this time to the format described in the 2017 draft guidance.*

3.3. REMS Requirements

3.3.1. Addition and Removal of ETASU

The December 16, 2021, REMS Modification Notification letters specified that the ETASU must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure the benefits of the drug outweigh the risks by:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices and hospitals (i.e., the "in-person dispensing requirement"), and;
- Adding a requirement that pharmacies that dispense the drug be specially certified.

The Sponsors proposed changes to the REMS as reflected in the subsections below.

3.3.2. REMS Participant Requirements and Materials

3.3.2.1. Prescriber Requirements

Consistent with the approved Mifepristone REMS Program prescribers must be specially certified. To become specially certified to prescribe mifepristone, healthcare providers who prescribe must review the Prescribing Information for mifepristone and complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet certain qualifications and will follow the guidelines for use of mifepristone. The guidelines for use include ensuring i) that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained; ii) that the healthcare provider (HCP) and the patient sign the *Patient Agreement Form*, iii) the patient receives a copy of the *Patient Agreement Form* and Medication Guide, iv) the *Patient Agreement Form* is placed in the patient's medical record; v) that any patient deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient. The language on the guidelines for use was revised from the Mifepristone REMS Program approved in 2021 to clarify that, if the certified prescriber supervises the dispensing of mifepristone, they must ensure the guidelines for use of mifepristone are followed by those under their supervision. This clarification reflects the ongoing implementation of the approved Mifepristone REMS Program. For example, consistent with the approved REMS, the *Patient Agreement Form* does not require the certified prescriber's signature, but rather the signature of the healthcare provider counseling the patient on the risks of mifepristone. Additional changes were made globally to provide consistency and clarity of the requirements for certified prescribers and healthcare providers who complete tasks under the supervision of certified prescribers.

A certified prescriber may submit the *Prescriber Agreement Form* to an authorized distributor if the certified prescriber wishes to dispense or supervise the dispensing of mifepristone; this is consistent with the current requirements of the Mifepristone REMS Program. Additional requirements were

added to incorporate mifepristone dispensing by a certified pharmacy. If a healthcare provider wishes to prescribe mifepristone by sending a prescription to a certified pharmacy for dispensing, the healthcare provider must become certified by providing the pharmacy a *Prescriber Agreement Form* signed by the provider. A certified prescriber must also assess the appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy.

The NDC and lot number of the dispensed drug will be recorded in the patient's record when mifepristone is dispensed by or under the supervision of a certified prescriber, replacing the requirement that serial numbers from each package of mifepristone be recorded in the patient's record. If prescribers become aware of the death of a patient for whom the mifepristone was dispensed from a certified pharmacy, the prescribers will be required to obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy.

The following materials support prescriber requirements:

- *Prescriber Agreement Form* for Danco Laboratories, LLC
- *Prescriber Agreement Form* for GenBioPro, Inc.
- *Patient Agreement Form*

Reviewer Comment: *We agree with the Sponsors' proposal.*

Although certain activities (review of the Patient Agreement Form with patients and answering any questions about treatment, signing, providing a copy to the patient and retaining the Patient Agreement Form, providing a copy of the Medication Guide, and ensuring any deaths are reported to the Mifepristone Sponsor, recording the NDC and lot number from drug dispensed from the certified prescriber or those under their supervision) may be conducted by healthcare providers under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. We agree with the additional language to further clarify that the certified prescriber must ensure the guidelines for use of mifepristone are followed.

As proposed, certified prescribers may either, 1) continue to submit the Prescriber Agreement Form to an authorized distributor if the certified prescriber is dispensing or supervising the dispensing of the drug (as already required in the REMS), or 2) if the drug will be dispensed from a certified pharmacy, submit the Prescriber Agreement Form to the certified pharmacy that will dispense the drug (as proposed in the modification). Regarding #2, the pharmacy can only fill prescriptions written by a certified prescriber.

Based on our review of the proposed changes, the review team finds it acceptable for prescribers to submit their Prescriber Agreement Form directly to the certified pharmacy. Although certified prescribers still have the option of in-person dispensing of the drug, not all prescribers may want to stock mifepristone. Typically due to the number of drugs that are available and the expense associated with stocking prescription medications intended for outpatient use, most prescribers do not stock many medications, if they stock medications at all.

The proposal to submit a Prescriber Agreement Form to a certified pharmacy provides another option for dispensing mifepristone. The burden of providing the Prescriber Agreement Form prior to or when the prescription is provided to a certified pharmacy does not create unreasonable burden for prescribers. The burden of prescriber certification has been minimized to the extent possible. The Prescriber Agreement Form is designed to require minimal time to complete and requires that the prescriber submit it to the authorized distributor once, and if the prescriber chooses to use a certified pharmacy to dispense mifepristone, they will need to submit the form to the certified pharmacy.

There is an additional requirement added for certified pharmacies and certified prescribers in the event that a patient will not receive their medication from the certified pharmacy within four calendar days of the pharmacy's receipt of the prescription (for example, if the medication is not in stock). In this circumstance, the pharmacy will be required to contact the certified prescriber to make them aware of the delay and will be required to obtain from the prescriber confirmation that it is appropriate to dispense mifepristone to the patient even though they will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy. This confirmation is intended to ensure timeliness of delivery in light of the labeled indication and gestational age. Additional details and rationale on the pharmacy requirements to dispense and ship drug in a timely manner are described in section 3.3.2.3.

If a certified prescriber becomes aware of a patient death that occurs subsequent to the use of mifepristone dispensed from a pharmacy, the certified prescriber must obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy. This information will be reported to the appropriate Mifepristone Sponsor in the same manner prescribers have done previously. This additional requirement to obtain the NDC and lot number from the pharmacy is needed to ensure consistent adverse event reporting when mifepristone is dispensed from a certified pharmacy.

Prescriber Agreement Form

The Sponsors' proposed changes to the *Prescriber Agreement Form* aligned with those described above. The proposed *Prescriber Agreement Form* explains the two methods of certification which are: 1) submitting the form to the authorized distributor and 2) submitting the form to the dispensing certified pharmacy. Further clarification was added that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification. The statement that certified prescribers are responsible for overseeing implementation and compliance with the REMS Program was also added. The following statement was added to the form: "I understand that the pharmacy may dispense mifepristone made by a different manufacturer than that stated on the Prescriber Agreement Form." The account set up information was removed and replaced with prescriber information response fields.

***Reviewer Comment**: We agree with the Sponsors' proposal. Changes in the above prescriber requirements were incorporated in the Prescriber Agreement Form.*

3.3.2.2. Patient Requirements

The *Patient Agreement Form* was updated to clarify that the signatures may be written or electronic, to reorganize the risk information about ectopic pregnancy, and to remove the statement that the Medication Guide will be taken to an emergency room or provided to a healthcare provider who did not prescribe mifepristone so that it is known that the patient had a medical abortion with mifepristone.

The following materials support patient requirements:

- *Patient Agreement Form*

***Reviewer Comment:** We agree with the Sponsors' proposal.*

The Patient Agreement Form continues to be an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the

patient, to provide the patient with the Patient Agreement Form, and to have the healthcare provider and patient sign the Patient Agreement Form, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The form is signed by the patient and the provider and placed in the patient's medical record, and a copy is provided to the patient, to document the patient's acknowledgment of receiving the information from the prescriber. The Agency agrees that the further clarification that signatures can be written or electronic is appropriate for the continued use of the form.

The reference to ectopic pregnancy has been reorganized in the document since it is not a risk of the drug. The signs and symptoms of an untreated ectopic pregnancy that may persist after mifepristone use have been clarified in the section of the form that explains the signs and symptoms of potential problems that may occur after mifepristone use.

The review team agrees with removing the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion. Although this statement has been in the Medication Guide for a number of years, upon further consideration, the Agency has concluded that patients seeking emergency medical care are not likely to carry a Medication Guide with them, the Medication Guide is readily available online, and information about medical conditions and previous treatments can be obtained at the point of care.

3.3.2.3. Pharmacy Requirements

The Sponsors proposed that certified pharmacies, in addition to certified prescribers and HCPs under the supervision of certified prescribers, can dispense mifepristone. In order for a pharmacy to become certified, the pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy. The Authorized Representative must certify that they have read and understood the Prescribing Information for mifepristone. Each location of the pharmacy must be able to receive *Prescriber Agreement Forms* by email and fax and be able to ship mifepristone using a shipping service that provides tracking information.

Additionally, each dispensing pharmacy location must put processes and procedures in place to fulfill the REMS requirements. Certified pharmacies must verify prescriber certification by confirming they have obtained a copy of the prescriber's signed *Prescriber Agreement Form* before dispensing. Certified pharmacies must dispense mifepristone such that it is received by the patient within four days from the day of prescription receipt by the pharmacy. If the pharmacy will not be able to deliver mifepristone to the patient within four days of receipt of the prescription, the pharmacy must contact the prescriber to confirm the appropriateness of dispensing mifepristone and document the certified prescriber's decision. The pharmacy must also record the NDC and lot number from each package of mifepristone dispensed in the patient's record, track and verify receipt of each shipment of mifepristone, dispense mifepristone in its original package, and only distribute, transfer, loan, or sell mifepristone to certified prescribers or between locations of the certified pharmacy. The pharmacy must also report any patient deaths to the prescriber, including the NDC and lot number from the package dispensed to the patient, and remind the prescriber of their obligation under the REMS to report patient deaths to the Sponsor that supplied the mifepristone; the certified pharmacy also must notify the Sponsor that supplied the mifepristone that the pharmacy submitted a report of a patient death to the prescriber and include the name and contact information for the prescriber as well as the NDC and lot number of the dispensed

product. Record-keeping requirements of the pharmacy include records of *Prescriber Agreement Forms*, mifepristone dispensing and shipping, and all processes and procedures and compliance with those processes and procedures. Pharmacies must train all relevant staff and participate in compliance audits. Pharmacies must also maintain the identity of patients and providers as confidential, including limiting access to patient and provider identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes. The requirement that mifepristone not be dispensed from retail pharmacies was removed.

The following materials support pharmacy requirements:

- *Pharmacy Agreement Form* for Danco Laboratories, LLC
- *Pharmacy Agreement Form* for GenBioPro, Inc.

Reviewer Comment: *We agree with the Sponsors' proposal. The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, mifepristone can be dispensed from a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that the prescriber is certified prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the Patient Agreement Form is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review and our consideration of the distribution model implemented by the Sponsors during the periods when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients.*

The requirement to maintain confidentiality, including limiting access to patient and provider identity only to those personnel necessary for dispensing under the Mifepristone REMS Program or as necessary for payment and/or insurance purposes, is included to avoid unduly burdening patient access.

The Sponsors proposed inclusion of this requirement because of concerns that patients may be reluctant or unwilling to seek to obtain mifepristone from pharmacies if they are concerned that confidentiality of their medical information could be compromised, potentially exposing them to intimidation, threats, or acts of violence by individuals opposed to the use of mifepristone for medical abortion.[e] *Further, unwillingness on the part of prescribers to participate in the Mifepristone REMS Program on the basis of*

[e] See e.g., *2020 Violence and Disruption Statistics,* National Abortion Federation (Dec. 16, 2021), https://prochoice.org/national-abortion-federation-releases-2020-violence-disruption-statistics/; Amanda Musa, CNN, *Wyoming Authorities Search for a Suspect Believed to Have Set an Abortion Clinic on Fire*, CNN WIRE (June 10, 2022), https://abc17news.com/news/2022/06/10/wyoming-authorities-search-for-a-suspect-believed-to-have-set-an-abortion-clinic-on-fire/.

similar confidentiality concerns may unduly burden patient access by limiting the number of prescribers who are willing to send prescriptions to certified pharmacies. Addition of this requirement protects patient access by requiring the pharmacy to put processes and procedures in place to limit access to confidential information to only those individuals who are essential for dispensing mifepristone under the Mifepristone REMS Program or as necessary for payment or insurance purposes. Inclusion of this requirement for certified pharmacies is consistent with the requirement in the current Mifepristone REMS Program, that distributors maintain secure and confidential records.

Reference to mifepristone not being available in retail pharmacies was removed from the REMS. There is no single definition of the term "retail pharmacy" and therefore the scope of the exclusion in the REMS was not well defined. Including a restriction in the Mifepristone REMS Program that retail pharmacies cannot participate in the REMS may unintentionally prohibit the participation of mail order and specialty pharmacies that could, under one or more definitions, also be considered a "retail pharmacy."

After reconsideration of the term, "retail," the Agency concluded that a more appropriate approach was to articulate the specific requirements that would be necessary for pharmacy certification. As modified, the REMS will not preclude the participation of any pharmacy that meets the certification requirements. However, we acknowledge that the provision in the REMS related to pharmacies' verification of prescriber enrollment will likely limit the types of pharmacies that will choose to certify in the REMS. The REMS requires that pharmacies dispense mifepristone only after verifying that the prescriber is certified. The REMS further requires that pharmacies be able to receive the Prescriber Agreement Forms by email and fax. (b) (4)

The pharmacy certification requirements include that the drug reach patients within four days of the certified pharmacy receiving the prescription. During the course of the review, the review team concluded that requiring medication delivery to the patient within four days of the pharmacy's receipt of a prescription is acceptable based on the labeled indication and literature,[13] while taking into account practical shipping considerations (e.g., shipping over weekends and holidays). For patients who will not receive the drug within four calendar days of the date the pharmacy receives the prescription, the pharmacy must notify the certified prescriber and the certified prescriber must determine if it is still appropriate for the certified pharmacy to dispense the drug. The pharmacy must document the certified prescriber's decision. A prescriber's confirmation that it is appropriate to dispense mifepristone when it will not be delivered to the patient within the allotted four days is intended to ensure timeliness of delivery in light of the labeled indication and gestational age.

Pharmacy Agreement Form

The proposed *Pharmacy Agreement Form* is a new form and is the means by which a pharmacy becomes certified to dispense mifepristone. The form, which is submitted by an authorized representative on behalf of a pharmacy seeking certification, outlines all requirements proposed above. Clarification is included in the form that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program, do not require pharmacy certification. Any new authorized representative must complete and submit the *Pharmacy Agreement Form*. Spaces for specific authorized representative information and pharmacy name and address are included. The completed form can be submitted by email or fax to the authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The Pharmacy Agreement Form aligns with the pharmacy requirements discussed above.*

3.3.2.4. Distributor Requirements

The Sponsors proposed that the distributors' processes and procedures in the approved Mifepristone REMS Program be updated to ensure that mifepristone is only shipped to clinics, medical offices and hospitals identified by certified prescribers and to certified pharmacies. Distributors will continue to complete the certification process for any *Prescriber Agreement Forms* they receive and also will complete the certification process for pharmacies upon receipt of a *Pharmacy Agreement Form*, including notifying pharmacies when they become certified. FDA was removed as a potential auditor for distributors.

Reviewer Comment: *We agree with the Sponsors' proposal. At this time, FDA does not audit distributors directly, it carries out inspections of Sponsors to monitor industry compliance with REMS requirements.*

3.3.3. REMS Sponsor Requirements

3.3.3.1. Sponsor Requirements to Support Prescriber Certification

The Sponsors proposed additions to this section of the REMS document, including that Sponsors will ensure prescribers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy, and that Sponsors will ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date. Sponsors will also ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*: (1) within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies, or (2) within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The requirement to confirm that the locations associated with the certified prescriber are current is parallel to the pharmacy requirement that the authorized representative's contact information is up to date. In determining the pharmacy requirement, which is necessary to ensure program compliance and is consistent with other approved REMS that include pharmacy certification, the Agency also concluded that a parallel requirement for certified prescribers should be added.*

With respect to recertification, it is important that active certified prescribers are informed of and agree to new REMS requirements to ensure the continued safe use of mifepristone. There is minimal burden to recertification and the timelines allow sufficient time to accomplish recertification.

3.3.3.2. Sponsor Requirements to Support Pharmacy Certification

The Sponsors proposed the addition of Sponsor requirements to support pharmacy certification and compliance, including ensuring that pharmacies are certified in accordance with the requirements in the Mifepristone REMS Program, de-certifying pharmacies that do not maintain compliance with the certification requirements, and ensuring that pharmacy certification can be completed by email and fax to an authorized distributor. Annually, the authorized representative's name and contact information will be verified to ensure it corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, a new authorized representative must certify for the pharmacy. All reference to the requirement in the 2021 Mifepristone REMS Program that mifepristone to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber, and not from retail pharmacies, was removed.

Reviewer Comment: *We agree with the Sponsors' proposal. Changes are in line with the REMS Modification Notification letters sent December 16, 2021. Refer to section 3.3.2.3 Reviewer Comments on Pharmacy Certification for rationale for removing the statement that mifepristone is not distributed to or dispensed from retail pharmacies. Ensuring that the authorized representative's contact information is up to date is necessary to ensure that there is always a point person who is responsible for implementing the Mifepristone REMS Program in their pharmacy and can address any changes that are needed if pharmacy audits identify a need for improvement.*

3.3.3.3. Sponsor Implementation Requirements

The Sponsors proposed that they will ensure that adequate records are maintained to demonstrate that REMS requirements have been met (including but not limited to records of mifepristone distribution, certification of prescribers and pharmacies, and audits of pharmacies and distributors), and that the records must be readily available for FDA inspections. The distributor audit requirement was updated to audit new distributors within 90 calendar days of becoming authorized and annually thereafter (a one-time audit requirement was previously required). The Sponsors also proposed a pharmacy audit requirement whereby certified pharmacies that order mifepristone are audited within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter for pharmacies that ordered in the previous 12 months.

Reviewer's Comment: *We agree with the Sponsors' proposal.*

The number of pharmacies that will certify in the REMS is uncertain; therefore, to obtain a reliable sample size for the audits, the Sponsors will need to audit all certified pharmacies within 180 calendar days after the pharmacy places its first order and annually thereafter for pharmacies that have ordered mifepristone in the previous 12 months. Audits performed at 180 days should allow time for establishment and implementation of audit protocols and for the Sponsors to perform the audits. With the addition of more stakeholders (i.e., certified pharmacies), it is also necessary to audit distributors annually to ensure the REMS requirements are followed. The requirement to conduct audits annually may be revisited if assessment data shows that the REMS is meeting its goal.

3.4. REMS Assessment Timetable

The Sponsors proposed that assessments must be submitted one year from the approval of the modified REMS and annually thereafter, instead of every three years as per the previous requirement.

Reviewer's Comment*: We agree with the Sponsors' proposal. With the addition of new pharmacy stakeholders and removal of the in-person dispensing requirement, more frequent assessment after this REMS modification is needed to ensure REMS processes are being followed and that the REMS is meeting its goal. The requirement can be revisited at a later date if assessment data shows that the modified REMS is meeting its goal. The NDA applicant is required to submit assessment reports as outlined in the timetable for submission of assessments. These reports address requirements for the Mifepristone REMS Program. The Sponsors have indicated that some data will be submitted as separate reports when Sponsor-specific information is needed to address the assessment metrics.*

4. Supporting Document

The Sponsors' REMS Supporting Document was substantially updated to include information regarding the proposed modification under review. Background and rationale from the 12/16/21 REMS Modification Notification letters was included. An updated description of the REMS goal and the ETASU was also included to align with the changes in the REMS Document and provide further clarification. Further explanation of prescriber requirements and rationale for various pharmacy requirements was also included.

Regarding implementation of the modified REMS, the Sponsors additionally proposed that pharmacies that received and shipped mifepristone during the Agency's exercise of enforcement discretion during the COVID-19 PHE, that wish to continue to dispense mifepristone, will be required to comply with the pharmacy certification requirements within 120 days of approval of the modified REMS.

The communication strategy to alert current and future prescriber and pharmacy stakeholders was outlined. Distributors, certified prescribers that purchased mifepristone in the last twelve months, and various professional organizations will receive information about REMS changes within 120 days of modification approval. The Sponsors proposed to list pharmacies that agree to be publicly disclosed on their respective product websites but disclosure of this nature is not a requirement of the REMS. The Sponsors indicated that they anticipate certified pharmacies that do not agree to public disclosure will communicate with the certified prescribers they wish to work with.

The REMS Assessment Plan is discussed in the following section.

Reviewer's Comment*: We agree with the Sponsors' proposal. The Supporting Document addresses all REMS requirements and provides sufficient clarification of implementation and maintenance of the REMS. The implementation requirements for pharmacies currently dispensing mifepristone under FDA's exercise of enforcement discretion during the COVID-19 PHE provide for continued use of these pharmacies without breaks in service. The communication strategy is also adequate given the efforts to reach both established certified prescribers and potentially new prescribers through professional organizations.*

The Sponsors' plan to communicate which pharmacies are certified to certified prescribers is adequate. For the reasons listed in section 3.3.2.3, confidentiality is a concern for REMS stakeholders. Disclosure of pharmacy certification status should be a choice made by individual certified pharmacies. The Sponsors have indicated that there will be some certified pharmacies that have agreed to publicly disclose their status, making this information available to certified prescribers who wish to use a pharmacy to dispense mifepristone.

5. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the REMS Modification Approval letter.

The REMS Assessment Plan was revised to align with the modified REMS goal and objectives.

The goal of the Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

b. Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

c. Informing patients about the risk of serious complications associated with mifepristone.
    - This objective will be indirectly assessed using REMS Certification Statistics to avoid compromising patient and prescriber confidentiality. As part of the certification process, healthcare providers agree to:
        - Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained
        - Ensure that the *Patient Agreement Form* is signed by the healthcare provider and the patient
        - Ensure that the patient is provided with a copy of the *Patient Agreement Form* and the Medication Guide
        - Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record

The following revisions were made from the Mifepristone REMS Assessment Plan in the April 11, 2019, Supplement Approval letter:

The Assessment Plan Categories of 1) Program Implementation and Operations and 2) Overall Assessment of REMS Effectiveness were added.

REMS Certification Statistics metrics were added to capture certification numbers for program stakeholders to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. The total number of certified prescribers who certified with the wholesaler/distributor and the total number of certified prescribers who submitted a *Prescriber Agreement Form* to certified pharmacies were added to capture the additional method of prescriber certification. The number of newly certified prescribers and the number of active certified prescribers (i.e., those who ordered mifepristone or submitted a prescription during the reporting period) were added. Metrics were also added to capture the total number of certified, newly certified, and active certified pharmacies as well as the total number of authorized, newly authorized, and active authorized wholesaler/distributors.

Drug Utilization Data metrics were added to obtain information on shipment and dispensing of mifepristone. Metrics were added to capture the total number of tablets shipped by the wholesaler/distributor and the number of prescriptions dispensed.

REMS Compliance Data metrics were added to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. These metrics capture program deviations and evaluate overall if the REMS is operating as intended. Metrics include certified pharmacies and wholesaler/distributor audit results and a summary of instances of non-compliance and actions taken to address non-compliance. Prescriber compliance metrics were added to assess if prescribers are decertified along with reasons why. Pharmacy compliance metrics were added to assess if prescriptions were dispensed that were written by non-certified prescribers or if mifepristone tablets were dispensed by non-certified pharmacies as well as the number of pharmacies that were decertified along with reasons why. Wholesaler/distributor metrics were added to assess if shipments were sent to non-certified prescribers and non-certified pharmacies and corrective actions taken. The audit plan and non-compliance plans will be submitted for FDA review within 60 days after the REMS modification approval.

The Sponsors were asked to develop an assessment of prescription delivery timelines to determine what percentage of prescriptions were delivered on time (within four calendar days) and what percentage were delivered late (more than four calendar days) along with the length of the delay and reasons for the delay (e.g., mifepristone is out of stock shipment issues, other). The protocol for this assessment will be submitted for FDA review within 60 days after the REMS modification approval.

The revised REMS Assessment Plan is in the Appendix.

Reviewer's Comment*: We agree with the Sponsors' proposed REMS Assessment Plan.*

6. Discussion

The Sponsors submitted changes to the REMS to remove the requirement that mifepristone be dispensed only in certain healthcare settings (i.e., the "in-person dispensing requirement") and to add that certified pharmacies can dispense the drug in order to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. The REMS goal was updated to this effect. Changes were required for prescriber requirements and Sponsors to support the change in ETASU, and new pharmacy requirements were introduced.

The qualifications to become a certified prescriber have not changed as a result of the modification to the Mifepristone REMS Program; however, clarification has been provided for certain prescriber requirements and new prescriber requirements have been added to support pharmacy dispensing. Although certain responsibilities may be conducted by staff under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. In order to clarify this, revisions were made throughout the prescriber requirements and REMS materials to reflect that the certified prescriber is responsible for ensuring that the prescriber requirements are met. Additionally, the review team finds it acceptable that certified prescribers who wish to use a certified pharmacy to dispense mifepristone submit their *Prescriber Agreement Form* to the dispensing certified pharmacy (b) (4) . The burden to prescriber and

pharmacy stakeholders of having certified prescribers submit the form directly to the certified pharmacy that will be dispensing the mifepristone is not unreasonable and has been minimized to the extent possible; it does not impact the safe use of the product. Prescriber requirements necessitated by the addition of some pharmacy requirements were added as well and include prescriber responsibilities in deciding whether or not mifepristone should be dispensed if the patient will receive the drug from the certified pharmacy more than four days after the pharmacy receives the prescription, and prescriber adverse event reporting requirements if a prescriber becomes aware of a patient death and the mifepristone was dispensed from a certified pharmacy. The addition of the latter requirements will ensure consistent adverse event data is relayed to the relevant Mifepristone Sponsor.

Changes were made to the *Patient Agreement Form.* Changes to the form were added to improve clarity of the safety messages. After further consideration, the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion has been removed from the *Patient Agreement Form*. The Medication Guide is not typically carried by patients and this information can be obtained at the point of care. Changes align with updates to labeling submitted with this modification.[13, 14]

The Agency and Sponsors agreed during this modification to focus on certification of pharmacies that can receive *Prescriber Agreement Forms* via email or fax to complete the prescriber certification process. The proposed pharmacy certification requirements also support timely dispensing of mifepristone. If the mifepristone is shipped to the patient, the REMS requires that it must be delivered within four calendar days from the receipt of the prescription by the pharmacy; if the patient will receive the mifepristone more than four calendar days from pharmacy receipt of prescription, the REMS requires the pharmacist to confirm with the certified prescriber that it is still appropriate to dispense the drug to the patient. This allows prescribers to make treatment decisions based on individual patient situations. A requirement to maintain confidentiality was also added to avoid unduly burdening patient access since patients and prescribers may not utilize pharmacy dispensing if they believe their personal information is at risk. Ultimately, the addition of pharmacy distribution with the proposed requirements will offer another option for dispensing mifepristone, alleviating burden associated with the REMS.

(b) (4)

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The Agency reviewed the REMS in 2021, and per the review team's conclusions, a REMS modification was necessary to remove the in-person dispensing requirement and add a requirement that pharmacies that dispense the drug be specially certified; the review team concluded that these changes could occur without compromising patient safety. There have been no new safety concerns identified relevant to the REMS ETASUs that the applicants proposed modifying in their June 22, 2022 submissions since the REMS Modification Notification letters dated 12/16/2021. It is still the position of the review team that the proposed modification is acceptable.

Because the modification proposed include changes to the ETASU of the Mifepristone REMS Program, the assessment plan and timetable of assessments were changed. The assessment plan will capture information on pharmacy dispensing and provide valuable insight as to whether the program is operating as intended Annual assessments are consistent with other approved REMS modifications for major modifications necessitating extensive assessment plan changes.

As part of the REMS Assessment Plan, the REMS goal and objectives are assessed using Program Implementation and Operations Metrics, including REMS Certification Statistics and REMS Compliance Data. The metrics will provide information on the number of certified prescribers, certified pharmacies, and authorized wholesalers/distributors as well as if mifepristone is dispensed by non-certified prescribers or pharmacies. The Sponsors will use the indirect measure of healthcare provider certification to address the objective of informing patients of the risk of serious complications of mifepristone, due to concerns with prescriber and patient confidentiality. Although we typically assess whether patients are informed of the risks identified in a REMS through patient surveys and/or focus groups, we agree that the Sponsors' continued use of the indirect measure of healthcare provider certification adequately addresses the Mifepristone REMS Program objective of informing patients. In addition, because of these prescriber and patient confidentiality concerns, we believe it is unlikely that the Agency would be able to use the typical methods of assessment of patient knowledge and understanding of the risks and safe use of mifepristone.

7. Conclusions and Recommendations

The review team finds the proposed REMS modification for the Mifepristone REMS Program, as submitted on June 22, 2022, and amended on October 19, 2022 (Danco) and October 20, 2022 (GBP), November 30, 2022 (both), December 9 (both), and December 16 (both) acceptable. The REMS materials were amended to be consistent with the revised REMS document. The review team recommends approval of the Mifepristone REMS Program, received on June 22, 2022, and last amended on December 16, 2022, and appended to this review.

8. References

1. (b) (6) Clinical Review of SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909590.

2. (b) (6) Summary Review for Regulatory Action for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909594.

3. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909588.

4. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909587.

5. Approval Letter for SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909592.

6. (b) (6) REMS Review for mifepristone, NDA 020687. February 22, 2018. DARRTS Reference ID: 4224674.

7. Approval Letter for SE-20 REMS Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 4418041.

8. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the

Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

9. (b) (6) REMS Modification Rationale Review for mifepristone, NDA 020687. December 16, 2021. DARRTS Reference ID: 4905882.

10. General Advice Letter for the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone, NDA 020687, April 15, 2022. DARRTS ID 4969358.

11. Format and Content of a REMS Document Guidance for Industry https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf. Accessed on December 18, 2022.

12. Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. Contraception 2022; 107:36-41. https://doi.org/10.1016/j.contraception.2021.09.008. This article was included in the literature review for the December 16, 2021 REMS Modification Rationale Review, while the article was still in press.

9. Appendices

REMS Document

Prescriber Agreement Form for Danco Laboratories, LLC

Prescriber Agreement Form for GenBioPro, Inc.

Patient Agreement Form

Pharmacy Agreement Form for Danco Laboratories, LLC

Pharmacy Agreement Form for GenBioPro, Inc.

Mifepristone REMS Assessment Plan

Initial Shared System REMS approval: 04/2019
Most Recent Modification: 01/2023

Mifepristone Tablets, 200 mg
Progestin Antagonist

RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG

I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
   a. To become specially certified to prescribe mifepristone, healthcare providers must:
      i. Review the Prescribing Information for mifepristone.
      ii. Complete a *Prescriber Agreement Form*. By signing[1] a *Prescriber Agreement Form*, prescribers agree that:
         1) They have the following qualifications:
            a) Ability to assess the duration of pregnancy accurately
            b) Ability to diagnose ectopic pregnancies
            c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
         2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
   b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
      i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
      ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form.*

[1] In this REMS, the terms "sign" and "signature" include electronic signatures.

iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.

iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.

v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

vi. If mifepristone will be dispensed by a certified pharmacy:

1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.

2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.

3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.

vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:

1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.

2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.

3) Ensure that healthcare providers under their supervision follow guidelines i.-v.

c. Mifepristone Sponsors must:

i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.

ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:

1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.

2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.

iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.

The following materials are part of the Mifepristone REMS Program:

- *Prescriber Agreement Form for Danco Laboratories, LLC*
- *Prescriber Agreement Form for GenBioPro, Inc.*
- *Patient Agreement Form*

2. Pharmacies that dispense mifepristone must be specially certified
   a. To become specially certified to dispense mifepristone, pharmacies must:
      i. Be able to receive *Prescriber Agreement Forms* by email and fax.
      ii. Be able to ship mifepristone using a shipping service that provides tracking information.
      iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.
      iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:
         1) Review the Prescribing Information for mifepristone.
         2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:
            a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.
            b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.
            c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
            d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
            e) Track and verify receipt of each shipment of mifepristone.
            f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.
            g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
            h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
            i) Maintain records of *Prescriber Agreement Forms*.
            j) Maintain records of dispensing and shipping.
            k) Maintain records of all processes and procedures including compliance with those processes and procedures.
            l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes.
            m) Train all relevant staff on the Mifepristone REMS Program requirements.

n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

b. Mifepristone Sponsors must:

i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.

ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.

i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
- *Pharmacy Agreement Form for GenBioPro, Inc.*

3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form*.

a. The patient must sign a *Patient Agreement Form* indicating that the patient has:

i. Received, read and been provided a copy of the *Patient Agreement Form*.

ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:

a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.

i. The distributors must put processes and procedures in place to:

1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.

2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.

3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.

4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.

5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.

ii. Put processes and procedures in place to maintain a distribution system that is secure,

confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

iii. Train all relevant staff on the Mifepristone REMS Program requirements.

iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.

2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.

3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.

4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.

5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.

6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.

7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (1/3/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

MIFEPREX® (Mifepristone) Tablets, 200 mg

PRESCRIBER AGREEMENT FORM

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.

*MIFEPREX is a registered trademark of Danco Laboratories, LLC
P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855—643-3463 toll-free), or by visiting www.MifeInfo.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc. that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If mifepristone will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to 1-877-239-8036

Approved 01/2023 [Doc control ID]

PATIENT AGREEMENT FORM Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   a. I will take mifepristone on Day 1.
   b. I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
   - heavy bleeding
   - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - severe stomach area (abdominal) pain or discomfort, or I am “feeling sick,” including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
     — these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

   My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name** (print): _____ **Date**: _____

Provider Signature: _____ **Provider Name** (print): _____ **Date**: _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

MIFEPREX®(Mifepristone) Tablets, 200mg

PHARMACY AGREEMENT FORM

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at www.earlyoptionpill.com; and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
    - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
    - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
    - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
    - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
    - Track and verify receipt of each shipment of Mifeprex.
    - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
    - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
    - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
    - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
    - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
    - Train all relevant staff on the Mifepristone REMS Program requirements.
    - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

DANCO
Support • Progress • Options

*MIFEPREX is a registered trademark of Danco Laboratories, LLC

P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

PHARMACY AGREEMENT FORM **Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at www.MifeInfo.com; and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
  - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
  - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
  - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
  - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
  - Track and verify receipt of each shipment of mifepristone.
  - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
  - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
  - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
  - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
  - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
  - Train all relevant staff on the Mifepristone REMS Program requirements.
  - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to **1-877-239-8036.**

The REMS Assessment Plan must include but is not limited to the following items.

Program Implementation and Operations

1. REMS Certification Statistics
   a. Prescribers
      i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
      ii. Number and percentage of newly certified prescribers
      iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

   b. Pharmacies
      i. Number of certified pharmacies
      ii. Number and percentage of newly certified pharmacies
      iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)
   c. Wholesalers/Distributors
      i. Number of authorized wholesalers/distributors
      ii. Number and percentage of newly authorized wholesalers/distributors
      iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data
   a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
   b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data
   a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
      i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
      ii. The number of audits expected, and the number of audits performed
      iii. The number and type of deficiencies noted
      iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
      v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)

vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)

b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:

i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)

ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):

1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
2. The source of the non-compliance data (e.g., self-reported, audit, other)
3. A root cause analysis of the non-compliance
4. Actions to prevent future occurrences and outcomes of such actions

iii. Prescriber compliance

1. Number and percentage of certified prescribers who became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

iv. Pharmacy compliance

1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
3. Number and percentage of pharmacies that became decertified as a result of non-compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

v. Wholesaler/distributor compliance

1. Number of healthcare providers who successfully ordered mifepristone who were not certified
2. Number of non-certified pharmacies that successfully ordered mifepristone
3. Number of shipments sent to non-certified prescriber receiving locations
4. Number of shipments sent to non-certified pharmacy receiving locations

5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Center for Drug Evaluation and Research (CDER)

[redacted]

Application Type	NDA and ANDA
Application Number	020687 and 91178
Reviewer Names	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	December 16, 2021

Subject	REMS Modification Rationale Review
Established Name	Mifepristone REMS
Name of Applicants	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablets

Table of Contents

EXECUTIVE SUMMARY 4

1. Introduction 5
2. Background 5
   - 2.1. PRODUCT AND REMS INFORMATION 5
   - 2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW 7
3. Rationale for Proposed REMS Modification 9
   - 3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS 10
   - 3.2. EVALUATION OF THE EVIDENCE 10
   - 3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A) 12
   - 3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D) 14
   - 3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C) 19
4. Discussion 36
5. Conclusions and Recommendations 41
6. References 42
7. Appendix 45

EXECUTIVE SUMMARY

This review provides the [redacted] rationale and conclusions regarding modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178.

ANDA 91178 was approved with the approval of the Mifepristone REMS Program on April 11, 2019 to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021. The REMS consists of elements to assure safe use (ETASU) under ETASU A, C and D, an implementation system, and a timetable for submission of assessments. To determine whether a modification to the REMS was warranted, FDA undertook a comprehensive review of the published literature; safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below.

The modifications to the REMS will consist of:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to here as the "in-person dispensing requirement" for brevity)
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified

A REMS Modification Notification letter will be sent to both Applicants in the Single Shared System.

1. Introduction

In connection with the *Chelius v. Becerra* litigation, FDA agreed to undertake a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[a] This review provides the analysis of the (b) (6) ((b) (6) and the (b) (6) ((b) (6) regarding whether any changes are warranted to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone (hereafter referred to as the Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178. The Mifeprex REMS was initially approved in 2011; the single, shared system REMS for mifepristone 200 mg, known as the Mifepristone REMS Program, was approved in 2019.

The last time the existing REMS elements to assure safe use (under ETASU A, C and D) were reviewed was in the context of our review of supplement S-020 to NDA 20687; these ETASU were updated following review and approval of supplement S-020 on March 29, 2016. The key changes approved in 2016 are summarized below.

Changes to labeling included:

- Changing the dosing of Mifeprex to 200 mg orally x 1
- Extension of maximum gestational age through 70 days
- Inclusion of misoprostol in the indication statement
- Replacing the term “physician” with “licensed healthcare provider”
- Removal of the phrase “Under Federal Law”

The Mifeprex REMS and REMS materials were updated to reflect the changes above, and additional changes were made including:

- Removing the Medication Guide as part of the REMS but retaining it as part of labeling.

2. Background

2.1. PRODUCT AND REMS INFORMATION

[a] Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000 with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed the risk of serious complications associated with mifepristone when used for medical abortion. Mifeprex was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the Mifeprex REMS was approved on June 8, 2011. On March 29, 2016, as noted above, a supplemental application and REMS modification was approved for Mifeprex. On April 11, 2019, ANDA 091178 was approved, and the Mifepristone REMS Program was approved. The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 91178.

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
b. Ensuring that mifepristone is only dispensed in certain healthcare settings, by or under the supervision of a certified prescriber (under ETASU C).
c. Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and follow the guidelines for use of mifepristone. Under ETASU C, mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The Mifepristone REMS Program also includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW

The following is a summary of significant regulatory history since approval of the REMS modification on March 29, 2016:

- 03/29/2016: FDA approved an efficacy supplement (S-020) that, among other things, provided a new dosing regimen (200 mg mifepristone, followed in 24 to 48 hours by 800 mcg buccal misoprostol), increased the gestational age (GA) to which mifepristone may be used (through 70 days gestation), and modified the REMS.

- 03/29/2019: A Citizen Petition was received requesting that FDA revise the product labeling to reflect pre-2016 provisions (including limiting GA to 49 days and requiring patients to make 3 office visits) and that FDA maintain the REMS.

- 04/11/2019: ANDA 91178 was approved along with the Single Shared System REMS for Mifepristone 200 mg (Mifepristone REMS Program) for NDA 20687 and ANDA 91178.

- 01/31/2020: the COVID-19 public health emergency (PHE) was declared by the Secretary of Health and Human Services (HHS) as having existed since January 27, 2020.[c]

- 7/13/2020: The United States (US) District Court of Maryland granted a preliminary injunction in the *ACOG v. FDA* litigation to temporarily bar enforcement of the Mifepristone REMS Program in-person dispensing requirement during the COVID-19 PHE.

- 1/12/2021: US Supreme Court granted a stay of that injunction.

- 04/12/2021: FDA issued a General Advice Letter to both the NDA and ANDA Applicants, stating that provided that all other requirements of the Mifepristone REMS Program are met, and given that in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare

[c] *See* Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued January 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx

personnel because it may involve a clinical visit solely for this purpose, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form.* FDA further stated that to the extent all of the other requirements of the Mifepristone REMS Program are met, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

- 05/07/2021: FDA stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with the REMS assessment provisions of section 505-1 of the FD&C Act.

- 05/14/2021: A modification was approved for the Mifepristone REMS Program. This modification was to revise the *Patient Agreement Form* to include gender-neutral language.

- 06/30/2021: An Information Request (IR) was sent to the Applicants for additional information on shipments and any program deviations, adverse events, or noncompliance with the REMS that occurred during the period from April 1, 2021 through September 30, 2021.

- 7/15/2021: An IR was sent to the Applicants to provide the total number of shipments during the period from April 1, 2021 to September 30, 2021 and details on whether any of those shipments were involved in any program deviation or non-compliance.

- 8/5/2021: An IR was sent to the Applicants for additional clinical and other information (e.g., adverse events and units of mifepristone shipped) for the period of March 29, 2016 through June 30, 2021, to be provided by August 31, 2021. This IR also requested information covering the period of July 1, 2021 through September 30, 2021 and an

aggregate summary (for the period of March 29, 2016 through September 30, 2021), to be provided by October 12, 2021.[d]

- 8/26/2021: The ANDA Applicant submitted a response to the IR issued on 8/5/2021.
- 08/27/2021: The NDA Applicant submitted a response to the IR issued on 8/5/2021.
- 10/08/2021: The NDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR. The NDA Applicant also included a follow-up to their initial response provided on August 27, 2021 to the August 5, 2021 IR.
- 10/12/2021: The ANDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR.
- 10/16/2021: The ANDA Applicant revised their Oct 12, 2012 response to provide a correction to the number of mifepristone tablets.
- (b) (4) .
- 11/02/2021: A (b) (6) ((b) (6) meeting was convened to obtain CDER concurrence on the removal of the in-person dispensing requirement and the addition of a certification requirement for pharmacies. The (b) (6) (b) (6) and senior CDER leadership concurred with removing the in-person dispensing and adding pharmacy certification.

3. Rationale for Proposed REMS Modification

[d] Multiple Information Requests were issued to obtain additional information on drug shipments, any program deviations or noncompliance, and use of alternative methods for drug distribution during the COVID-19 PHE. These IRs are referenced as appropriate in this document and the one-year REMS Assessment Review of the Mifepristone REMS Program, December 16, 2021.

3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS

The Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use in the current REMS include a prescriber certification requirement (ETASU A), a requirement that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and a requirement that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions under ETASU D consists of a *Patient Agreement Form* between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone 200 mg for medical termination of early pregnancy.

3.2. EVALUATION OF THE EVIDENCE

We reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation. Below is an overview of how information relevant to the current Mifepristone REMS Program was retrieved, analyzed, and applied to each of the individual ETASUs to determine if further changes should be considered.

Methods for the literature search

(b) (6) conducted a literature search in PubMed and Embase to retrieve publications relevant to this review. The time period used for this literature search was between March 29, 2016 (when the Mifeprex labeling and REMS were last substantially revised) through July 26, 2021. The search terms used were “medical abortion” and “mifepristone” and “pregnancy termination and mifepristone.”

The search retrieved 306 publications from PubMed and 613 from Embase, respectively; the search yielded 646 unique publications after eliminating duplications between the two databases. The result of our literature search was also supplemented by an examination of literature references provided by advocacy groups, individuals, plaintiffs in the *Chelius* litigation, and the Applicants, as well as letters from healthcare providers and researchers.

References included in these letters were considered for inclusion in this review using identical selection criteria to the (b) (6) literature search (outlined below).

For this review of the REMS, (b) (6) focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS ETASUs. We excluded systematic reviews and meta-analyses because these publications did not include original safety data related to the outcomes of medical abortion. The following are examples of materials that were excluded from our literature search:

- Information from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, even if the study assessed REMS ETASUs. These surveys or qualitative studies did not include objective safety data related to outcomes of medical abortion.

- Opinions, commentaries, or policy/advocacy statements. These publications did not include objective safety data related to outcomes of medical abortion.

- Safety data related to mifepristone use for second trimester medical abortion. These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data related to mifepristone use for spontaneous first trimester abortion (i.e., miscarriages). These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data that pertained only to surgical abortion or did not separate out medical abortion from surgical abortion.

- Other safety information unrelated to the REMS elements (e.g., articles limited to case reports or those discussing unrelated gynecologic or medical issues)

- Publications for which it was not possible to conduct a full review of the methods or results, i.e., the references were limited to an abstract of the study methods and results.

- Publications that provided only general statistics on abortion care in the United States.

- Information pertinent to molecular or other basic science aspects of mifepristone.

- Data on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care.

- Publications that provided data not related specifically to abortion care or the REMS (e.g., references focused on federal poverty guidelines, poverty data, or the financial impact of the COVID-19 pandemic).

One exception to the above literature search criteria was the inclusion in Section 3.2.2 of this review, which discusses the *Patient Agreement Form*, of publications that discussed changes in provider volume. The data discussed in relation to provider volume was obtained from surveys. This data was included because changes in provider volume could only be obtained from well-conducted survey studies.

Regarding medical/scientific references submitted with letters from the plaintiffs in the *Chelius* litigation, we applied the same criteria as for the literature search, as described above.

Letters from the plaintiffs in the *Chelius* litigation included several references that preceded our 2016 review of the REMS. Two of those pre-2016 studies were not captured in our 2016 literature search. These two studies were assessed as part of our current review; their results are consistent with the existing safety profile of the approved medical abortion regimen, and therefore, support our current conclusions regarding the REMS. See Appendix A.

3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A)

In order to become specially certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet the qualifications listed below:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to

ensure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the *Patient Agreement Form* with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the *Patient Agreement Form*.
- Provide the patient with a copy of the *Patient Agreement Form* and the Medication Guide.
- Place the signed *Patient Agreement Form* in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

The literature review was the primary source of information that contributed to our reassessment of ETASU A.

We continue to be concerned that absent these provider qualifications, serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed. Our review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our review continues to support the conclusion that a healthcare provider who prescribes mifepristone should meet the above qualifications. We conclude it is reasonable to maintain the requirement for a one-time prescriber certification where prescribers attest to having the ability to diagnose an intrauterine

pregnancy, to diagnose an ectopic pregnancy,[e] and to either manage serious complications themselves or arrange for other providers to provide the needed care in a timely manner.

In addition, in signing the *Prescriber Agreement Form* and placing it in the patient's medical record, the prescribers acknowledge the requirement to report patient deaths associated with mifepristone to the manufacturer. Such a requirement ensures that the manufacturer receives all reports of patient deaths and, in turn, fulfills its regulatory obligations to report those deaths to the FDA.

As discussed in Section 3.2.2 below, there is a potential for doubling of the number of prescribers of mifepristone if the in-person dispensing requirement in ETASU C is removed from the Mifepristone REMS Program. Given the potential addition of new prescribers, in addition to the considerations described above, we conclude that we should maintain the requirement for prescriber certification, to ensure that providers meet the necessary qualifications and adhere to the guidelines for use. Our literature review supports that these requirements are still necessary, and the potential increase in new prescribers under the REMS is a further reason to maintain prescriber certification. Healthcare provider certification continues to be a necessary component of the REMS to ensure the benefits of mifepristone for medical abortion outweigh the risks. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one time for each applicant.

3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D)

In order to receive mifepristone for medical termination of pregnancy through 70 days gestation, the patient must sign a *Patient Agreement Form* indicating that the patient has received, read, and been provided a copy of the *Patient Agreement Form* and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The *Patient Agreement Form* ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication.

[e] American College of Obstetricians and Gynecologists (ACOG) Practice Bulleting Number 191, February 2018. Tubal Ectopic Pregnancy. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/03/tubal-ectopic-pregnancy. Mifepristone is not effective for terminating ectopic pregnancy. Some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. A missed ectopic pregnancy that ruptures is a medical emergency that requires immediate surgical intervention.

In a number of approved REMS, *Patient Agreement Forms* or *Patient Enrollment Forms* ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[f]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the *Patient Agreement Form* with the patient, fully explaining the risks of the treatment regimen, and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the *Patient Agreement Form*, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the *Patient Agreement Form* serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed *Patient Agreement Form* in the patient's medical record.

Prior to the March 29, 2016 approval of the S-020 efficacy supplement for Mifeprex, FDA undertook a review of all elements of the REMS. At that time, the (b) (6) ((b) (6)), along with the (b) (6) ((b) (6)), recommended removal of the *Patient Agreement Form* (ETASU D). This recommendation received concurrence from the (b) (6) on February 23, 2016. The rationale for this recommendation in the 2016 review[g] is summarized here as follows:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and documentation of informed consent and evidence shows that practitioners are providing appropriate patient

[f] REMS@FDA, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.
[g] (b) (6) Clinical Review, NDA 020687/S20, dated March 29, 2016. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af803dc7bd&_afrRedirect=386175573203745

counseling and education; the *Patient Agreement Form* is duplicative of these established practices.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines are duplicated in the *Patient Agreement Form*.
- ETASUs A and C remain in place: The *Prescriber Agreement Form* and the requirement that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals under the supervision of a certified prescriber, remain in place.

In light of a memorandum from the Director of the Center for Drug Evaluation and Research, an addendum to the (b) (6) March 29, 2016 review and a memorandum from the signatory authority in (b) (6) indicated that the *Patient Agreement Form* would be retained in the REMS.[h,i]

The current review of literature from March 29, 2016 to July 26, 2021, is relevant to our assessment of the necessity of the *Patient Agreement Form* as part of the REMS. While our literature search yielded no publications which directly addressed this element of the REMS, we identified the following literature that focused on the informed consent process. These studies were reviewed for their potential relevance on this topic, though the articles do not directly assess the need for the *Patient Agreement Form* as a condition necessary to assure safe use of Mifepristone under ETASU D.

- Two studies[1,2] (both authored by Dr. Grossman in 2021) used the *Patient Agreement Form* and additional clinic-specific written informed consent forms as part of the study methodology. One study evaluated medical abortion with pharmacist dispensing of mifepristone and another evaluated mail-order pharmacy dispensing. Safety and efficacy outcomes were not assessed regarding the element of consent in isolation or the *Patient Agreement Form*.
- Several studies included use of electronic or verbal consent. Two studies were conducted using signed electronic consent (Chong[3], Kerestes[4]). Aiken[5] reported that patients had the option of providing consent verbally and the discussion had to be recorded in the notes. Rocca[6] described obtaining verbal informed consent from patients seeking medical abortion provided in pharmacies or government-certified

h (b) (6) Review of proposed REMS modifications to Mifeprex. March 29, 2106.
i (b) (6) Summary of Regulatory Action for Mifeprex. March 29, 2016.

public health facilities by auxiliary nurse midwives (ANMs) in Nepal. Outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

- A retrospective chart review (Wiebe[7]) was conducted in Canada. This study included telemedicine abortions between January 31, 2017 and January 31, 2019 and a similar group of controls seen in the clinic during the same time frame, matched by date of initial appointment. As part of the telemedicine process, patients read a consent form (not specified whether they could view an electronic version) and gave verbal consent "witnessed by the counselor". Again, outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

After review, we conclude that there are no outcome data from these studies that address the need for the *Patient Agreement Form* as a condition necessary to assure safe use of mifepristone. Nor do any of these studies provide evidence of whether the patient's informed consent has been adequately documented under the process set out in the study protocol. Therefore, these studies do not provide evidence that would support removing ETASU D.

Although (b) (6) agrees that informed consent in medicine is an established practice, the National Abortion Federation's 2020 Clinical Policy Guidelines for Abortion Care[8] continue to include a detailed section on patient education, counseling, and informed consent. The guidelines state that these steps are essential parts of the abortion process; that they should be conducted by appropriate personnel, with accurate information, including about alternatives and potential risks and benefits; and that the patients must have an opportunity to have any questions answered to their satisfaction prior to any intervention. Under these guidelines, documentation must show that the patient affirms that they understand all the information provided and that the decision to undergo an abortion is voluntary. The guidelines specifically list the risks that must be addressed at a minimum, including those pertinent to medical abortion: hemorrhage, infection, continuing pregnancy, and death. Additionally, Practice Bulletins from ACOG[9] and the Society of Family Planning also support detailed patient counseling.

In addition, trends in US clinical practice are developing which could negatively impact adequate patient counseling about the risks of medical abortion. One survey by Jones 2017[10] of abortion providers in the United States and Canada prior to the COVID-19 pandemic did reveal strong adherence to evidence-based guidelines. However, this same survey noted continued increasing uptake of medical abortion by US providers. Grossman[11] conducted a US survey in

2019 which suggested that the number of obstetrician/gynecologists providing medical abortion care may be increasing and that uptake might increase if mifepristone were dispensed by pharmacies instead of being dispensed in-person. A subsequent survey of US obstetricians/ gynecologists by Daniel in 2021[12] evaluated a subsample (n = 868) from a prior national survey of providers and found that 164 (19%) reported providing medical abortion in the previous year. Of those obstetrician/gynecologists not providing medical abortion, 171 (24%) said they would offer the method to their patients if the in-person dispensing requirement for mifepristone were removed. This indicates a potential doubling of providers (+ 104%, 95% confidence interval (CI): 97% −112%). There were geographical variations, with the largest potential increases being in the Midwest (+ 189%, 95% CI: 172% −207%) and the South (+ 118%, 95% CI: 103% −134%).

Based on the articles discussed above, removal of the in-person dispensing requirement from the Mifepristone REMS Program (as discussed below in section 3.2.3) could significantly increase the number of providers to a larger group of practitioners. The *Patient Agreement Form* is an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the patient, to provide the patient with the *Patient Agreement Form*, and to have the healthcare provider and patient sign the *Patient Agreement Form*, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The single-page *Patient Agreement Form* is in line with other elements of this REMS, in that it supports the requirement that certified prescribers be able to accurately assess a patient, counsel a patient appropriately and recognize and manage potential complications. The form is placed in the patient's medical record to document the patient's acknowledgment of receiving the information from the prescriber and a copy is provided to the patient. We determined, consistent with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients, and that the *Patient Agreement Form* remains necessary to assure the safe use of Mifepristone.

After considering potential burden on healthcare providers and patients and considering the available data discussed above, including the potential for increased prescribing of mifepristone if in-patient dispensing is removed from the REMS, we conclude that the *Patient Agreement Form* should remain a safe use condition in the REMS.

3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C)

Mifepristone applicants must ensure that mifepristone is available to be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This creates what we refer to in this document as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office or hospital when the drug is dispensed. The mifepristone REMS document states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than these.

The following information contributed to our analysis of this requirement: Mifepristone REMS Program year-one assessment data, postmarketing safety information and literature review.

REMS Assessment Data

Reporting period for the Mifepristone REMS Program - April 11, 2019 through February 29, 2020

We evaluated information included in the one-year (1st)[j] REMS assessment reports for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, compliance data, audit results and patient exposure data.[13] The assessment reports were submitted on April 10, 2020 by the NDA Applicant and April 15, 2020 by the ANDA Applicant and cover a reporting period from April 11, 2019 through February 29, 2020. During this reporting period, the NDA Applicant reported (b) (4) newly certified healthcare providers, and the ANDA Applicant reported (b) (4) newly certified healthcare providers in the Mifepristone REMS Program. The NDA Applicant reported a total of (b) (4) certified healthcare providers (includes new and previously certified) ordered mifepristone during the assessment reporting period, and the ANDA Applicant reported a total of (b) (4) certified healthcare providers ordered mifepristone during the assessment reporting period. The NDA Applicant estimated that a total of (b) (4) patients were exposed to mifepristone during the assessment reporting period. The ANDA Applicant reported an estimated total of (b) (4) patients were exposed to mifepristone during the reporting period.

During the reporting period, a small number of non-compliance events were reported. The authorized distributor for the NDA applicant reported to the NDA Applicant that they experienced deviations with scanning of the product serial numbers which were confirmed during the February 2020 audit. The authorized distributor conducted a root cause analysis and developed a corrective and preventive action (CAPA) on February 12, 2020. The CAPA was

[j] This REMS assessment report was the first to be submitted following the approval of the single, shared system REMS for mifepristone.

validated and deployed with monitoring of the system through April 10, 2020. The corrective action will prevent similar events from occurring in the future.

January 27, 2020 through September 30, 2021

During the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not being enforced.

- On July 13, 2020, the United States District Court for the District of Maryland granted a preliminary injunction in the *ACOG* case to temporarily bar enforcement of the in-person dispensing requirement during the COVID-19 PHE.
- On January 12, 2021, the United States Supreme Court issued a stay of the injunction.
- On April 12, 2021, the FDA issued a General Advice Letter informing the applicants of the Agency's intent to exercise enforcement discretion during the COVID-19 public health emergency regarding the in-person dispensing requirement in the Mifepristone REMS Program.[k,l]

To better understand whether there was any impact on safety or noncompliance during the periods when the in-person dispensing requirement was not being enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or noncompliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. As part of an additional request for information for the REMS assessment report, the Applicants were also asked to submit the adverse events to FAERS and to notify FDA that the reports were submitted.

Between January 27, 2020 and September 30, 2021, the NDA Applicant distributed (b) (4) shipments representing (b) (4) tablets. The NDA Applicant reported that there were (b) (4) shipments representing a total of (b) (4) tablets sent to (b) (4) non-certified healthcare providers.[m,n] (b) (4) of these healthcare providers subsequently became certified while (b) (4) did not. Of the (b) (4) healthcare providers who were not subsequently certified, (b) (4) returned a total of (b) (4)

[k] FDA General Advice Letter for NDA 20687, April 12, 2021.
[l] FDA General Advice Letter for ANDA 091178, April 12, 2021.

[m] NDA 020687 September 9, 2021 response to the FDA's September 2, 2021 Information Request.
[n] NDA 020687 October 8, 2021 response to the FDA's June 30, 2021 Information Request.

Mifeprex tablets to the distributor. (b) (4) non-certified healthcare provider dispensed (b) (4) to a patient; no adverse events were reported. The NDA Applicant attributed the non-compliance observed to the authorized distributor's transition to a new platform. The NDA Applicant implemented a corrective and preventative action to address this issue, which we found to be acceptable.

The ANDA Applicant distributed (b) (4) shipments representing (b) (4) tablets of mifepristone from January 27, 2020 to September 30, 2021 and reported no instances of shipments to non-certified healthcare providers during this timeframe.

The NDA and the ANDA applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described in the section below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events. Further analysis of the adverse events is included below in the section on Pharmacovigilance Data.

Pharmacovigilance Data

The (b) (6) ((b) (6) conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy.[o,p]

The data for this time period were then further divided into date ranges when the in-person dispensing requirement was being enforced per the REMS (January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021) versus when the in-person dispensing requirement was not being enforced (July 13, 2020 - January 12, 2021 (in-person dispensing requirement was temporarily enjoined) & April 13, 2021 - September 30, 2021 (in-person dispensing requirement was not being enforced because of the COVID-19 PHE)).

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[o] (b) (6). Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized April 12, 2021.

[p] (b) (6) Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized December 16, 2021.

A total of eight cases that met the search criteria were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when the in-person dispensing requirement in the REMS was being enforced (i.e., January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when the in-person dispensing requirement was not being enforced (i.e., July 13, 2020 - January 12, 2021 & April 13, 2021 - September 30, 2021). These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Although these adverse events occurred during the period when the in-person dispensing requirement was not being enforced, the narratives provided in the FAERS reports for cases 5, 6, and 7 explicitly stated that mifepristone was dispensed in-person. Of note, ongoing pregnancy, and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case from July 2021 reported the occurrence of oral pain/soreness (case 8) but did not provide sufficient information to determine the exact date of the adverse event. Based upon the U.S. postmarketing data reviewed, no new safety concerns were identified by (b) (6)

In addition to the FAERS data provided above, (b) (6) routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy. (b) (6) has not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy.

To enable additional review of adverse events, the Applicants were requested[q] to provide a summary and analysis of adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department (ED)/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided a summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021, on August 27 and October 8, 2021. During the time period in question, (b) (4) tablets were shipped, and

[q] On August 5, 2021, an IR was sent to the Applicants requesting a summary and analysis of adverse events from March 29, 2016 through June 30, 2021 and from July 1, 2021 through September 30, 2021.

48 adverse events were received. The 48 adverse events included 4 deaths (one of which occurred in 2010 but was reported in 2017), 25 incomplete abortions requiring surgical intervention, 17 blood transfusions following heavy vaginal bleeding, 2 ectopic pregnancies, 7 infections (1 sepsis and 6 infection without sepsis), 13 hospitalizations, and 43 ED or urgent care visits related to medical abortion. For the period between January 27, 2020 and September 30, 2021, a time frame that includes the entire period when the COVID-19 public health emergency (PHE) has been in effect, there were three adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 1 (uterine/vaginal bleeding), case 2 (uterine/vaginal bleeding and sepsis), and case 4 (drug intoxication and death).

The ANDA Applicant provided a summary of postmarketing safety information from April 11, 2019 (date of ANDA approval) through September 30, 2021. On August 26, 2021, the Applicant provided distribution and adverse event information from April 11, 2019 through June 30, 2021. During this time period, a total of (b) (4) tablets were shipped. There were 7 adverse events including 3 deaths (1 from sepsis, 1 from bilateral pulmonary artery thromboemboli, 1 in a patient who complained of not being able to breathe), 1 ongoing pregnancy treated with uterine aspiration, 2 blood transfusions, 1 sepsis (with death), 1 hospitalization, and 3 ED or urgent care visits related to medical abortion. On October 12, 2021 the Applicant provided information from July 1, 2021 to September 30, 2021; there were no additional adverse events. For the period between January 27, 2020 and September 30, 2021, there were four adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 3 (ongoing pregnancy), case 5 (death unknown cause), case 6 (sepsis and death), and case 7 (pulmonary embolism).[r]

The postmarketing data from FAERS were analyzed by (b) (6) to determine if there was a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. Based on this review, we conclude that there does not appear to be a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. This suggests that mifepristone may be safely used without an in-person dispensing requirement.

[r] The eighth FAERS case, oral pain/soreness, was not within the scope of the August 5, 2021 IR and was not considered for this review of postmarketing safety information submitted by the Applicants in response to the IRs.

(b) (6) review of the Applicants' IR responses, which included the same cases identified by (b) (6) from FAERS, did not change our conclusion.[s]

Literature Review

Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or an equivalent healthcare provider in countries other than the US). Some studies have examined replacing in-person dispensing in certain health care settings with dispensing at retail pharmacies (Grossman[2], Wiebe[7], Rocca[6]) and dispensing mifepristone from pharmacies by mail (Grossman[1], Upadhyay[14], Hyland[15]). Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to women (Gynuity study [Raymond[16], Chong[3], Anger[17]], Kerestes[4], Aiken[5] (2021)) and (2) prescribers using couriered delivery of medications (Reynolds-Wright[18]). Other studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization" (Aiken[19] (2017), Norton[20], Endler[21]). For ease of review, in the sections below that describe these studies, we have separated relevant references by the methodology used to dispense mifepristone.

Retail pharmacy dispensing

Three studies report medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation. Grossman[2] conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic where the participant had an evaluation by ultrasound and counseling. Of the 266 participants enrolled, 260 had known abortion outcomes. Complete abortion without additional procedure occurred in 243 participants (93.5% of those with known outcomes). Seventeen participants (6.5% of those with known outcomes) were diagnosed with incomplete abortion and underwent uterine aspiration. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. However, the finding represents a lower-than-expected efficacy based on the cohort's GA (84% of participants were at ≤ 56 days GA, a cohort for which the labeled success rate is 96.8%). No participants experienced a serious adverse event, were hospitalized, or required transfusion. Three participants had ED visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study's

[s] The reporting period of (b) (6) assessment of the adverse events in FAERS is not identical to the time period for summaries of adverse events in the IRs to the Applicants. Therefore, the numbers of cases and adverse events summarized in (b) (6) assessment may differ from the numbers of cases and adverse events summarized by the Applicants in their responses to IRs (note that each case report may include more than one adverse event).

safety and efficacy outcomes are consistent with labeled frequencies. The majority of participants (65%) were very satisfied with the experience. There were some complaints from participants about not receiving all prescribed medications at the initial pharmacy visit, privacy not being adequately maintained, and perceived negative pharmacist attitude.

Overall, we conclude that this study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to US retail pharmacies; there is insufficient information to assess this. Rocca[6] conducted an observational study evaluating 605 participants at ≤63 days GA who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. Participants who presented to pharmacy study sites underwent clinical screening including a pelvic exam by trained nurse midwives at the pharmacy (which was equipped with an examination room) and if eligible for medical abortion, were dispensed mifepristone and misoprostol in the pharmacy at the time of their visit. Participants who presented to public health facilities underwent clinical screening including pelvic examination by abortion providers including trained nurse midwives and if eligible for medical abortion were dispensed mifepristone and misoprostol in the clinic at the time of their visit. The authors reported that, with respect to complete abortion (>97%) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[7] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of 182 women at ≤ 70 days GA who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of 199 women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (90%, calculated maintaining subjects with unknown outcomes in the denominator; ≥ 95% calculated with known outcomes only). The telemedicine group had one case of hemorrhage (0.5%) and one case of infection requiring antibiotics (0.5%) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3% compared to 1.5% in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

None of the three studies described above allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the studies to the current retail pharmacy environment in the US. The outcome findings from the one US study (Grossman[2]), in which the pharmacies were partnered with prescribers, may not be generalizable to much of the US as they do not reflect typical prescription medication availability with use of retail pharmacy dispensing. Although retail pharmacy dispensing of mifepristone and misoprostol in Canada has been described in the literature, there are important differences in healthcare systems between Canada and the US that render the findings from studies in Canada (Wiebe[7]) not generalizable to the US. In the Wiebe study, timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that allow timely access to medications for medical abortion would occur in retail pharmacies throughout the US. Canada's federal government has reaffirmed that abortion is an essential health service[t] which may have implications affecting access to medical abortion from retail pharmacies in Canada. The Rocca[6] study evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the US retail setting.

Mail order pharmacy

Grossman[1] published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. All participants were evaluated for eligibility during a clinic visit with GA up to 63 days confirmed with either an ultrasound or examination; instead of receiving medication at the clinic visit, participants received medications from a mail-order pharmacy. A total of 240 participants have been enrolled; three participants did not take either medication. A total of 227 (94.6%) provided some outcome information, of whom 224 provided abortion outcome information. Complete abortion without additional procedures occurred in 217 participants (96.9% of those with known outcomes). Two (0.9%) participants experienced serious adverse events (SAE); one received a blood transfusion, and one was hospitalized overnight. Nine (4%) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies. With respect to the time interval between a

[t] As noted in Mark[23] and Martin[24], most provincial and federal health insurance programs in Canada cover medical abortion, and covered services are free at the point of care.

participant's clinic visit and receipt of medications, of the 224 participants with known abortion outcomes, 184 (82.1%) received medication within 3 days. However, 17% received between 4-7 days and one participant waited over 7 days for receipt. Seven of 216 (3.2%) participants who completed the day-3 survey reported compromised confidentiality (e.g., someone found their medication, privacy concerns).

Upadhyay[14] reports findings from a retrospective cohort study of 141 women undergoing medical abortion in the US without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Three interactions via text, messaging or telephone occurred to confirm medication administration, assessment of expulsion and pregnancy symptoms, and results of a 4-week home pregnancy test. Abortion outcome was determined by either the day 3 assessment or the 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95% (105 participants out of 110 for whom outcomes were known) and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. Additionally, a substantial number of participants (31) provided no outcomes information. Among the 141 participants enrolled, 128 had any follow-up contact with the study staff, and 110 provided outcomes information. Excluding outcomes of 22% of the cohort is a limitation of this study. This study used a model with numerous deviations from standard provision of medical abortion in the US, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication, no confirmation of self-reported medical, surgical, and menstrual history. Further, follow-up information based on a 3-day period is insufficient to determine outcome rates or safety findings. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[15] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. All participants obtained screening tests including ultrasound confirmation of GA. A total of 1010 participants completed the screening process and were provided mifepristone and misoprostol. Abortion outcomes were determined for 754 (75%) of the 1010. Outcomes for the remaining 256 participants (25%) were not included because 31 provided no relevant information after shipment, 14 reported not taking misoprostol, and 211 did not have "full follow up" (i.e., known outcome of either complete medical abortion, uterine evacuation, or ongoing pregnancy with plan to continue).

Complete abortions without additional procedures occurred in 727 participants (96% of those with definitively documented outcomes) and is consistent with labeled efficacy. Of the 754 participants included in the analysis 717 (95%) had no face-to-face clinical encounters after medications were mailed while 21 (3%) were admitted to the hospital and 16 (2%) had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up". The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. The reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported number of hospitalizations (3%) is higher than the less than 1% in the FDA-approved mifepristone labeling, conclusions regarding the safety findings in this study cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters, and not reporting outcomes of 25% of the enrolled cohort.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that the efficacy of medical abortion is maintained with mail order pharmacy dispensing. In the Grossman[1] study, the interim analysis, although small, does not raise serious safety concerns. We note that 18% of participants did not receive medications within 3 days; the potential for delay in receiving medication by mail could limit the GA eligible for medical abortion through mail order pharmacy dispensing, because women at GA closer to 70 days might not receive medication in time. A small proportion (3%) of participants raised concerns regarding the issues of confidentiality and privacy. Safety findings from the Hyland[15] study are difficult to interpret. Although only one transfusion is reported, and the authors state the findings demonstrate safety, the higher hospitalization rates, and lack of information on the reasons for hospitalization do not allow any conclusions about safety findings. Lastly, the Upadhyay[14] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the US.

Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail.[3,4,5,16,17] Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population

exclusively: Raymond[16] from May 2016 to December 2018, Chong[3] from May 2016 to September 2020 and Anger[17] from March 2020 to September 2020. Due to the pandemic, the Gynuity study deviated from the protocol requirement of confirmation of GA by examination or ultrasound for many participants treated from March 2020 onward (although none of the three publications reported on the single element of dispensing mifepristone from the healthcare setting by mail). A fourth study, Kerestes,[4] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020: seventy-five (of whom 71 were enrolled in the Gynuity study) of the 334 participants in Kerestes were dispensed mifepristone by mail after a telemedicine consult. The section below discusses these four studies from the US as well as a large UK study by Aiken[5] (2021).

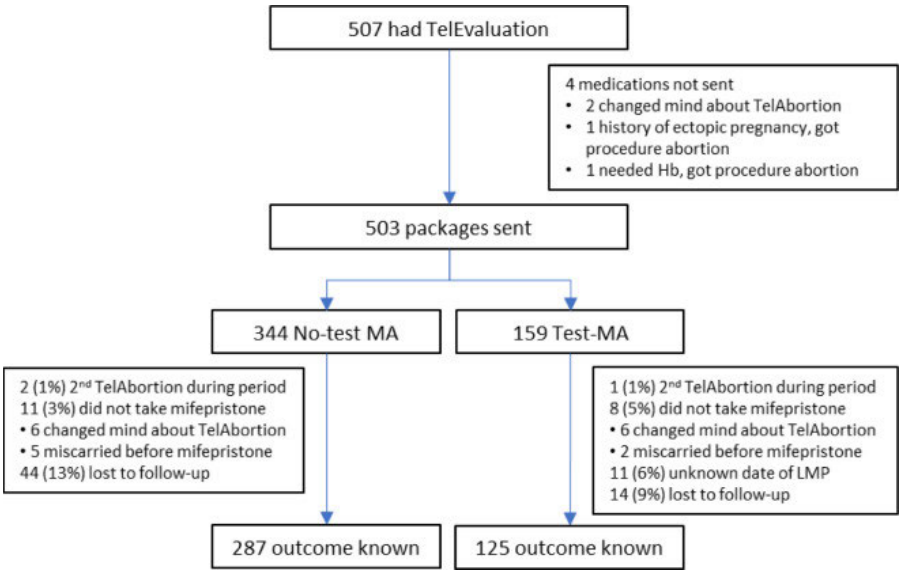
Raymond [16] (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider by videoconference. If the participant was eligible for treatment, the provider dispensed the medications by mail. Of 433 women screened, 165 (38%) either declined to schedule the videoconference or did not keep the videoconference appointment. Among the 268 participants evaluated via videoconference, medication packages were sent to 248. Abortion outcomes were determined for 190 (77%) of the 248; outcomes for 58 (23%) participants were unknown. Complete abortion without additional procedures occurred in 177 participants (93% of those with known outcomes). The investigators obtained follow-up information from 217 participants after package shipment; there were two hospitalizations (one received a transfusion for severe anemia despite having had a complete abortion), and 16 other participants (7%) had clinical encounters in ED and urgent care centers. The reported outcomes in Raymond[16] (2019) are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7%) exceeded the ED visits in approved labeling (2.9-4.6%). The authors note that half of the ED/urgent care visits did not entail any medical treatment and opine that the increased number of visits may have been due to the study participants living farther from the abortion providers.[16] All participants received medications within 8 days.

Chong[3] updated the findings from the Gynuity study described in Raymond[16] and reported on 1157 medical abortion outcomes, of which approximately 50% occurred during the period of the COVID-19 PHE. Although a screening ultrasound was required per the protocol, sites determined in 52% (346/669) of abortions that occurred during the period of the COVID-19 PHE that, in order to avoid potential exposure to COVID-19 at a health care facility, those

participants were not required to obtain a screening ultrasound. Use of urine pregnancy test to confirm abortion completion also increased from 67% (144/214) in the 6 months prior to the pandemic to 90% (602/669) in the 6 months during the pandemic. Of the 1390 participants to whom medicine packages (containing both mifepristone and misoprostol) were mailed, 1157 (83.2%) had known abortion outcomes. Complete abortion without a procedure occurred in 1103 participants (95% of the those with a known outcome). Ten women experienced an SAE (5 transfusions (0.4%) and 7 hospitalizations (0.7%)) and 70 (6%) participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 47 participants (4.1% of 1390) to complete abortion. The reported outcomes in this study are similar to outcomes described in approved labeling, except that the combined ED/urgent care center encounters (6%) exceeded the ED visits in approved labeling (2.9-4.6%).

Anger[17] compared outcomes among participants enrolled in the Gynuity study who did versus did not have confirmation of GA/intrauterine location with an examination or ultrasound from 10 jurisdictions across the US. These participants were screened for enrollment from March 25 through September 15, 2020. All participants had a telemedicine consultation and received mifepristone and misoprostol by mail from the healthcare facility. Determination of which participants did not require confirmation of GA by examination or ultrasound to be eligible depended on the study clinician's assessment of eligibility for "no-test medication abortion"[u] based on a sample protocol published by Raymond[22] (2020). There were two key differences between the two groups. Participants for whom the study clinician determined a pre-abortion ultrasound was required were more likely than the participants who had no ultrasound or examination to live further than 150 miles from the clinic (51.2% vs. 31.7%) and were more likely to have a GA above 63 days (12.0% vs. 1.7%). The study sites shipped 503 medication packages during the analysis period; 344 packages went to the "no test" group while 159 went to the "test" medical abortion cohort (see figure below). However, because the two cohorts were not randomized in this study, they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

[u] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination, or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al.[22]



Source: Figure 1 in this publication. MA= medical abortion.

The investigators' analyses excluded 91 (18% of 503; 57 in the no-test group and 34 in the test group) participants because they did not provide a date of the last menstrual period (LMP), did not take mifepristone, or did not have a recorded abortion outcome. Overall, 410 participants (81.5% of 503) provided outcomes data. There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the no-test group, complete medical abortion was confirmed in 271 participants who took medications (94% among those with known outcome). In the no-test cohort, two participants were "hospitalized and/or blood transfusion," and 36 (12.5%) had an unplanned clinical encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion).

In the test medical abortion group, complete abortion was confirmed in 123 participants (of 125 with known outcomes); the completion rate was 98% among those with known outcomes. In the test medical abortion group, one participant was "hospitalized and/or blood transfusion," and 10 (8.0%) had an unplanned clinical encounter. The authors concluded that, compared to participants who had an ultrasound prior to medical abortion, those without an examination prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.

Kerestes[4] was the only publication that linked outcomes of medical abortion with different delivery models. Participants included in the report had GA up to 77 days and received

medications in Hawaii between April 2020 and January 2020. A total of 334 medication packages (to 330 unique participants) were dispensed containing mifepristone and misoprostol; three different delivery models were used concurrently: 110 (32.9%) had traditional in-person visits, 149 (44.6%) had telemedicine consultation with in-person pick-up of medications, and 75 (22.5%) were sent medications by mail (71 of these were enrolled through Gynuity's TelAbortion study). Seven participants of the 330 participants who received 334 medication packages reported that they did not take them and were excluded from analysis of the outcomes. Among participants with follow-up data, the rates of successful medical abortion without surgery were 93.6%, 96.8%, and 97.1% in the in-clinic group, telemedicine + in-person pickup group, and telemedicine + mail group, respectively; these were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine + in-person pickup group). Eleven participants went to an ED. Although ED visits occurred the most frequently in the telemedicine + mail group (four participants or 5.8%) and the least in the in-person group (two participants or 2.1%), the study reported no increases in other serious adverse events.

Taken together, the three Gynuity study reports[3,16,17] and Kerestes[4] support dispensing mifepristone and misoprostol by mail after a telemedicine visit. Efficacy was maintained in all four studies. All of the studies reported SAEs frequencies comparable to labeled rates, except two of the Gynuity study reports (Raymond[16], Chong[3]) and Kerestes[4] report a higher frequency of ED/urgent care visits than the labeled frequency of ED visits. We do not know whether the reporting of combined ED and urgent care visits represents an increased rate of ED visits compared to the labeled rate of ED visits (2.9-4.6%). Other labeled SAEs (e.g., transfusion) occur infrequently (< 1%).

Aiken[5] (2021) reports outcomes of medical abortion up to 70 days GA in the UK before and during the pandemic in a retrospective cohort study. In the UK, prior to the COVID-19 pandemic, all patients attended an in-clinic visit where they received an ultrasound, were administered mifepristone in the clinic, and given misoprostol in-clinic for use at home (traditional model). During the pandemic, medical abortion consultations were performed remotely by telephone or video. Based on the consultation and questionnaire (including date of last menstrual period; menstrual, contraceptive and medical history; symptoms; risk for ectopic pregnancy), an assessment of eligibility for treatment via telemedicine was made. If eligible, medications were delivered to participants via mail or were made available for collection from the clinic for use at home. If the participant was assessed to be ineligible for treatment via

telemedicine, an in-person assessment with ultrasound was performed and medications were provided from the clinic for home use (hybrid model).

The study compared the two cohorts: 22,158 obtained medical abortion before the pandemic and had in-person visits and dispensing (traditional model) and 29,984 obtained medical abortion during the pandemic with either in-person visit and in-person dispensing, or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Outcomes were obtained from electronic records and incident databases. Outcomes of all hospitalizations related to abortion, ED visits, infection without sepsis, and hemorrhage without transfusion were not reported. The investigators' analysis for non-inferiority determined the efficacy and safety were comparable between both cohorts. Complete abortion occurred in > 98% in both cohorts. Hemorrhage requiring transfusion was reported in 0.04% and 0.02% of the traditional and hybrid cohorts, respectively; this is lower than the labeled 0.5% transfusion rate. There were no severe infections requiring hospitalization, major surgery or deaths reported.

A secondary analysis of the hybrid cohort was reported. Within the 29,984-person hybrid model cohort, 11,549 (39%) abortions were conducted in-person (in-person assessment with ultrasound was performed and medications provided from the clinic for home use) and 18,435 (61%) abortions were provided by telemedicine visit, without tests or confirmation of GA/intrauterine position by ultrasound, and medications either mailed or picked up from the clinic. Outcomes stratified by type of mifepristone dispensing were not reported. The rate of complete abortion was slightly higher in the telemedicine group (99.2%) than that in the in-person group (98.1%). There were no significant differences in the rates of reported SAEs. Adjustments for clinical and demographic characteristics were made because the two groups differed in baseline characteristics, including a higher proportion of pregnancies with GA over 6 weeks in the in-person group (68.2% compared with 55.1%). The authors conclude a hybrid model for medical abortion that includes no-test medical abortion[u] (no ultrasound, no pelvic exam, no pregnancy test) is effective and safe.

We conclude that although the Aiken[5] (2021) study has a large sample size and includes 85% of all medical abortions performed in England and Wales during the study period, the study has limitations. The authors acknowledge the main limitation of their study was that analysis was based on deidentified information in the NHS database and the investigators were unable to verify the outcomes extracted. Other limitations included that their search only captured

outcomes in electronic records and incident databases that met the authors' defined threshold for SAE reporting, and that the labeled abortion outcomes considered serious, such as hospitalizations related to abortion, infection without sepsis, hemorrhage without transfusion, or ED/urgent care visits, were not all included in the authors' definition of serious adverse event.

Data from the mail order dispensing studies with telemedicine visits from Gynuity (Raymond, Chong and Anger),[3,16,17] Kerestes[4], and Aiken[5] (2021) support that efficacy of medical abortion was maintained. The Aiken[5] study appears to be of sufficient sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings. Study reports of Raymond[16] Chong[3], and Kerestes[4] all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail without increases in other adverse events. Anger's[17] comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. Overall, despite the limitations noted, these studies support that dispensing by mail is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other SAEs related to mifepristone use. One reason for the increase in frequent ED/urgent care visits in the Raymond[16] publication, according to its authors, may have been that a substantial proportion of participants lived significant distances from their providers and increased distances have been associated with higher use of ED following treatment. Raymond[16] reported that half of the participants who had an ED/urgent care visit did not require medical treatment.

Clinic dispensing by courier

Reynolds-Wright[18] reported findings from a prospective cohort study of 663 women at less than 12 weeks' GA in Scotland undergoing medical abortion at home with use of telemedicine during the pandemic (from April 1 to July 9, 2020). The majority of medical abortions (78.7%) used telemedicine visits, eliminated pre-abortion ultrasound, and provided mifepristone for pick up at the service or by couriered delivery to woman's home. The number of couriered deliveries was not reported; thus, this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. With access to NHS regional hospital databases, the investigators were able to verify pregnancy outcomes and complications. Of the 663 participants, 642 (98.2%) were under 10 weeks GA, 21 (1.8%) were between 10 and 12 weeks

GA, and one participant was never pregnant. A total of 650 participants had complete abortion without requiring surgical intervention (98%), 5 (0.8%) an ongoing pregnancy and 4 (0.6%) an incomplete abortion. The outcomes from this study in Scotland are consistent with labeled mifepristone outcomes. The study shares the same limitations as the Aiken[5] (2021) study.

Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail.[v] Medical abortion eligibility is determined using an online questionnaire with asynchronous physician review. If eligible, medications are mailed to the women. WoW provides help and support by email or instant messaging.

Aiken[19] (2017) conducted a population-based study analyzing findings from 1,636 women in the Republic of Ireland and Northern Ireland who were sent medications between 2010 and 2012. Receipt of medications was confirmed for 1,181 women, among whom 1,023 confirmed use of mifepristone and misoprostol; outcome information was available for 1,000 (61% of women sent medications). Of the 1,000 women, the majority (781, 78%) were less than 7 weeks GA and 219 (22%) were at 7-9 weeks. Complete abortion without surgical intervention occurred in 947 (94.7% of 1,000 with known outcome); 7 (0.7%) women received a blood transfusion, 26 (2.6%) received antibiotics (route of administration undetermined) and 87 (8.7%) sought medical care at a hospital or clinic for symptoms related to medical abortion. Hospitalizations related to abortion were not reported. The reported proportion of complete abortion is within the range labeled for medical abortion up to 70 days (92.7-98.1%). However, the finding of 94.7% complete abortion represents a lower-than-expected efficacy based on the cohort's GA (almost 80% less than 7 weeks, labeled success for medical abortion ≤ 49 days is 98.1%). This study has limitations, including outcomes based on self-report without validation of completed abortion by examination or laboratory testing, and no known outcomes for 39% of study cohort. Additionally, the authors noted medical abortion was provided in a legally-restrictive setting, where the law provided a maximum penalty of life imprisonment for the woman undergoing the abortion, which may affect participants' self-reporting.

[v] In March 2019, FDA sent a WL to Aidaccess.org, a group affiliated with WoW. Aidaccess.org received this WL because it was introducing misbranded and unapproved new drugs into the U.S. In the context of this REMS review, studies involving WoW are included solely for purposes of evaluating of data regarding the methods of dispensing mifepristone.

Endler[21] and Norten[20] have reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail, because neither provide meaningful outcomes data for consideration. Endler[21] compared the outcomes of self-reported heavy bleeding and clinical visits occurring during the "first or second day of abortion" that occurred in women undergoing medical abortion at 9 weeks GA or less, with outcomes from women at more than 9 weeks GA. Outcome data from day 1 or 2 is of limited usefulness. Norten[20] describes findings from a survey of women who were sent medical abortion medication through WoW and provided self-reported outcomes. Results were based on surveys returned from only 37% of participants, a return rate that is too low for the study to be considered valid.

WoW uses a model with numerous deviations from the standard provision of medical abortion in the US. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Further, although Aiken[19] (2017) is a large cohort study, the outcomes are self-reported with no verification of complete abortion by laboratory or clinical evaluation and 39% of outcomes are unaccounted for. These limitations in the Aiken study result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

4. Discussion

After review of the published literature, safety information collected during the COVID-19 PHE, postmarketing data, information from the first Mifepristone REMS Program assessment report, responses to information requests to the Applicants, and information provided by advocacy groups, individuals and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that the REMS can be modified to reduce burden without compromising patient safety.

Prescriber Certification

None of the publications we reviewed would support a conclusion that a healthcare provider who prescribes mifepristone does not need to meet the qualifications included in the Mifepristone REMS Program as described above in section 3.2.1. Absent these provider qualifications, serious complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed.

We conclude that prescriber certification (ETASU A) should be maintained. The current process requires the prescriber to agree to the requirements of the Mifepristone REMS Program and to attest that they meet the qualifications described in section 3.2.1 above. The REMS has been structured to minimize burden to prescribers by requiring only a one-time certification by the prescriber for each Applicant. We have determined that healthcare provider certification continues to be necessary to ensure the benefits outweigh the risks, especially considering that, if the in-person dispensing requirement is removed from the Mifepristone REMS Program, the number of new providers may increase (see discussion in section 3.2.2 above).

Drug to be dispensed with evidence or other documentation of safe use conditions

The requirement to counsel the patient and provide them with the *Patient Agreement Form* ensures that each patient is informed of the appropriate use of mifepristone, the risks associated with treatment, and what to do if they experience symptoms that may require emergency care.

In 2016, we initially recommended eliminating the *Patient Agreement Form* (see section 3.2.2), though the form was ultimately maintained as part of the REMS. As discussed above, our current literature review has indicated that there is no basis to remove the *Patient Agreement Form* from the REMS. In addition, surveys we reviewed suggest that if the in-person dispensing requirement for mifepristone is removed, there could be a potential doubling of medical abortion providers. This potential doubling of medical abortion providers supports the continued need to ensure that patients are consistently provided patient education under the Mifepristone REMS Program regarding the use and risks of mifepristone. The *Patient Agreement Form* is an important part of standardizing the medication information that prescribers communicate to their patients, including new prescribers, and also provides the information in a brief and understandable format to patients. We determined, in accordance with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients.[w]

Given the likelihood of a potential increase in new prescribers if the in-person dispensing requirement is removed from the Mifepristone REMS Program, we conclude that maintaining the *Patient Agreement Form* remains necessary to assure safe use at this time.

[w] *The Patient Agreement Form* can be signed in person or through other means.

Drug to be dispensed only in certain healthcare settings

As discussed above in section 3.2.3, our evaluation of information submitted by the applicants in the one-year (1st) REMS assessment report for the Mifepristone REMS Program and in response to follow-up requests from the Agency indicates that the number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these adverse events. We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.

Alternatives to in-person dispensing of mifepristone have been investigated in several studies and countries. The literature review identified 15 publications[x] that assessed safety outcomes from various medication delivery models (US, UK, Canada, Ireland, Australia, Nepal), including dispensing by retail and mail order pharmacies, prescribers mailing medications or using couriered service to deliver medications, and dispensing by "partner organizations". The ability to generalize the results of these studies to the US population is hampered by differences in pre-abortion care (e.g., telemedicine versus in-person, testing), and the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy.

In addition, there are factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation; for example, most studies on mail dispensing of mifepristone also include telemedicine consultation, and (2) because most SAEs with medical abortion are infrequent, though they can be life threatening, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the US.

[x] The 15 publications correspond to endnote numbers: 1-7, 14-21.

Based on the literature identified by our review, dispensing mifepristone by mail from the clinic or from a mail order pharmacy does not appear to jeopardize the efficacy of medical abortion. The studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, although the safety and efficacy outcomes reported in these studies remain within the ranges described in mifepristone labeling except for increased numbers of ED/urgent care visits and hospitalizations.

Four publications (Raymond[16], Chong[3], Anger[17] and Kerestes[4]), describe a relevant US cohort where dispensing mifepristone from the clinic by mail was paired with telemedicine visits. These studies showed that efficacy was maintained and there was no increased frequency of SAEs except for higher ED/urgent care visits. The increased ED/urgent care visits were not associated with increases of other SAEs, and in the view of one study's authors (Raymond[16]), may be associated with participants being located significant distances from their providers. The Aiken[5] (2021) study of a large UK cohort where the clinics mailed mifepristone report small (lower than labeled) occurrences of transfusion and no significant infections requiring hospitalization. In Grossman[1] and Hyland[15], where the pharmacies mailed mifepristone after prescribers confirmed GA, efficacy is maintained. Grossman's[1] interim analysis found no increases in SAEs. Hyland[15] reported higher numbers of hospitalizations but did not report increases of other SAEs. Overall, while the studies assessing mifepristone dispensing by mail suggest more frequent encounters with healthcare providers, they generally support a conclusion that dispensing by mail is safe. Despite the limitations of the studies we reviewed, we conclude that overall, the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe, and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, our review of the literature, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met, and pharmacy certification is added as described below.

Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to

ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the REMS, the Mifepristone REMS Program should be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

New requirement to be added for pharmacy certification

The current distribution model requires the certified prescriber to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. During the periods when the in-person dispensing requirement was not being enforced, both applicants used mail order pharmacies to receive and hold mifepristone on behalf of the certified healthcare providers who had purchased the product.[j,y,z] Pursuant to a prescription for mifepristone, the mail order pharmacy would ship the product to a named patient.

The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, the drug is no longer required to be dispensed only in a clinic, medical office or hospital. Under the REMS as modified, mifepristone can be dispensed through a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies under ETASU B. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that ETASU A is met prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the *Patient Agreement Form* (ETASU D) is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review of the safety data and our consideration of the distribution model implemented by the Applicants during the periods

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y ANDA 091178: September 23, 2021 response to the September 15, 2021 information request; October 11 and 16, 2021 responses to the June 30, 2021 and July 15, 2021 information requests; October 26, 2021 response to the October 22, 2021 information request; October 29, 2021 response to the October 27 information request.
z NDA 020687: September 20, 2021 response to the September 15, 2021 information request; October 26, 2021 response to the October 22 information request.

when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients. As modified, the REMS would allow, for example, dispensing by mail order or specialty pharmacies, similar to the distribution model used by applicants during the periods when the in-person dispensing requirement was not being enforced.[aa]

The above recommendations were discussed with the (b) (6) ((b) (6) and senior leadership from CDER on November 2, 2021. The (b) (6) (b) (4) along with senior CDER leadership, concurred with removing the in-person dispensing requirement provided that all of the remaining REMS requirements are met, including but not limited to prescriber certification where prescribers need to attest to having certain qualifications, and maintaining the *Patient Agreement Form*. The (b) (6) (b) (4) and senior leadership from CDER were also in favor of adding pharmacy certification to assure the safe use of mifepristone.

5. Conclusions and Recommendations

Based on the results of REMS assessments; our review of safety data collected during the PHE as well as data from FAERS; our literature search; and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, (b) (6) and (b) (6) have concluded that a REMS modification is necessary and should include the following changes:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

[aa] Our current conclusion that the REMS would allow dispensing by mail order or specialty pharmacies is based on data received from Applicants relating to the periods when the in-person dispensing requirement was not enforced and mail-order pharmacies were used to dispense the product, as well as our analysis of postmarketing safety data and available literature. At this time we do not have data (from the Applicants or from other sources) to assess the certification of retail pharmacies under the REMS. We have not yet determined the details of pharmacy certification requirements, including whether any limitations on the types of pharmacies that may dispense the product are necessary.

(b) (6) and (b) (6) recommend the Applicants be issued a REMS Modification Notification Letter that requests submission within 120 days from the date of the letter.

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7. Appendix A

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Chong, et al. Contraception 2021; 104(1) 43-48	
Daniel S. et al. Contraception 2021; 104(1): 73-76	
References excluded from the REMS review	**Rationale for Exclusion**
Am. Coll. of Obstetricians & Gynecologists, *Position Statement: Improving Access to Mifepristone for Reproductive Health Indications* (June 2018), https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications	Policy/advocacy statement
House of Delegates, Am. Med. Ass'n., *Memorial Resolutions Adopted Unanimously No. 504 (2018)* https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-resolutions.pdf	Policy/advocacy statement
Cong. Of Delegates, Am. Acad. Of Fam. Physicians, *Resolution No. 506 (CoSponsored C) Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization of Mifepristone* (May 24, 2018) https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf	Policy/advocacy statement
Schummers L et al, Contraception 2020; 102(4): 273	Abstract
Upadhyay UD et al.) Obstet & Gynecol 2015; 125: 175	Published prior to March 29, 2016-July 26, 2021 timeframe for current literature review. We note that the extensive literature review conducted as part of the 2016 review, which was consistent with the division's standard approach for reviewing an efficacy supplement

	and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
Kapp N et al. Best Pract Clin Obstet Gynaecol. 2020;63:37-44	Abstract. Also outside the scope of first trimester medical abortion.
Fuentes L et al. J Women's Health 2019; 28 (12): 1623, 1625 Bearak JM, Lancet Pub Health 2017 Nov;2(11): e493, e495-96 Cartwright A et al 20 J Med Internet Res 2018 20(5):e10235 Barr-Walker J, et al PLoS One 2019;14(4): e0209991 Grossman et al JAMA Network 2017;317(4):437, 437-438 Dobie S et al 31 Fam Plan Persp 1999; 31(5): 241-244 Shelton JD 8 Fam Plan Persp 1976; 8(6):260, 260-262 Norris AH et al Am J Pub Health 2020; 110 (8): 1228,1232 Upadhyay UD et al Am J Pub Health 2014; 104(9):1687, 1689	Focused on the logistics of accessing abortion care.
CDC MMWR Abortion Surveillance – United States, 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5_down	Contains primarily general statistics on abortion care by state.

References cited in appendix from *Chelius v. Becerra* Plaintiffs (September 29, 2021)
References included in the REMS review
None

References excluded from the REMS review	Rationale for Exclusion
Jones RK et al Guttmacher Institute Abortion Incidence and Service Availability in the United States, 2017 (2019) Guttmacher Inst, Induced Abortion in the United States (2019)	Contains primarily general statistics on abortion care and logistics of accessing abortion care.
University of Minnesota Healthy Youth Dev. Prevention Rsch Ctr, 2019 Minnesota Adolescent Sexual Health Report 3 (2019)	Not related specifically to abortion care.
Jerman J et al Guttmacher Inst, Characteristics of U.S. Abortion Patients in 2014 and Changes since 2008 (2016)	Contains figures on patient characteristics from 2008-2014.
Roberts CM et al Women's Health Issues 2014; 24:e211, e215	Focused on cost of abortion.
CDC MMWR Abortion Surveillance 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7 down (last updated Nov. 7, 2020)	Contains primarily statistics on number of abortions in the US.
Jones RK Persp on Sexual & Reprod Health 2017; 49:17, 20	Focused on abortion incidence and service availability.
Fuentes L et al (as above) Bearak JM et al (as above) Cartwright A et al (as above) Johns NE et al. BMC Health Serv Res 2017; 17: 287, 294	Focused on logistics of accessing abortion care.

References cited in letter from Society of Family Planning (August 11, 2021)
References included in the REMS review
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Chen MJ et al. Obstet Gynecol 2015;126(1):12-21 reviewed in 2016 memo	
Chong et al. Contraception 2021;104(1): 43-48	
Aiken A et al. BJOG 2021; 128 (9): 1464 -1474	
Hyland 2018 et al. Aust New Zeal J Obstet Gynaecol 2018; 58 (3): 335-340	
References excluded from the REMS review	**Rationale for Exclusion**
Schummers L et al. BMJ Sex Reprod Heal 2021;47(e1)	Abstract
Kapp et al. 2020 (as above)	Abstract
Upadhyay et al. 2015 (as above)	(See rationale above)
Srinivasulu et al. Contraception 2021; 104(1):92-97	Survey on clinician perspectives on access to mifepristone.
Calloway D et al. Contraception 2021; 104(1): 24-28	Primarily addresses provider stigma around abortion care.
Rasmussen et al. Contraception; 104(1): 98-103	Opinion/commentary
Cleland et al. Obstet Gynecol 2013;121(1):166-171	Published prior to March 29, 2016 - July 26, 2021 timeframe for current literature review. We note that the extensive literature search conducted as part of the 2016 clinical review, which was consistent with the division's standard approach for reviewing an efficacy supplement and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
National Academy of Sciences, Engineering, and Medicine. Safety and Quality of Abortion Care in the US 2018	General information about abortion care in the US. Did not provide safety data relevant to the elements of the REMS
Raymond EG. Obstet Gynecol 2012: 119(2): 215-219	Does not separate out medical and surgical abortion.

Bartlett LA et al. Obstet Gynecol 2004; 103(4): 729-737	Focused on surgical abortion.
Jones RK, Jerman J. Time to appointment and delays in accessing care among U.S. abortion patients, Guttmacher 2016	Focused on logistics of accessing abortion care.
Foster DG et al. Perspect Sex Reprod Health 2013; 45(4):210-218	Focused on second trimester abortion.
Ely G et al. Heal Soc Work 2019;44(1):13-21	Focused on logistics of accessing abortion care.
Munro S et al. Ann Fam Med 2020; 18(5):413-421.	Survey on physician perspectives on implementing medical abortion with mifepristone.

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EXHIBIT 51

Center for Drug Evaluation and Research, Application Numbers: 020687 and 91178 Rationale Review
(Dec. 16, 2021)
("FDA 2021 Rationale Review")

Center for Drug Evaluation and Research (CDER)

(b) (6)

Application Type	NDA and ANDA
Application Number	020687 and 91178
Reviewer Names	(b) (6)
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Review Completion Date	December 16, 2021

Subject	REMS Modification Rationale Review
Established Name	Mifepristone REMS
Name of Applicants	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablets

Table of Contents

EXECUTIVE SUMMARY 4

1. Introduction 5
2. Background 5
   - 2.1. PRODUCT AND REMS INFORMATION 5
   - 2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW 7
3. Rationale for Proposed REMS Modification 9
   - 3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS 10
   - 3.2. EVALUATION OF THE EVIDENCE 10
   - 3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A) 12
   - 3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D) 14
   - 3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C) 19
4. Discussion 36
5. Conclusions and Recommendations 41
6. References 42
7. Appendix 45

EXECUTIVE SUMMARY

This review provides the [redacted] rationale and conclusions regarding modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178.

ANDA 91178 was approved with the approval of the Mifepristone REMS Program on April 11, 2019 to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021. The REMS consists of elements to assure safe use (ETASU) under ETASU A, C and D, an implementation system, and a timetable for submission of assessments. To determine whether a modification to the REMS was warranted, FDA undertook a comprehensive review of the published literature; safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below.

The modifications to the REMS will consist of:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to here as the "in-person dispensing requirement" for brevity)
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified

A REMS Modification Notification letter will be sent to both Applicants in the Single Shared System.

1. Introduction

In connection with the *Chelius v. Becerra* litigation, FDA agreed to undertake a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[a] This review provides the analysis of the (b) (6) ((b) (6) and the (b) (6) ((b) (6) regarding whether any changes are warranted to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone (hereafter referred to as the Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178. The Mifeprex REMS was initially approved in 2011; the single, shared system REMS for mifepristone 200 mg, known as the Mifepristone REMS Program, was approved in 2019.

The last time the existing REMS elements to assure safe use (under ETASU A, C and D) were reviewed was in the context of our review of supplement S-020 to NDA 20687; these ETASU were updated following review and approval of supplement S-020 on March 29, 2016. The key changes approved in 2016 are summarized below.

Changes to labeling included:

- Changing the dosing of Mifeprex to 200 mg orally x 1
- Extension of maximum gestational age through 70 days
- Inclusion of misoprostol in the indication statement
- Replacing the term “physician” with “licensed healthcare provider”
- Removal of the phrase “Under Federal Law”

The Mifeprex REMS and REMS materials were updated to reflect the changes above, and additional changes were made including:

- Removing the Medication Guide as part of the REMS but retaining it as part of labeling.

2. Background

2.1. PRODUCT AND REMS INFORMATION

[a] Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000 with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed the risk of serious complications associated with mifepristone when used for medical abortion. Mifeprex was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the Mifeprex REMS was approved on June 8, 2011. On March 29, 2016, as noted above, a supplemental application and REMS modification was approved for Mifeprex. On April 11, 2019, ANDA 091178 was approved, and the Mifepristone REMS Program was approved. The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 91178.

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
b. Ensuring that mifepristone is only dispensed in certain healthcare settings, by or under the supervision of a certified prescriber (under ETASU C).
c. Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and follow the guidelines for use of mifepristone. Under ETASU C, mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The Mifepristone REMS Program also includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW

The following is a summary of significant regulatory history since approval of the REMS modification on March 29, 2016:

- 03/29/2016: FDA approved an efficacy supplement (S-020) that, among other things, provided a new dosing regimen (200 mg mifepristone, followed in 24 to 48 hours by 800 mcg buccal misoprostol), increased the gestational age (GA) to which mifepristone may be used (through 70 days gestation), and modified the REMS.

- 03/29/2019: A Citizen Petition was received requesting that FDA revise the product labeling to reflect pre-2016 provisions (including limiting GA to 49 days and requiring patients to make 3 office visits) and that FDA maintain the REMS.

- 04/11/2019: ANDA 91178 was approved along with the Single Shared System REMS for Mifepristone 200 mg (Mifepristone REMS Program) for NDA 20687 and ANDA 91178.

- 01/31/2020: the COVID-19 public health emergency (PHE) was declared by the Secretary of Health and Human Services (HHS) as having existed since January 27, 2020.[c]

- 7/13/2020: The United States (US) District Court of Maryland granted a preliminary injunction in the *ACOG v. FDA* litigation to temporarily bar enforcement of the Mifepristone REMS Program in-person dispensing requirement during the COVID-19 PHE.

- 1/12/2021: US Supreme Court granted a stay of that injunction.

- 04/12/2021: FDA issued a General Advice Letter to both the NDA and ANDA Applicants, stating that provided that all other requirements of the Mifepristone REMS Program are met, and given that in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare

[c] *See* Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued January 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx

personnel because it may involve a clinical visit solely for this purpose, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form.* FDA further stated that to the extent all of the other requirements of the Mifepristone REMS Program are met, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

- 05/07/2021: FDA stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with the REMS assessment provisions of section 505-1 of the FD&C Act.

- 05/14/2021: A modification was approved for the Mifepristone REMS Program. This modification was to revise the *Patient Agreement Form* to include gender-neutral language.

- 06/30/2021: An Information Request (IR) was sent to the Applicants for additional information on shipments and any program deviations, adverse events, or noncompliance with the REMS that occurred during the period from April 1, 2021 through September 30, 2021.

- 7/15/2021: An IR was sent to the Applicants to provide the total number of shipments during the period from April 1, 2021 to September 30, 2021 and details on whether any of those shipments were involved in any program deviation or non-compliance.

- 8/5/2021: An IR was sent to the Applicants for additional clinical and other information (e.g., adverse events and units of mifepristone shipped) for the period of March 29, 2016 through June 30, 2021, to be provided by August 31, 2021. This IR also requested information covering the period of July 1, 2021 through September 30, 2021 and an

aggregate summary (for the period of March 29, 2016 through September 30, 2021), to be provided by October 12, 2021.[d]

- 8/26/2021: The ANDA Applicant submitted a response to the IR issued on 8/5/2021.
- 08/27/2021: The NDA Applicant submitted a response to the IR issued on 8/5/2021.
- 10/08/2021: The NDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR. The NDA Applicant also included a follow-up to their initial response provided on August 27, 2021 to the August 5, 2021 IR.
- 10/12/2021: The ANDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR.
- 10/16/2021: The ANDA Applicant revised their Oct 12, 2012 response to provide a correction to the number of mifepristone tablets.
- (b) (4)
- 11/02/2021: A (b) (6) ((b) (6) meeting was convened to obtain CDER concurrence on the removal of the in-person dispensing requirement and the addition of a certification requirement for pharmacies. The (b) (6) (b) (6) and senior CDER leadership concurred with removing the in-person dispensing and adding pharmacy certification.

3. Rationale for Proposed REMS Modification

[d] Multiple Information Requests were issued to obtain additional information on drug shipments, any program deviations or noncompliance, and use of alternative methods for drug distribution during the COVID-19 PHE. These IRs are referenced as appropriate in this document and the one-year REMS Assessment Review of the Mifepristone REMS Program, December 16, 2021.

3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS

The Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use in the current REMS include a prescriber certification requirement (ETASU A), a requirement that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and a requirement that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions under ETASU D consists of a *Patient Agreement Form* between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone 200 mg for medical termination of early pregnancy.

3.2. EVALUATION OF THE EVIDENCE

We reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation. Below is an overview of how information relevant to the current Mifepristone REMS Program was retrieved, analyzed, and applied to each of the individual ETASUs to determine if further changes should be considered.

Methods for the literature search

(b) (6) conducted a literature search in PubMed and Embase to retrieve publications relevant to this review. The time period used for this literature search was between March 29, 2016 (when the Mifeprex labeling and REMS were last substantially revised) through July 26, 2021. The search terms used were “medical abortion” and “mifepristone” and “pregnancy termination and mifepristone.”

The search retrieved 306 publications from PubMed and 613 from Embase, respectively; the search yielded 646 unique publications after eliminating duplications between the two databases. The result of our literature search was also supplemented by an examination of literature references provided by advocacy groups, individuals, plaintiffs in the *Chelius* litigation, and the Applicants, as well as letters from healthcare providers and researchers.

References included in these letters were considered for inclusion in this review using identical selection criteria to the (b) (6) literature search (outlined below).

For this review of the REMS, (b) (6) focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS ETASUs. We excluded systematic reviews and meta-analyses because these publications did not include original safety data related to the outcomes of medical abortion. The following are examples of materials that were excluded from our literature search:

- Information from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, even if the study assessed REMS ETASUs. These surveys or qualitative studies did not include objective safety data related to outcomes of medical abortion.

- Opinions, commentaries, or policy/advocacy statements. These publications did not include objective safety data related to outcomes of medical abortion.

- Safety data related to mifepristone use for second trimester medical abortion. These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data related to mifepristone use for spontaneous first trimester abortion (i.e., miscarriages). These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data that pertained only to surgical abortion or did not separate out medical abortion from surgical abortion.

- Other safety information unrelated to the REMS elements (e.g., articles limited to case reports or those discussing unrelated gynecologic or medical issues)

- Publications for which it was not possible to conduct a full review of the methods or results, i.e., the references were limited to an abstract of the study methods and results.

- Publications that provided only general statistics on abortion care in the United States.

- Information pertinent to molecular or other basic science aspects of mifepristone.

- Data on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care.

- Publications that provided data not related specifically to abortion care or the REMS (e.g., references focused on federal poverty guidelines, poverty data, or the financial impact of the COVID-19 pandemic).

One exception to the above literature search criteria was the inclusion in Section 3.2.2 of this review, which discusses the *Patient Agreement Form*, of publications that discussed changes in provider volume. The data discussed in relation to provider volume was obtained from surveys. This data was included because changes in provider volume could only be obtained from well-conducted survey studies.

Regarding medical/scientific references submitted with letters from the plaintiffs in the *Chelius* litigation, we applied the same criteria as for the literature search, as described above.

Letters from the plaintiffs in the *Chelius* litigation included several references that preceded our 2016 review of the REMS. Two of those pre-2016 studies were not captured in our 2016 literature search. These two studies were assessed as part of our current review; their results are consistent with the existing safety profile of the approved medical abortion regimen, and therefore, support our current conclusions regarding the REMS. See Appendix A.

3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A)

In order to become specially certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet the qualifications listed below:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to

ensure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the *Patient Agreement Form* with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the *Patient Agreement Form*.
- Provide the patient with a copy of the *Patient Agreement Form* and the Medication Guide.
- Place the signed *Patient Agreement Form* in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

The literature review was the primary source of information that contributed to our reassessment of ETASU A.

We continue to be concerned that absent these provider qualifications, serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed. Our review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our review continues to support the conclusion that a healthcare provider who prescribes mifepristone should meet the above qualifications. We conclude it is reasonable to maintain the requirement for a one-time prescriber certification where prescribers attest to having the ability to diagnose an intrauterine

pregnancy, to diagnose an ectopic pregnancy,[e] and to either manage serious complications themselves or arrange for other providers to provide the needed care in a timely manner.

In addition, in signing the *Prescriber Agreement Form* and placing it in the patient's medical record, the prescribers acknowledge the requirement to report patient deaths associated with mifepristone to the manufacturer. Such a requirement ensures that the manufacturer receives all reports of patient deaths and, in turn, fulfills its regulatory obligations to report those deaths to the FDA.

As discussed in Section 3.2.2 below, there is a potential for doubling of the number of prescribers of mifepristone if the in-person dispensing requirement in ETASU C is removed from the Mifepristone REMS Program. Given the potential addition of new prescribers, in addition to the considerations described above, we conclude that we should maintain the requirement for prescriber certification, to ensure that providers meet the necessary qualifications and adhere to the guidelines for use. Our literature review supports that these requirements are still necessary, and the potential increase in new prescribers under the REMS is a further reason to maintain prescriber certification. Healthcare provider certification continues to be a necessary component of the REMS to ensure the benefits of mifepristone for medical abortion outweigh the risks. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one time for each applicant.

3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D)

In order to receive mifepristone for medical termination of pregnancy through 70 days gestation, the patient must sign a *Patient Agreement Form* indicating that the patient has received, read, and been provided a copy of the *Patient Agreement Form* and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The *Patient Agreement Form* ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication.

[e] American College of Obstetricians and Gynecologists (ACOG) Practice Bulleting Number 191, February 2018. Tubal Ectopic Pregnancy. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/03/tubal-ectopic-pregnancy. Mifepristone is not effective for terminating ectopic pregnancy. Some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. A missed ectopic pregnancy that ruptures is a medical emergency that requires immediate surgical intervention.

In a number of approved REMS, *Patient Agreement Forms* or *Patient Enrollment Forms* ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[f]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the *Patient Agreement Form* with the patient, fully explaining the risks of the treatment regimen, and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the *Patient Agreement Form*, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the *Patient Agreement Form* serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed *Patient Agreement Form* in the patient's medical record.

Prior to the March 29, 2016 approval of the S-020 efficacy supplement for Mifeprex, FDA undertook a review of all elements of the REMS. At that time, the (b) (6) ((b) (6)), along with the (b) (6) ((b) (6)), recommended removal of the *Patient Agreement Form* (ETASU D). This recommendation received concurrence from the (b) (6) on February 23, 2016. The rationale for this recommendation in the 2016 review[g] is summarized here as follows:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and documentation of informed consent and evidence shows that practitioners are providing appropriate patient

[f] REMS@FDA, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.
[g] (b) (6) Clinical Review, NDA 020687/S20, dated March 29, 2016. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af803dc7bd&_afrRedirect=386175573203745

counseling and education; the *Patient Agreement Form* is duplicative of these established practices.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines are duplicated in the *Patient Agreement Form*.
- ETASUs A and C remain in place: The *Prescriber Agreement Form* and the requirement that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals under the supervision of a certified prescriber, remain in place.

In light of a memorandum from the Director of the Center for Drug Evaluation and Research, an addendum to the (b) (6) March 29, 2016 review and a memorandum from the signatory authority in (b) (6) indicated that the *Patient Agreement Form* would be retained in the REMS.[h,i]

The current review of literature from March 29, 2016 to July 26, 2021, is relevant to our assessment of the necessity of the *Patient Agreement Form* as part of the REMS. While our literature search yielded no publications which directly addressed this element of the REMS, we identified the following literature that focused on the informed consent process. These studies were reviewed for their potential relevance on this topic, though the articles do not directly assess the need for the *Patient Agreement Form* as a condition necessary to assure safe use of Mifepristone under ETASU D.

- Two studies[1,2] (both authored by Dr. Grossman in 2021) used the *Patient Agreement Form* and additional clinic-specific written informed consent forms as part of the study methodology. One study evaluated medical abortion with pharmacist dispensing of mifepristone and another evaluated mail-order pharmacy dispensing. Safety and efficacy outcomes were not assessed regarding the element of consent in isolation or the *Patient Agreement Form*.
- Several studies included use of electronic or verbal consent. Two studies were conducted using signed electronic consent (Chong[3], Kerestes[4]). Aiken[5] reported that patients had the option of providing consent verbally and the discussion had to be recorded in the notes. Rocca[6] described obtaining verbal informed consent from patients seeking medical abortion provided in pharmacies or government-certified

h (b) (6) Review of proposed REMS modifications to Mifeprex. March 29, 2106.
i (b) (6) Summary of Regulatory Action for Mifeprex. March 29, 2016.

public health facilities by auxiliary nurse midwives (ANMs) in Nepal. Outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

- A retrospective chart review (Wiebe[7]) was conducted in Canada. This study included telemedicine abortions between January 31, 2017 and January 31, 2019 and a similar group of controls seen in the clinic during the same time frame, matched by date of initial appointment. As part of the telemedicine process, patients read a consent form (not specified whether they could view an electronic version) and gave verbal consent "witnessed by the counselor". Again, outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

After review, we conclude that there are no outcome data from these studies that address the need for the *Patient Agreement Form* as a condition necessary to assure safe use of mifepristone. Nor do any of these studies provide evidence of whether the patient's informed consent has been adequately documented under the process set out in the study protocol. Therefore, these studies do not provide evidence that would support removing ETASU D.

Although (b) (6) agrees that informed consent in medicine is an established practice, the National Abortion Federation's 2020 Clinical Policy Guidelines for Abortion Care[8] continue to include a detailed section on patient education, counseling, and informed consent. The guidelines state that these steps are essential parts of the abortion process; that they should be conducted by appropriate personnel, with accurate information, including about alternatives and potential risks and benefits; and that the patients must have an opportunity to have any questions answered to their satisfaction prior to any intervention. Under these guidelines, documentation must show that the patient affirms that they understand all the information provided and that the decision to undergo an abortion is voluntary. The guidelines specifically list the risks that must be addressed at a minimum, including those pertinent to medical abortion: hemorrhage, infection, continuing pregnancy, and death. Additionally, Practice Bulletins from ACOG[9] and the Society of Family Planning also support detailed patient counseling.

In addition, trends in US clinical practice are developing which could negatively impact adequate patient counseling about the risks of medical abortion. One survey by Jones 2017[10] of abortion providers in the United States and Canada prior to the COVID-19 pandemic did reveal strong adherence to evidence-based guidelines. However, this same survey noted continued increasing uptake of medical abortion by US providers. Grossman[11] conducted a US survey in

2019 which suggested that the number of obstetrician/gynecologists providing medical abortion care may be increasing and that uptake might increase if mifepristone were dispensed by pharmacies instead of being dispensed in-person. A subsequent survey of US obstetricians/gynecologists by Daniel in 2021[12] evaluated a subsample (n = 868) from a prior national survey of providers and found that 164 (19%) reported providing medical abortion in the previous year. Of those obstetrician/gynecologists not providing medical abortion, 171 (24%) said they would offer the method to their patients if the in-person dispensing requirement for mifepristone were removed. This indicates a potential doubling of providers (+ 104%, 95% confidence interval (CI): 97% −112%). There were geographical variations, with the largest potential increases being in the Midwest (+ 189%, 95% CI: 172% −207%) and the South (+ 118%, 95% CI: 103% −134%).

Based on the articles discussed above, removal of the in-person dispensing requirement from the Mifepristone REMS Program (as discussed below in section 3.2.3) could significantly increase the number of providers to a larger group of practitioners. The *Patient Agreement Form* is an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the patient, to provide the patient with the *Patient Agreement Form*, and to have the healthcare provider and patient sign the *Patient Agreement Form*, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The single-page *Patient Agreement Form* is in line with other elements of this REMS, in that it supports the requirement that certified prescribers be able to accurately assess a patient, counsel a patient appropriately and recognize and manage potential complications. The form is placed in the patient's medical record to document the patient's acknowledgment of receiving the information from the prescriber and a copy is provided to the patient. We determined, consistent with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients, and that the *Patient Agreement Form* remains necessary to assure the safe use of Mifepristone.

After considering potential burden on healthcare providers and patients and considering the available data discussed above, including the potential for increased prescribing of mifepristone if in-patient dispensing is removed from the REMS, we conclude that the *Patient Agreement Form* should remain a safe use condition in the REMS.

3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C)

Mifepristone applicants must ensure that mifepristone is available to be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This creates what we refer to in this document as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office or hospital when the drug is dispensed. The mifepristone REMS document states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than these.

The following information contributed to our analysis of this requirement: Mifepristone REMS Program year-one assessment data, postmarketing safety information and literature review.

REMS Assessment Data

Reporting period for the Mifepristone REMS Program - April 11, 2019 through February 29, 2020

We evaluated information included in the one-year (1st)[j] REMS assessment reports for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, compliance data, audit results and patient exposure data.[13] The assessment reports were submitted on April 10, 2020 by the NDA Applicant and April 15, 2020 by the ANDA Applicant and cover a reporting period from April 11, 2019 through February 29, 2020. During this reporting period, the NDA Applicant reported (b) (4) newly certified healthcare providers, and the ANDA Applicant reported (b) (4) newly certified healthcare providers in the Mifepristone REMS Program. The NDA Applicant reported a total of (b) (4) certified healthcare providers (includes new and previously certified) ordered mifepristone during the assessment reporting period, and the ANDA Applicant reported a total of (b) (4) certified healthcare providers ordered mifepristone during the assessment reporting period. The NDA Applicant estimated that a total of (b) (4) patients were exposed to mifepristone during the assessment reporting period. The ANDA Applicant reported an estimated total of (b) (4) patients were exposed to mifepristone during the reporting period.

During the reporting period, a small number of non-compliance events were reported. The authorized distributor for the NDA applicant reported to the NDA Applicant that they experienced deviations with scanning of the product serial numbers which were confirmed during the February 2020 audit. The authorized distributor conducted a root cause analysis and developed a corrective and preventive action (CAPA) on February 12, 2020. The CAPA was

[j] This REMS assessment report was the first to be submitted following the approval of the single, shared system REMS for mifepristone.

validated and deployed with monitoring of the system through April 10, 2020. The corrective action will prevent similar events from occurring in the future.

January 27, 2020 through September 30, 2021

During the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not being enforced.

- On July 13, 2020, the United States District Court for the District of Maryland granted a preliminary injunction in the *ACOG* case to temporarily bar enforcement of the in-person dispensing requirement during the COVID-19 PHE.
- On January 12, 2021, the United States Supreme Court issued a stay of the injunction.
- On April 12, 2021, the FDA issued a General Advice Letter informing the applicants of the Agency's intent to exercise enforcement discretion during the COVID-19 public health emergency regarding the in-person dispensing requirement in the Mifepristone REMS Program.[k,l]

To better understand whether there was any impact on safety or noncompliance during the periods when the in-person dispensing requirement was not being enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or noncompliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. As part of an additional request for information for the REMS assessment report, the Applicants were also asked to submit the adverse events to FAERS and to notify FDA that the reports were submitted.

Between January 27, 2020 and September 30, 2021, the NDA Applicant distributed (b) (4) shipments representing (b) (4) tablets. The NDA Applicant reported that there were (b) (4) shipments representing a total of (b) (4) tablets sent to (b) (4) non-certified healthcare providers.[m,n] (b) (4) of these healthcare providers subsequently became certified while (b) (4) did not. Of the (b) (4) healthcare providers who were not subsequently certified, (b) (4) returned a total of 12 of the 13

[k] FDA General Advice Letter for NDA 20687, April 12, 2021.
[l] FDA General Advice Letter for ANDA 091178, April 12, 2021.

[m] NDA 020687 September 9, 2021 response to the FDA's September 2, 2021 Information Request.
[n] NDA 020687 October 8, 2021 response to the FDA's June 30, 2021 Information Request.

Mifeprex tablets to the distributor. [redacted] non-certified healthcare provider dispensed one tablet to a patient; no adverse events were reported. The NDA Applicant attributed the non-compliance observed to the authorized distributor's transition to a new platform. The NDA Applicant implemented a corrective and preventative action to address this issue, which we found to be acceptable.

The ANDA Applicant distributed [redacted] shipments representing [redacted] tablets of mifepristone from January 27, 2020 to September 30, 2021 and reported no instances of shipments to non-certified healthcare providers during this timeframe.

The NDA and the ANDA applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described in the section below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events. Further analysis of the adverse events is included below in the section on Pharmacovigilance Data.

Pharmacovigilance Data

The [redacted] ([redacted]) conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy.[o,p]

The data for this time period were then further divided into date ranges when the in-person dispensing requirement was being enforced per the REMS (January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021) versus when the in-person dispensing requirement was not being enforced (July 13, 2020 - January 12, 2021 (in-person dispensing requirement was temporarily enjoined) & April 13, 2021 - September 30, 2021 (in-person dispensing requirement was not being enforced because of the COVID-19 PHE)).

[redacted]. Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. [redacted] # 2007-525. Finalized April 12, 2021.

[redacted] Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. [redacted] # 2007-525. Finalized December 16, 2021.

A total of eight cases that met the search criteria were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when the in-person dispensing requirement in the REMS was being enforced (i.e., January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when the in-person dispensing requirement was not being enforced (i.e., July 13, 2020 - January 12, 2021 & April 13, 2021 - September 30, 2021). These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Although these adverse events occurred during the period when the in-person dispensing requirement was not being enforced, the narratives provided in the FAERS reports for cases 5, 6, and 7 explicitly stated that mifepristone was dispensed in-person. Of note, ongoing pregnancy, and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case from July 2021 reported the occurrence of oral pain/soreness (case 8) but did not provide sufficient information to determine the exact date of the adverse event. Based upon the U.S. postmarketing data reviewed, no new safety concerns were identified by (b) (6)

In addition to the FAERS data provided above, (b) (6) routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy. (b) (6) has not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy.

To enable additional review of adverse events, the Applicants were requested[q] to provide a summary and analysis of adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department (ED)/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided a summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021, on August 27 and October 8, 2021. During the time period in question, (b) (4) tablets were shipped, and

[q] On August 5, 2021, an IR was sent to the Applicants requesting a summary and analysis of adverse events from March 29, 2016 through June 30, 2021 and from July 1, 2021 through September 30, 2021.

48 adverse events were received. The 48 adverse events included 4 deaths (one of which occurred in 2010 but was reported in 2017), 25 incomplete abortions requiring surgical intervention, 17 blood transfusions following heavy vaginal bleeding, 2 ectopic pregnancies, 7 infections (1 sepsis and 6 infection without sepsis), 13 hospitalizations, and 43 ED or urgent care visits related to medical abortion. For the period between January 27, 2020 and September 30, 2021, a time frame that includes the entire period when the COVID-19 public health emergency (PHE) has been in effect, there were three adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 1 (uterine/vaginal bleeding), case 2 (uterine/vaginal bleeding and sepsis), and case 4 (drug intoxication and death).

The ANDA Applicant provided a summary of postmarketing safety information from April 11, 2019 (date of ANDA approval) through September 30, 2021. On August 26, 2021, the Applicant provided distribution and adverse event information from April 11, 2019 through June 30, 2021. During this time period, a total of (b) (4) tablets were shipped. There were 7 adverse events including 3 deaths (1 from sepsis, 1 from bilateral pulmonary artery thromboemboli, 1 in a patient who complained of not being able to breathe), 1 ongoing pregnancy treated with uterine aspiration, 2 blood transfusions, 1 sepsis (with death), 1 hospitalization, and 3 ED or urgent care visits related to medical abortion. On October 12, 2021 the Applicant provided information from July 1, 2021 to September 30, 2021; there were no additional adverse events. For the period between January 27, 2020 and September 30, 2021, there were four adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 3 (ongoing pregnancy), case 5 (death unknown cause), case 6 (sepsis and death), and case 7 (pulmonary embolism).[r]

The postmarketing data from FAERS were analyzed by (b) (6) to determine if there was a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. Based on this review, we conclude that there does not appear to be a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. This suggests that mifepristone may be safely used without an in-person dispensing requirement.

[r] The eighth FAERS case, oral pain/soreness, was not within the scope of the August 5, 2021 IR and was not considered for this review of postmarketing safety information submitted by the Applicants in response to the IRs.

(b) (6) review of the Applicants' IR responses, which included the same cases identified by (b) (6) from FAERS, did not change our conclusion.[s]

Literature Review

Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or an equivalent healthcare provider in countries other than the US). Some studies have examined replacing in-person dispensing in certain health care settings with dispensing at retail pharmacies (Grossman[2], Wiebe[7], Rocca[6]) and dispensing mifepristone from pharmacies by mail (Grossman[1], Upadhyay[14], Hyland[15]). Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to women (Gynuity study [Raymond[16], Chong[3], Anger[17]], Kerestes[4], Aiken[5] (2021)) and (2) prescribers using couriered delivery of medications (Reynolds-Wright[18]). Other studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization" (Aiken[19] (2017), Norton[20], Endler[21]). For ease of review, in the sections below that describe these studies, we have separated relevant references by the methodology used to dispense mifepristone.

Retail pharmacy dispensing

Three studies report medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation. Grossman[2] conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic where the participant had an evaluation by ultrasound and counseling. Of the 266 participants enrolled, 260 had known abortion outcomes. Complete abortion without additional procedure occurred in 243 participants (93.5% of those with known outcomes). Seventeen participants (6.5% of those with known outcomes) were diagnosed with incomplete abortion and underwent uterine aspiration. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. However, the finding represents a lower-than-expected efficacy based on the cohort's GA (84% of participants were at ≤ 56 days GA, a cohort for which the labeled success rate is 96.8%). No participants experienced a serious adverse event, were hospitalized, or required transfusion. Three participants had ED visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study's

[s] The reporting period of (b) (6) assessment of the adverse events in FAERS is not identical to the time period for summaries of adverse events in the IRs to the Applicants. Therefore, the numbers of cases and adverse events summarized in (b) (6) assessment may differ from the numbers of cases and adverse events summarized by the Applicants in their responses to IRs (note that each case report may include more than one adverse event).

safety and efficacy outcomes are consistent with labeled frequencies. The majority of participants (65%) were very satisfied with the experience. There were some complaints from participants about not receiving all prescribed medications at the initial pharmacy visit, privacy not being adequately maintained, and perceived negative pharmacist attitude.

Overall, we conclude that this study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to US retail pharmacies; there is insufficient information to assess this. Rocca[6] conducted an observational study evaluating 605 participants at ≤63 days GA who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. Participants who presented to pharmacy study sites underwent clinical screening including a pelvic exam by trained nurse midwives at the pharmacy (which was equipped with an examination room) and if eligible for medical abortion, were dispensed mifepristone and misoprostol in the pharmacy at the time of their visit. Participants who presented to public health facilities underwent clinical screening including pelvic examination by abortion providers including trained nurse midwives and if eligible for medical abortion were dispensed mifepristone and misoprostol in the clinic at the time of their visit. The authors reported that, with respect to complete abortion (>97%) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[7] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of 182 women at ≤ 70 days GA who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of 199 women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (90%, calculated maintaining subjects with unknown outcomes in the denominator; ≥ 95% calculated with known outcomes only). The telemedicine group had one case of hemorrhage (0.5%) and one case of infection requiring antibiotics (0.5%) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3% compared to 1.5% in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

None of the three studies described above allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the studies to the current retail pharmacy environment in the US. The outcome findings from the one US study (Grossman[2]), in which the pharmacies were partnered with prescribers, may not be generalizable to much of the US as they do not reflect typical prescription medication availability with use of retail pharmacy dispensing. Although retail pharmacy dispensing of mifepristone and misoprostol in Canada has been described in the literature, there are important differences in healthcare systems between Canada and the US that render the findings from studies in Canada (Wiebe[7]) not generalizable to the US. In the Wiebe study, timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that allow timely access to medications for medical abortion would occur in retail pharmacies throughout the US. Canada's federal government has reaffirmed that abortion is an essential health service[t] which may have implications affecting access to medical abortion from retail pharmacies in Canada. The Rocca[6] study evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the US retail setting.

Mail order pharmacy

Grossman[1] published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. All participants were evaluated for eligibility during a clinic visit with GA up to 63 days confirmed with either an ultrasound or examination; instead of receiving medication at the clinic visit, participants received medications from a mail-order pharmacy. A total of 240 participants have been enrolled; three participants did not take either medication. A total of 227 (94.6%) provided some outcome information, of whom 224 provided abortion outcome information. Complete abortion without additional procedures occurred in 217 participants (96.9% of those with known outcomes). Two (0.9%) participants experienced serious adverse events (SAE); one received a blood transfusion, and one was hospitalized overnight. Nine (4%) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies. With respect to the time interval between a

[t] As noted in Mark[23] and Martin[24], most provincial and federal health insurance programs in Canada cover medical abortion, and covered services are free at the point of care.

participant's clinic visit and receipt of medications, of the 224 participants with known abortion outcomes, 184 (82.1%) received medication within 3 days. However, 17% received between 4-7 days and one participant waited over 7 days for receipt. Seven of 216 (3.2%) participants who completed the day-3 survey reported compromised confidentiality (e.g., someone found their medication, privacy concerns).

Upadhyay[14] reports findings from a retrospective cohort study of 141 women undergoing medical abortion in the US without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Three interactions via text, messaging or telephone occurred to confirm medication administration, assessment of expulsion and pregnancy symptoms, and results of a 4-week home pregnancy test. Abortion outcome was determined by either the day 3 assessment or the 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95% (105 participants out of 110 for whom outcomes were known) and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. Additionally, a substantial number of participants (31) provided no outcomes information. Among the 141 participants enrolled, 128 had any follow-up contact with the study staff, and 110 provided outcomes information. Excluding outcomes of 22% of the cohort is a limitation of this study. This study used a model with numerous deviations from standard provision of medical abortion in the US, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication, no confirmation of self-reported medical, surgical, and menstrual history. Further, follow-up information based on a 3-day period is insufficient to determine outcome rates or safety findings. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[15] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. All participants obtained screening tests including ultrasound confirmation of GA. A total of 1010 participants completed the screening process and were provided mifepristone and misoprostol. Abortion outcomes were determined for 754 (75%) of the 1010. Outcomes for the remaining 256 participants (25%) were not included because 31 provided no relevant information after shipment, 14 reported not taking misoprostol, and 211 did not have "full follow up" (i.e., known outcome of either complete medical abortion, uterine evacuation, or ongoing pregnancy with plan to continue).

Complete abortions without additional procedures occurred in 727 participants (96% of those with definitively documented outcomes) and is consistent with labeled efficacy. Of the 754 participants included in the analysis 717 (95%) had no face-to-face clinical encounters after medications were mailed while 21 (3%) were admitted to the hospital and 16 (2%) had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up". The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. The reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported number of hospitalizations (3%) is higher than the less than 1% in the FDA-approved mifepristone labeling, conclusions regarding the safety findings in this study cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters, and not reporting outcomes of 25% of the enrolled cohort.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that the efficacy of medical abortion is maintained with mail order pharmacy dispensing. In the Grossman[1] study, the interim analysis, although small, does not raise serious safety concerns. We note that 18% of participants did not receive medications within 3 days; the potential for delay in receiving medication by mail could limit the GA eligible for medical abortion through mail order pharmacy dispensing, because women at GA closer to 70 days might not receive medication in time. A small proportion (3%) of participants raised concerns regarding the issues of confidentiality and privacy. Safety findings from the Hyland[15] study are difficult to interpret. Although only one transfusion is reported, and the authors state the findings demonstrate safety, the higher hospitalization rates, and lack of information on the reasons for hospitalization do not allow any conclusions about safety findings. Lastly, the Upadhyay[14] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the US.

Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail.[3,4,5,16,17] Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population

exclusively: Raymond[16] from May 2016 to December 2018, Chong[3] from May 2016 to September 2020 and Anger[17] from March 2020 to September 2020. Due to the pandemic, the Gynuity study deviated from the protocol requirement of confirmation of GA by examination or ultrasound for many participants treated from March 2020 onward (although none of the three publications reported on the single element of dispensing mifepristone from the healthcare setting by mail). A fourth study, Kerestes,[4] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020: seventy-five (of whom 71 were enrolled in the Gynuity study) of the 334 participants in Kerestes were dispensed mifepristone by mail after a telemedicine consult. The section below discusses these four studies from the US as well as a large UK study by Aiken[5] (2021).

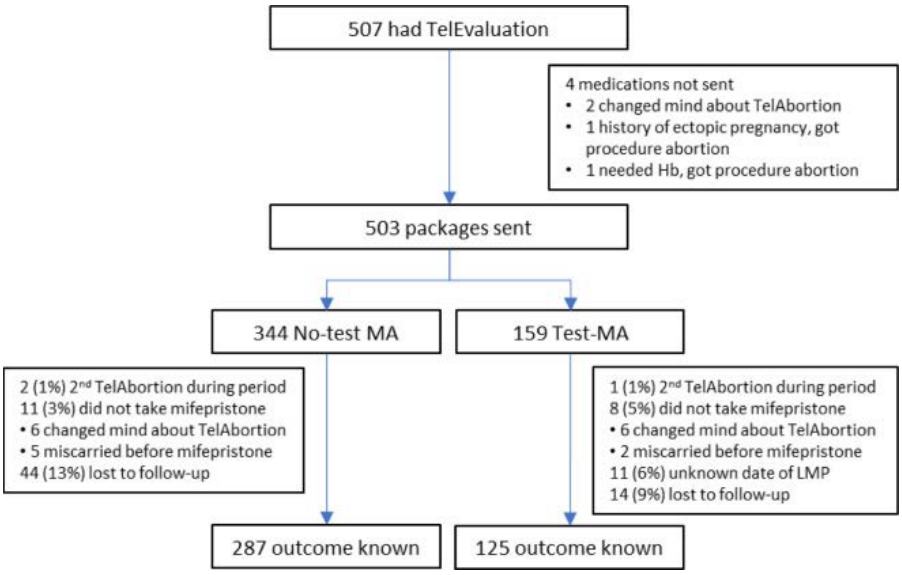
Raymond [16] (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider by videoconference. If the participant was eligible for treatment, the provider dispensed the medications by mail. Of 433 women screened, 165 (38%) either declined to schedule the videoconference or did not keep the videoconference appointment. Among the 268 participants evaluated via videoconference, medication packages were sent to 248. Abortion outcomes were determined for 190 (77%) of the 248; outcomes for 58 (23%) participants were unknown. Complete abortion without additional procedures occurred in 177 participants (93% of those with known outcomes). The investigators obtained follow-up information from 217 participants after package shipment; there were two hospitalizations (one received a transfusion for severe anemia despite having had a complete abortion), and 16 other participants (7%) had clinical encounters in ED and urgent care centers. The reported outcomes in Raymond[16] (2019) are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7%) exceeded the ED visits in approved labeling (2.9-4.6%). The authors note that half of the ED/urgent care visits did not entail any medical treatment and opine that the increased number of visits may have been due to the study participants living farther from the abortion providers.[16] All participants received medications within 8 days.

Chong[3] updated the findings from the Gynuity study described in Raymond[16] and reported on 1157 medical abortion outcomes, of which approximately 50% occurred during the period of the COVID-19 PHE. Although a screening ultrasound was required per the protocol, sites determined in 52% (346/669) of abortions that occurred during the period of the COVID-19 PHE that, in order to avoid potential exposure to COVID-19 at a health care facility, those

participants were not required to obtain a screening ultrasound. Use of urine pregnancy test to confirm abortion completion also increased from 67% (144/214) in the 6 months prior to the pandemic to 90% (602/669) in the 6 months during the pandemic. Of the 1390 participants to whom medicine packages (containing both mifepristone and misoprostol) were mailed, 1157 (83.2%) had known abortion outcomes. Complete abortion without a procedure occurred in 1103 participants (95% of the those with a known outcome). Ten women experienced an SAE (5 transfusions (0.4%) and 7 hospitalizations (0.7%)) and 70 (6%) participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 47 participants (4.1% of 1390) to complete abortion. The reported outcomes in this study are similar to outcomes described in approved labeling, except that the combined ED/urgent care center encounters (6%) exceeded the ED visits in approved labeling (2.9-4.6%).

Anger[17] compared outcomes among participants enrolled in the Gynuity study who did versus did not have confirmation of GA/intrauterine location with an examination or ultrasound from 10 jurisdictions across the US. These participants were screened for enrollment from March 25 through September 15, 2020. All participants had a telemedicine consultation and received mifepristone and misoprostol by mail from the healthcare facility. Determination of which participants did not require confirmation of GA by examination or ultrasound to be eligible depended on the study clinician's assessment of eligibility for "no-test medication abortion"[u] based on a sample protocol published by Raymond[22] (2020). There were two key differences between the two groups. Participants for whom the study clinician determined a pre-abortion ultrasound was required were more likely than the participants who had no ultrasound or examination to live further than 150 miles from the clinic (51.2% vs. 31.7%) and were more likely to have a GA above 63 days (12.0% vs. 1.7%). The study sites shipped 503 medication packages during the analysis period; 344 packages went to the "no test" group while 159 went to the "test" medical abortion cohort (see figure below). However, because the two cohorts were not randomized in this study, they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

[u] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination, or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al.[22]



Source: Figure 1 in this publication. MA= medical abortion.

The investigators' analyses excluded 91 (18% of 503; 57 in the no-test group and 34 in the test group) participants because they did not provide a date of the last menstrual period (LMP), did not take mifepristone, or did not have a recorded abortion outcome. Overall, 410 participants (81.5% of 503) provided outcomes data. There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the no-test group, complete medical abortion was confirmed in 271 participants who took medications (94% among those with known outcome). In the no-test cohort, two participants were "hospitalized and/or blood transfusion," and 36 (12.5%) had an unplanned clinical encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion).

In the test medical abortion group, complete abortion was confirmed in 123 participants (of 125 with known outcomes); the completion rate was 98% among those with known outcomes. In the test medical abortion group, one participant was "hospitalized and/or blood transfusion," and 10 (8.0%) had an unplanned clinical encounter. The authors concluded that, compared to participants who had an ultrasound prior to medical abortion, those without an examination prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.

Kerestes[4] was the only publication that linked outcomes of medical abortion with different delivery models. Participants included in the report had GA up to 77 days and received

medications in Hawaii between April 2020 and January 2020. A total of 334 medication packages (to 330 unique participants) were dispensed containing mifepristone and misoprostol; three different delivery models were used concurrently: 110 (32.9%) had traditional in-person visits, 149 (44.6%) had telemedicine consultation with in-person pick-up of medications, and 75 (22.5%) were sent medications by mail (71 of these were enrolled through Gynuity's TelAbortion study). Seven participants of the 330 participants who received 334 medication packages reported that they did not take them and were excluded from analysis of the outcomes. Among participants with follow-up data, the rates of successful medical abortion without surgery were 93.6%, 96.8%, and 97.1% in the in-clinic group, telemedicine + in-person pickup group, and telemedicine + mail group, respectively; these were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine + in-person pickup group). Eleven participants went to an ED. Although ED visits occurred the most frequently in the telemedicine + mail group (four participants or 5.8%) and the least in the in-person group (two participants or 2.1%), the study reported no increases in other serious adverse events.

Taken together, the three Gynuity study reports[3,16,17] and Kerestes[4] support dispensing mifepristone and misoprostol by mail after a telemedicine visit. Efficacy was maintained in all four studies. All of the studies reported SAEs frequencies comparable to labeled rates, except two of the Gynuity study reports (Raymond[16], Chong[3]) and Kerestes[4] report a higher frequency of ED/urgent care visits than the labeled frequency of ED visits. We do not know whether the reporting of combined ED and urgent care visits represents an increased rate of ED visits compared to the labeled rate of ED visits (2.9-4.6%). Other labeled SAEs (e.g., transfusion) occur infrequently (< 1%).

Aiken[5] (2021) reports outcomes of medical abortion up to 70 days GA in the UK before and during the pandemic in a retrospective cohort study. In the UK, prior to the COVID-19 pandemic, all patients attended an in-clinic visit where they received an ultrasound, were administered mifepristone in the clinic, and given misoprostol in-clinic for use at home (traditional model). During the pandemic, medical abortion consultations were performed remotely by telephone or video. Based on the consultation and questionnaire (including date of last menstrual period; menstrual, contraceptive and medical history; symptoms; risk for ectopic pregnancy), an assessment of eligibility for treatment via telemedicine was made. If eligible, medications were delivered to participants via mail or were made available for collection from the clinic for use at home. If the participant was assessed to be ineligible for treatment via

telemedicine, an in-person assessment with ultrasound was performed and medications were provided from the clinic for home use (hybrid model).

The study compared the two cohorts: 22,158 obtained medical abortion before the pandemic and had in-person visits and dispensing (traditional model) and 29,984 obtained medical abortion during the pandemic with either in-person visit and in-person dispensing, or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Outcomes were obtained from electronic records and incident databases. Outcomes of all hospitalizations related to abortion, ED visits, infection without sepsis, and hemorrhage without transfusion were not reported. The investigators' analysis for non-inferiority determined the efficacy and safety were comparable between both cohorts. Complete abortion occurred in > 98% in both cohorts. Hemorrhage requiring transfusion was reported in 0.04% and 0.02% of the traditional and hybrid cohorts, respectively; this is lower than the labeled 0.5% transfusion rate. There were no severe infections requiring hospitalization, major surgery or deaths reported.

A secondary analysis of the hybrid cohort was reported. Within the 29,984-person hybrid model cohort, 11,549 (39%) abortions were conducted in-person (in-person assessment with ultrasound was performed and medications provided from the clinic for home use) and 18,435 (61%) abortions were provided by telemedicine visit, without tests or confirmation of GA/intrauterine position by ultrasound, and medications either mailed or picked up from the clinic. Outcomes stratified by type of mifepristone dispensing were not reported. The rate of complete abortion was slightly higher in the telemedicine group (99.2%) than that in the in-person group (98.1%). There were no significant differences in the rates of reported SAEs. Adjustments for clinical and demographic characteristics were made because the two groups differed in baseline characteristics, including a higher proportion of pregnancies with GA over 6 weeks in the in-person group (68.2% compared with 55.1%). The authors conclude a hybrid model for medical abortion that includes no-test medical abortion[u] (no ultrasound, no pelvic exam, no pregnancy test) is effective and safe.

We conclude that although the Aiken[5] (2021) study has a large sample size and includes 85% of all medical abortions performed in England and Wales during the study period, the study has limitations. The authors acknowledge the main limitation of their study was that analysis was based on deidentified information in the NHS database and the investigators were unable to verify the outcomes extracted. Other limitations included that their search only captured

outcomes in electronic records and incident databases that met the authors' defined threshold for SAE reporting, and that the labeled abortion outcomes considered serious, such as hospitalizations related to abortion, infection without sepsis, hemorrhage without transfusion, or ED/urgent care visits, were not all included in the authors' definition of serious adverse event.

Data from the mail order dispensing studies with telemedicine visits from Gynuity (Raymond, Chong and Anger),[3,16,17] Kerestes[4], and Aiken[5] (2021) support that efficacy of medical abortion was maintained. The Aiken[5] study appears to be of sufficient sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings. Study reports of Raymond[16] Chong[3], and Kerestes[4] all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail without increases in other adverse events. Anger's[17] comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. Overall, despite the limitations noted, these studies support that dispensing by mail is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other SAEs related to mifepristone use. One reason for the increase in frequent ED/urgent care visits in the Raymond[16] publication, according to its authors, may have been that a substantial proportion of participants lived significant distances from their providers and increased distances have been associated with higher use of ED following treatment. Raymond[16] reported that half of the participants who had an ED/urgent care visit did not require medical treatment.

Clinic dispensing by courier

Reynolds-Wright[18] reported findings from a prospective cohort study of 663 women at less than 12 weeks' GA in Scotland undergoing medical abortion at home with use of telemedicine during the pandemic (from April 1 to July 9, 2020). The majority of medical abortions (78.7%) used telemedicine visits, eliminated pre-abortion ultrasound, and provided mifepristone for pick up at the service or by couriered delivery to woman's home. The number of couriered deliveries was not reported; thus, this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. With access to NHS regional hospital databases, the investigators were able to verify pregnancy outcomes and complications. Of the 663 participants, 642 (98.2%) were under 10 weeks GA, 21 (1.8%) were between 10 and 12 weeks

GA, and one participant was never pregnant. A total of 650 participants had complete abortion without requiring surgical intervention (98%), 5 (0.8%) an ongoing pregnancy and 4 (0.6%) an incomplete abortion. The outcomes from this study in Scotland are consistent with labeled mifepristone outcomes. The study shares the same limitations as the Aiken[5] (2021) study.

Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail.[v] Medical abortion eligibility is determined using an online questionnaire with asynchronous physician review. If eligible, medications are mailed to the women. WoW provides help and support by email or instant messaging.

Aiken[19] (2017) conducted a population-based study analyzing findings from 1,636 women in the Republic of Ireland and Northern Ireland who were sent medications between 2010 and 2012. Receipt of medications was confirmed for 1,181 women, among whom 1,023 confirmed use of mifepristone and misoprostol; outcome information was available for 1,000 (61% of women sent medications). Of the 1,000 women, the majority (781, 78%) were less than 7 weeks GA and 219 (22%) were at 7-9 weeks. Complete abortion without surgical intervention occurred in 947 (94.7% of 1,000 with known outcome); 7 (0.7%) women received a blood transfusion, 26 (2.6%) received antibiotics (route of administration undetermined) and 87 (8.7%) sought medical care at a hospital or clinic for symptoms related to medical abortion. Hospitalizations related to abortion were not reported. The reported proportion of complete abortion is within the range labeled for medical abortion up to 70 days (92.7-98.1%). However, the finding of 94.7% complete abortion represents a lower-than-expected efficacy based on the cohort's GA (almost 80% less than 7 weeks, labeled success for medical abortion ≤ 49 days is 98.1%). This study has limitations, including outcomes based on self-report without validation of completed abortion by examination or laboratory testing, and no known outcomes for 39% of study cohort. Additionally, the authors noted medical abortion was provided in a legally-restrictive setting, where the law provided a maximum penalty of life imprisonment for the woman undergoing the abortion, which may affect participants' self-reporting.

[v] In March 2019, FDA sent a WL to Aidaccess.org, a group affiliated with WoW. Aidaccess.org received this WL because it was introducing misbranded and unapproved new drugs into the U.S. In the context of this REMS review, studies involving WoW are included solely for purposes of evaluating of data regarding the methods of dispensing mifepristone.

Endler[21] and Norten[20] have reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail, because neither provide meaningful outcomes data for consideration. Endler[21] compared the outcomes of self-reported heavy bleeding and clinical visits occurring during the "first or second day of abortion" that occurred in women undergoing medical abortion at 9 weeks GA or less, with outcomes from women at more than 9 weeks GA. Outcome data from day 1 or 2 is of limited usefulness. Norten[20] describes findings from a survey of women who were sent medical abortion medication through WoW and provided self-reported outcomes. Results were based on surveys returned from only 37% of participants, a return rate that is too low for the study to be considered valid.

WoW uses a model with numerous deviations from the standard provision of medical abortion in the US. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Further, although Aiken[19] (2017) is a large cohort study, the outcomes are self-reported with no verification of complete abortion by laboratory or clinical evaluation and 39% of outcomes are unaccounted for. These limitations in the Aiken study result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

4. Discussion

After review of the published literature, safety information collected during the COVID-19 PHE, postmarketing data, information from the first Mifepristone REMS Program assessment report, responses to information requests to the Applicants, and information provided by advocacy groups, individuals and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that the REMS can be modified to reduce burden without compromising patient safety.

Prescriber Certification

None of the publications we reviewed would support a conclusion that a healthcare provider who prescribes mifepristone does not need to meet the qualifications included in the Mifepristone REMS Program as described above in section 3.2.1. Absent these provider qualifications, serious complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed.

We conclude that prescriber certification (ETASU A) should be maintained. The current process requires the prescriber to agree to the requirements of the Mifepristone REMS Program and to attest that they meet the qualifications described in section 3.2.1 above. The REMS has been structured to minimize burden to prescribers by requiring only a one-time certification by the prescriber for each Applicant. We have determined that healthcare provider certification continues to be necessary to ensure the benefits outweigh the risks, especially considering that, if the in-person dispensing requirement is removed from the Mifepristone REMS Program, the number of new providers may increase (see discussion in section 3.2.2 above).

Drug to be dispensed with evidence or other documentation of safe use conditions

The requirement to counsel the patient and provide them with the *Patient Agreement Form* ensures that each patient is informed of the appropriate use of mifepristone, the risks associated with treatment, and what to do if they experience symptoms that may require emergency care.

In 2016, we initially recommended eliminating the *Patient Agreement Form* (see section 3.2.2), though the form was ultimately maintained as part of the REMS. As discussed above, our current literature review has indicated that there is no basis to remove the *Patient Agreement Form* from the REMS. In addition, surveys we reviewed suggest that if the in-person dispensing requirement for mifepristone is removed, there could be a potential doubling of medical abortion providers. This potential doubling of medical abortion providers supports the continued need to ensure that patients are consistently provided patient education under the Mifepristone REMS Program regarding the use and risks of mifepristone. The *Patient Agreement Form* is an important part of standardizing the medication information that prescribers communicate to their patients, including new prescribers, and also provides the information in a brief and understandable format to patients. We determined, in accordance with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients.[w]

Given the likelihood of a potential increase in new prescribers if the in-person dispensing requirement is removed from the Mifepristone REMS Program, we conclude that maintaining the *Patient Agreement Form* remains necessary to assure safe use at this time.

[w] *The Patient Agreement Form* can be signed in person or through other means.

Drug to be dispensed only in certain healthcare settings

As discussed above in section 3.2.3, our evaluation of information submitted by the applicants in the one-year (1st) REMS assessment report for the Mifepristone REMS Program and in response to follow-up requests from the Agency indicates that the number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these adverse events. We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.

Alternatives to in-person dispensing of mifepristone have been investigated in several studies and countries. The literature review identified 15 publications[x] that assessed safety outcomes from various medication delivery models (US, UK, Canada, Ireland, Australia, Nepal), including dispensing by retail and mail order pharmacies, prescribers mailing medications or using couriered service to deliver medications, and dispensing by "partner organizations". The ability to generalize the results of these studies to the US population is hampered by differences in pre-abortion care (e.g., telemedicine versus in-person, testing), and the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy.

In addition, there are factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation; for example, most studies on mail dispensing of mifepristone also include telemedicine consultation, and (2) because most SAEs with medical abortion are infrequent, though they can be life threatening, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the US.

[x] The 15 publications correspond to endnote numbers: 1-7, 14-21.

Based on the literature identified by our review, dispensing mifepristone by mail from the clinic or from a mail order pharmacy does not appear to jeopardize the efficacy of medical abortion. The studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, although the safety and efficacy outcomes reported in these studies remain within the ranges described in mifepristone labeling except for increased numbers of ED/urgent care visits and hospitalizations.

Four publications (Raymond[16], Chong[3], Anger[17] and Kerestes[4]), describe a relevant US cohort where dispensing mifepristone from the clinic by mail was paired with telemedicine visits. These studies showed that efficacy was maintained and there was no increased frequency of SAEs except for higher ED/urgent care visits. The increased ED/urgent care visits were not associated with increases of other SAEs, and in the view of one study's authors (Raymond[16]), may be associated with participants being located significant distances from their providers. The Aiken[5] (2021) study of a large UK cohort where the clinics mailed mifepristone report small (lower than labeled) occurrences of transfusion and no significant infections requiring hospitalization. In Grossman[1] and Hyland[15], where the pharmacies mailed mifepristone after prescribers confirmed GA, efficacy is maintained. Grossman's[1] interim analysis found no increases in SAEs. Hyland[15] reported higher numbers of hospitalizations but did not report increases of other SAEs. Overall, while the studies assessing mifepristone dispensing by mail suggest more frequent encounters with healthcare providers, they generally support a conclusion that dispensing by mail is safe. Despite the limitations of the studies we reviewed, we conclude that overall, the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe, and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, our review of the literature, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met, and pharmacy certification is added as described below.

Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to

ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the REMS, the Mifepristone REMS Program should be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

New requirement to be added for pharmacy certification

The current distribution model requires the certified prescriber to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. During the periods when the in-person dispensing requirement was not being enforced, both applicants used mail order pharmacies to receive and hold mifepristone on behalf of the certified healthcare providers who had purchased the product.[j,y,z] Pursuant to a prescription for mifepristone, the mail order pharmacy would ship the product to a named patient.

The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, the drug is no longer required to be dispensed only in a clinic, medical office or hospital. Under the REMS as modified, mifepristone can be dispensed through a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies under ETASU B. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that ETASU A is met prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the *Patient Agreement Form* (ETASU D) is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review of the safety data and our consideration of the distribution model implemented by the Applicants during the periods

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y ANDA 091178: September 23, 2021 response to the September 15, 2021 information request; October 11 and 16, 2021 responses to the June 30, 2021 and July 15, 2021 information requests; October 26, 2021 response to the October 22, 2021 information request; October 29, 2021 response to the October 27 information request.
z NDA 020687: September 20, 2021 response to the September 15, 2021 information request; October 26, 2021 response to the October 22 information request.

when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients. As modified, the REMS would allow, for example, dispensing by mail order or specialty pharmacies, similar to the distribution model used by applicants during the periods when the in-person dispensing requirement was not being enforced.[aa]

The above recommendations were discussed with the (b) (6) ((b) (6) and senior leadership from CDER on November 2, 2021. The (b) (6) (b) (6) along with senior CDER leadership, concurred with removing the in-person dispensing requirement provided that all of the remaining REMS requirements are met, including but not limited to prescriber certification where prescribers need to attest to having certain qualifications, and maintaining the *Patient Agreement Form*. The (b) (6) (b) (6) and senior leadership from CDER were also in favor of adding pharmacy certification to assure the safe use of mifepristone.

5. Conclusions and Recommendations

Based on the results of REMS assessments; our review of safety data collected during the PHE as well as data from FAERS; our literature search; and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, (b) (6) and (b) (6) have concluded that a REMS modification is necessary and should include the following changes:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

[aa] Our current conclusion that the REMS would allow dispensing by mail order or specialty pharmacies is based on data received from Applicants relating to the periods when the in-person dispensing requirement was not enforced and mail-order pharmacies were used to dispense the product, as well as our analysis of postmarketing safety data and available literature. At this time we do not have data (from the Applicants or from other sources) to assess the certification of retail pharmacies under the REMS. We have not yet determined the details of pharmacy certification requirements, including whether any limitations on the types of pharmacies that may dispense the product are necessary.

(b) (6) and (b) (6) recommend the Applicants be issued a REMS Modification Notification Letter that requests submission within 120 days from the date of the letter.

6. References

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7. Appendix A

References Cited in Letters from Plaintiffs

References cited in letter from *Chelius v. Becerra* Plaintiffs (September 29, 2021)	
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Aiken A et al. BJOG 2021: 128 (9): 1464-1474	
Chong, et al. Contraception 2021; 104(1) 43-48	
Daniel S. et al. Contraception 2021; 104(1): 73-76	
References excluded from the REMS review	**Rationale for Exclusion**
Am. Coll. of Obstetricians & Gynecologists, *Position Statement: Improving Access to Mifepristone for Reproductive Health Indications* (June 2018), https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications	Policy/advocacy statement
House of Delegates, Am. Med. Ass'n., *Memorial Resolutions Adopted Unanimously No. 504 (2018)* https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-resolutions.pdf	Policy/advocacy statement
Cong. Of Delegates, Am. Acad. Of Fam. Physicians, *Resolution No. 506 (CoSponsored C) Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization of Mifepristone* (May 24, 2018) https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf	Policy/advocacy statement
Schummers L et al, Contraception 2020; 102(4): 273	Abstract
Upadhyay UD et al.) Obstet & Gynecol 2015; 125: 175	Published prior to March 29, 2016-July 26, 2021 timeframe for current literature review. We note that the extensive literature review conducted as part of the 2016 review, which was consistent with the division's standard approach for reviewing an efficacy supplement

	and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
Kapp N et al. Best Pract Clin Obstet Gynaecol. 2020;63:37-44	Abstract. Also outside the scope of first trimester medical abortion.
Fuentes L et al. J Women's Health 2019; 28 (12): 1623, 1625 Bearak JM, Lancet Pub Health 2017 Nov;2(11): e493, e495-96 Cartwright A et al 20 J Med Internet Res 2018 20(5):e10235 Barr-Walker J, et al PLoS One 2019;14(4): e0209991 Grossman et al JAMA Network 2017;317(4):437, 437-438 Dobie S et al 31 Fam Plan Persp 1999; 31(5): 241-244 Shelton JD 8 Fam Plan Persp 1976; 8(6):260, 260-262 Norris AH et al Am J Pub Health 2020; 110 (8): 1228,1232 Upadhyay UD et al Am J Pub Health 2014; 104(9):1687, 1689	Focused on the logistics of accessing abortion care.
CDC MMWR Abortion Surveillance – United States, 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5_down	Contains primarily general statistics on abortion care by state.

References cited in appendix from *Chelius v. Becerra* Plaintiffs (September 29, 2021)
References included in the REMS review
None

References excluded from the REMS review	Rationale for Exclusion
Jones RK et al Guttmacher Institute Abortion Incidence and Service Availability in the United States, 2017 (2019) Guttmacher Inst, Induced Abortion in the United States (2019)	Contains primarily general statistics on abortion care and logistics of accessing abortion care.
University of Minnesota Healthy Youth Dev. Prevention Rsch Ctr, 2019 Minnesota Adolescent Sexual Health Report 3 (2019)	Not related specifically to abortion care.
Jerman J et al Guttmacher Inst, Characteristics of U.S. Abortion Patients in 2014 and Changes since 2008 (2016)	Contains figures on patient characteristics from 2008-2014.
Roberts CM et al Women's Health Issues 2014; 24:e211, e215	Focused on cost of abortion.
CDC MMWR Abortion Surveillance 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7 down (last updated Nov. 7, 2020)	Contains primarily statistics on number of abortions in the US.
Jones RK Persp on Sexual & Reprod Health 2017; 49:17, 20	Focused on abortion incidence and service availability.
Fuentes L et al (as above) Bearak JM et al (as above) Cartwright A et al (as above) Johns NE et al. BMC Health Serv Res 2017; 17: 287, 294	Focused on logistics of accessing abortion care.

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References included in the REMS review
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Chong et al. Contraception 2021;104(1): 43-48	
Aiken A et al. BJOG 2021; 128 (9): 1464 -1474	
Hyland 2018 et al. Aust New Zeal J Obstet Gynaecol 2018; 58 (3): 335-340	
References excluded from the REMS review	**Rationale for Exclusion**
Schummers L et al. BMJ Sex Reprod Heal 2021;47(e1)	Abstract
Kapp et al. 2020 (as above)	Abstract
Upadhyay et al. 2015 (as above)	(See rationale above)
Srinivasulu et al. Contraception 2021; 104(1):92-97	Survey on clinician perspectives on access to mifepristone.
Calloway D et al. Contraception 2021; 104(1): 24-28	Primarily addresses provider stigma around abortion care.
Rasmussen et al. Contraception; 104(1): 98-103	Opinion/commentary
Cleland et al. Obstet Gynecol 2013;121(1):166-171	Published prior to March 29, 2016 - July 26, 2021 timeframe for current literature review. We note that the extensive literature search conducted as part of the 2016 clinical review, which was consistent with the division's standard approach for reviewing an efficacy supplement and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
National Academy of Sciences, Engineering, and Medicine. Safety and Quality of Abortion Care in the US 2018	General information about abortion care in the US. Did not provide safety data relevant to the elements of the REMS
Raymond EG. Obstet Gynecol 2012: 119(2): 215-219	Does not separate out medical and surgical abortion.

Bartlett LA et al. Obstet Gynecol 2004; 103(4): 729-737	Focused on surgical abortion.
Jones RK, Jerman J. Time to appointment and delays in accessing care among U.S. abortion patients, Guttmacher 2016	Focused on logistics of accessing abortion care.
Foster DG et al. Perspect Sex Reprod Health 2013; 45(4):210-218	Focused on second trimester abortion.
Ely G et al. Heal Soc Work 2019;44(1):13-21	Focused on logistics of accessing abortion care.
Munro S et al. Ann Fam Med 2020; 18(5):413-421.	Survey on physician perspectives on implementing medical abortion with mifepristone.

EXHIBIT 52

FDA Adverse Events Reporting System
(FAERS) Public Dashboard

FDA Adverse Events Reporting System (FAERS) Public Dashboard

The FAERS public dashboard is a new, user-friendly and interactive web-based tool that was created to give the public the ability to query the FDA FAERS database and improve transparency. The data presented in the FAERS public dashboard has several key limitations. The existence of adverse event reports for a drug or biologic in FAERS does not mean that the drug or biologic caused the adverse event. Importantly, the FAERS data is not an indicator of the safety profile of the drug or biologic. For more information, please refer to the question What points should I consider while viewing the dashboard content?

Frequently Asked Questions (FAQs)

Expand all | Collapse all

General Questions

− What is FAERS?

The FDA Adverse Event Reporting System (FAERS) is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation (ICH E2B). Adverse events and medication errors are coded using terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

− How does FDA use the information in FAERS?

FAERS is a useful tool for FDA for activities such as looking for new safety concerns that might be related to a marketed product, evaluating a manufacturer's compliance to reporting regulations and responding to outside requests for information. The reports in FAERS are evaluated by clinical reviewers, in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), to monitor the safety of products after they are approved by FDA.

If a potential safety concern is identified in FAERS, further evaluation is performed. Further evaluation might include conducting studies using other large databases, such as those available in the Sentinel System. Based on an evaluation of the potential safety concern, FDA may take regulatory action(s) to improve product safety and protect the public health, such as updating a product's labeling information, restricting the use of the drug, communicating new safety information to the public, or, in rare cases, removing a product from the market.

− Who sends reports to FAERS?

Healthcare professionals, consumers, and manufacturers submit reports to FAERS. FDA receives voluntary reports directly from healthcare professionals (such as physicians, pharmacists, nurses and others) and consumers (such as patients, family members, lawyers and others). Healthcare professionals and consumers may also report to the products' manufacturers. If a manufacturer receives a report from a healthcare professional or consumer, it is required to send the report to FDA as specified by regulations.

− How can I report an adverse event or medication error to FDA?

The MedWatch website provides information about voluntary and mandatory reporting.

− Can mandatory reporters submit adverse events electronically?

Yes, the FDA Adverse Events Reporting System (FAERS) Electronic Submissions website provides drug and therapeutic biological product manufacturers, distributors, packers, and other interested parties with information about FDA Adverse Event Reporting System (FAERS) electronic submissions and instructions on how to electronically submit post-marketing individual case safety reports (ICSRs), with and without attachments.

− Does FAERS data have limitations?

Yes, FAERS data does have limitations. First, there is no certainty that the reported event (adverse event or medication error) was due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Furthermore, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. There are also duplicate reports where the same report was submitted by a consumer and by the sponsor. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population. For more information, please refer to the question What points should I consider while viewing the dashboard content?

− Is FAERS data available to the public?

FAERS data is available to the public in the following ways:

- FAERS dashboard: a highly interactive web-based tool that allows for the querying of FAERS data in a user friendly fashion.
- FAERS data files: provides raw data consisting of individual case safety reports extracted from the FAERS database. A simple search of FAERS data cannot be performed with these files by persons who are not familiar with the creation of relational databases.
- Individual case safety reports from the FAERS database can also be obtained by sending a Freedom of Information (FOI) request to FDA.

– How do I find or confirm my report is in FAERS?

To confirm that your report is in FAERS, please send a Freedom of Information (FOI) request to FDA.

– What are the benefits of the FAERS public dashboard?

This tool makes the data easier to query and produces user-friendly information and charts. For example, users can view a summary of adverse event reports received from 1968 to the present or for a specific timeframe. In addition, users can search for products or reactions of interest within a specific timeframe.

– Will there be a tutorial so I can learn how to use this database?

Yes, a recorded webinar is available which reviews the capabilities, and limitations, of the FAERS public dashboard.

Please note that a new webinar addressing the version 2.0 updates to the FAERS Public dashboard will be available soon.

– Is the FAERS public dashboard accessible on an Android™ or iPhone®?

Yes, but the user interface layout may not be very user friendly. FDA will continue to work on the dashboard to make the user interface Android and iPhone friendly.

– Can I download my search results from the dashboard?

Yes, you will be able to export a limited set of search data to an Excel® spreadsheet and then download it. FDA will still continue to provide the FAERS Latest Quarterly Data Files online.

– Where else can I find safety information?

- Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS): quarterly reports on potential serious side effects identified by FAERS.
- Post-marketing Drug and Biologic Safety Evaluations: provides summary information about ongoing and completed post-marketing safety evaluations of adverse experience reports made to FDA for New Drug Applications (NDAs) and Biologic License Applications (BLAs) approved since September 27, 2007.
- Center for Drug Evaluation and Research (CDER): Drug Safety and Availability
- Post-market Drug Safety Information for Patients and Providers
- MedWatch: The FDA Safety Information and Adverse Event Reporting Program

– How are versions of a case in FAERS handled?

Each unique submission of a case received is assigned a version number (for example, Case #1234567, version 1). The initial version received will be version 1. If a follow up is received on a previously submitted case, then that version of the case will be version 2, and so on. The latest version of a case represents the most current information about that case.

– How frequently is the data in the FAERS public dashboard updated?

The data is updated quarterly. Dates for upcoming dashboard updates are shown below:

Quarter	Estimated data update
Q1 – 2019 (January – March)	*Updated on 8-May-2019*
Q2 – 2019 (April – June)	*Updated on 1-Aug-2019*
Q3 – 2019 (July – September)	*Updated on 7-Nov-2019*
Q4 – 2019 (October – December)	*Updated on 5-Feb-2019*
Q1 – 2020 (January – March)	*Updated on 30-Apr-2020*
Q2 – 2020 (April – June)	*Updated on 4-Aug-2020*
Q3 – 2020 (July – September)	*Updated on 17-Nov-2020*
Q4 – 2020 (October – December)	*Updated on 29-Jan-2021*
Q1 – 2021 (January – March)	*Updated on 10-May-2021*
Q2 – 2021 (April – June)	*Updated on 3-Aug-2021*
Q3 – 2021 (July – September)	*Updated on 4-Nov-2021*
Q4 – 2021 (October – December)	*Updated on 15-Feb-2022*
Q1 – 2022 (January – March)	*Updated on 2-May-2022*
Q2 – 2022 (April – June)	*Updated on 1-Aug-2022*
Q3 – 2022 (July – September)	*Updated on 4-Nov-2022*
Q4 – 2022 (October – December)	*Updated on 30-Jan-2023*
Q1 – 2023 (January – March)	*Updated on 27-Jan-2023*
Q2 – 2023 (April – June)	*Updated on 1-Aug-2023*
Q3 – 2023 (July – September)	*Updated on 2-Nov-2023*
Q4 – 2023 (October – December)	*Updated on 23-Jan-2024*
Q1 – 2024 (January – March)	*Updated on 22-Apr-2024*
Q2 – 2024 (April – June)	*Updated on 30-Jul-2024*
Q3 – 2024 (July – September)	*Updated on 30-Oct-2024*

Q4 – 2024 (October – December)	*Updated on 28-Jan-2025*
Q1 – 2025 (January – March)	*Updated on 28-Apr-2025*
Q2 – 2025 (April – June)	30-July-2025

– What points should I consider while viewing the dashboard content?

When you view the website output of reported reactions (side effects or adverse drug reactions) for a drug product, it is important to consider the following points:

- **Data Quality:** There are many instances of duplicative reports and some reports do not contain all the necessary information. Duplicate reporting occurs when the same report is submitted by the consumer and the sponsor. The information in FAERS evolves daily and the number of individual cases may increase or decrease. It is therefore possible that the information on this website may change over time.
- **Existence of a report does not establish causation:** For any given report, there is no certainty that a suspected drug caused the reaction. While consumers and healthcare professionals are encouraged to report adverse events, the reaction may have been related to the underlying disease being treated, or caused by some other drug being taken concurrently, or occurred for other reasons. The information in these reports reflects only the reporter's observations and opinions.
- **Information in reports has not been verified:** Submission of a report does not mean that the information included in it has been medically confirmed nor is it necessarily a conclusion from the reporter that the drug caused or contributed to the event.
- **Rates of occurrence cannot be established with reports:** The number of suspected reactions in FAERS should not be used to determine the likelihood of a side effect occurring. The FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, information in these reports cannot be used to estimate the incidence (occurrence rates) of the reactions reported.
- **Patients should talk to their doctor** before stopping or changing how they take their medications.
- **Patient Outcomes received in FAERS**: These data describe the outcome of the patient as defined in U.S. reporting regulations (21 CFR 310.305, 314.80, 314.98, 600.80). Serious means that one or more of the following outcomes were documented in the report: death, hospitalization, life-threatening, disability, congenital anomaly, and/or other serious outcome. Documenting one or more of these outcomes in a report does not necessarily mean that the suspect product(s) named in the report was the cause of the outcomes.

Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug.

Back to top

Data Questions

– How do I know if a side effect I saw on the dashboard is related to the drug I was taking?

The best sources of information for the known side effects of a drug are the FDA approved product information (also known as full prescribing information or US package insert) and your health care provider. This dashboard tells you what was reported to the FDA, but it is difficult to know what caused a particular event in a particular patient from the information on the dashboard. Even if a symptom is a known side effect for a drug, it can be difficult to know if the symptom that a patient had was caused by a particular drug, since there may be other possible causes as well. For example, some medications cause headaches, but many people have headaches even when they aren't on any medications.

– If an adverse event wasn't caused by a drug, what could have caused it?

Although some adverse events can be caused by a drug, there are also other possible explanations for symptoms that appear while a patient is taking a drug. For example, the adverse event could be related to a disease that a patient already has, something in the environment, diet, or sleep habits, to name a few, could cause symptoms that could be misinterpreted as adverse events caused by a drug.

– Is every adverse event reported with a drug on the dashboard caused by the drug?

Although it is difficult to generalize, it is unlikely that every adverse event reported for a given drug was caused by that drug.

– Are drugs with fewer side effects reported to the dashboard safer than those that have a higher number of side effects reported?

The FAERS dashboard should not be used to determine the safety profile of one drug compared to another. Even identical drug products can have widely differing levels of adverse event reporting due to the voluntary nature of the reporting system.

– How should reports of death be interpreted?

The same caution that applies to all of the FAERS reports should be applied to death reports. The existence of a death report in the FAERS dashboard does not mean that the drug caused the person to die. Fatal outcome could be from the natural progression of the disease being treated.

– Does the FAERS Dashboard have all the side effects that have occurred with a drug?

No. The FAERS database contains only a small fraction of the side effects that occur with a drug. This is due to a variety of reasons. Most importantly, there is no requirement for healthcare professionals and consumers to report side effects to either the FDA or to the manufacturer. Even for side effects that have been reported to the manufacturer, only certain categories of adverse events are required to be submitted to the FDA. Lastly, there are a variety of factors that can cause more or less reporting to both the FDA and manufacturers, including whether a particular side effect is known for a drug, how long a drug has been on the market and even whether there have been recent news reports about possible side effects for a given drug or a group of drugs.

– What is the difference between an adverse event, a side effect, and an adverse drug reaction?

An adverse event (AE) is any symptom that occurs while taking a drug, which may or may not have been caused by the drug. This is different from an adverse drug reaction (ADR), where there is specific evidence that the AE is related to the drug. A side effect is the same as an ADR. As a result, ADR is always an AE, but an AE may or may not be an ADR.

– Should I discontinue a prescription drug I'm taking if I think that it's causing an adverse event?

You should always check with your healthcare provider before discontinuing any medication that you have been prescribed.

– I looked up a drug that I am taking on the FAERS dashboard and the list of adverse events includes deaths. What should I do?

You should check with your healthcare provider if you have any concerns about a medication that you are taking. You and your healthcare provider should decide if the potential benefits of you taking a particular drug outweigh its potential risks as well as the risks of an illness being left untreated.

– Where can I find the safety profile of the drug?

Please consult with your health care provider to discuss the safety profile and the overall benefit-safety balance of the drug.

– After the data refresh for Q4 2021, why do I now see reduced counts in the Home page for previous time periods (Q3 2021 and older)?

The **Home** page displays the count of reports received each year and quarter by the FDA. This includes both initial and follow-ups reports submitted in FAERS.
In Q4 2021, the FAERS system was modernized and the data was migrated to a new database. The new database handles deletion of report submissions slightly differently compared to the previous system. Whenever a case is deleted, the previous system deleted only the latest follow-up report for the case and left the older reports in the case untouched. As a result, the counts displayed in the **Home** page included older reports for deleted cases. However, in the new FAERS database currently in use, all reports (initial and follow-ups) for a case are deleted upon the deletion of a case. Because of this, the counts of reports displayed in the **Home** page are now reduced compared to previous iterations of the FAERS Public Dashboard.

As an example, the comparison below highlights the difference in counts of reports for Q1 2021 before and after the data refresh for Q4 2021.

Q1 2021 report count before the data refresh for Q4 2021:

Reports received by Report Type

Quarter	Report Type Total Reports
Total Reports	1,801,429
Q1 2021	587,876
Q2 2021	593,598
Q3 2021	619,955

Q1 2021 report count after the data refresh for Q4 2021:

Reports received by Report Type

Quarter	Report Type	Total Reports
Total Reports		2,333,453
Q1 2021		581,801
Q2 2021		591,197
Q3 2021		617,295
Q4 2021		543,160

Back to top

Technical Questions

− Which internet browsers can I use to access the dashboard?

You can use any of the following internet browsers to access and view the dashboard:
Microsoft Internet Explorer 11, Microsoft Edge, Google Chrome, Mozilla Firefox, Apple Safari.

− What is the recommended screen resolution for viewing the dashboard?

For the best dashboard viewing experience, the recommended screen resolution for your desktop or laptop is 1920x1080.

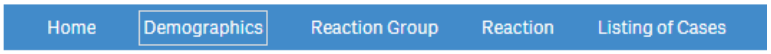
− How do I navigate through different sheets of the dashboard?

You may use the navigation bar on the top of the dashboard to navigate through different sheets. Depending on the sheet you are currently viewing, you may see different options to select in the navigation bar.

When viewing the “Home” or “Search” sheets, you will see the options shown below in the navigation bar.



When viewing any other page in the dashboard after searching for a product, you will see the options shown below.

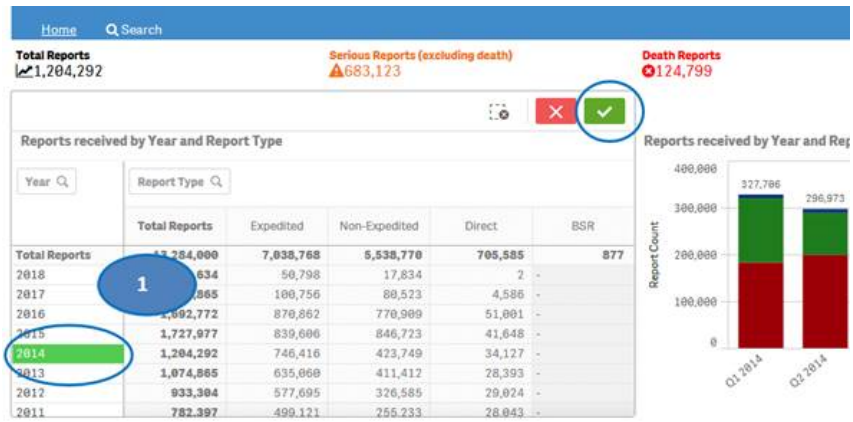


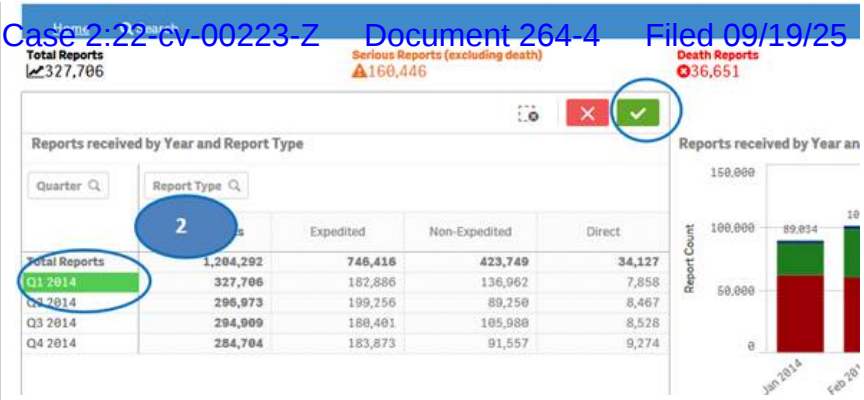
− How can I view report statistics for quarters and months of a specific year?

The “Home” sheet displays report statistics for all the years by default. But you may view report statistics for quarters and months of any specific year. You can view statistics for quarters of only one year at time. You can view statistics for months of only one quarter at a time.

1. Click on any year in the table or chart and confirm selection to view statistics for the year by quarters.
2. Then select any quarter by clicking on it to view statistics for the months of the selected quarter.
3. Clear the selected quarter to go back to view statistics by quarters.
4. Clear the year selection to go back to view statistics for all year.

Note: If a year has just one quarter of data, selecting the year will directly display months for the year without displaying quarters.





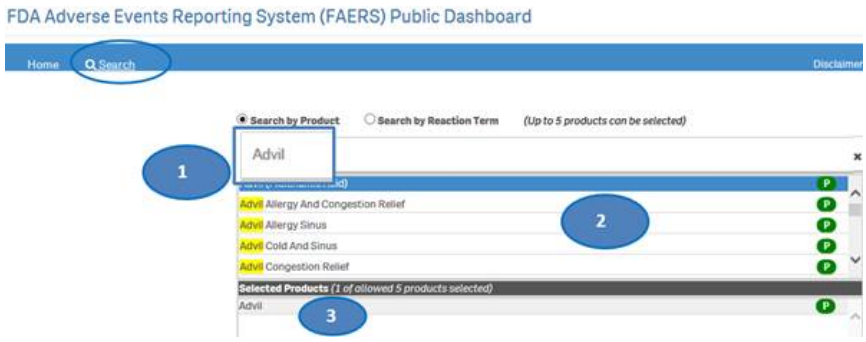


[–] How do I search for cases for a product or products?

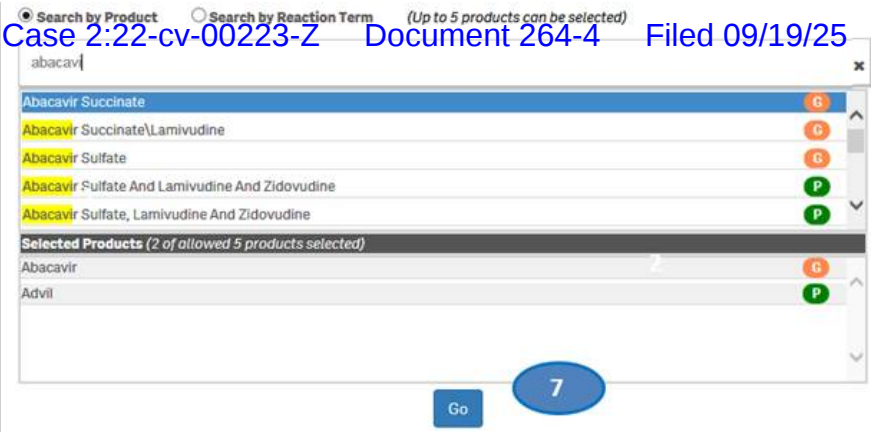
After accepting the disclaimer, click on the “Search” option and then:

1. Type a product value in the search bar.
2. Click or double-click on a desired value from the list of values to select it.
3. The selected product will be displayed under the list “Selected Products”.
4. To clear the search text, click on the ‘X’ button in the right corner of the search bar.
5. If you want to add more products to your search, repeat the steps above for the products you are interested in. You may select up to five products for your search.
6. If you want to deselect a product you have already selected, click or double-click on the product you want to deselect from the list “Selected Products”.
7. Once you have selected all the products you want to search for, click on the “Go” button.

Please note that you can select no more than five products at a time for your search.







– Can I search for generic products as well as specific trade names?

es. You can search for a generic product or a specific trade name by simply typing the name in the search bar. The search box pop-p includes icons to indicate whether a suggested product is a trade name or a generic product based on FDA's internal product ctionary.

- P indicates that the suggested value is a product name or trade name.
- G indicates that the suggested value is a generic product.



– How can I change my product search?

f you have already done a product search, the navigation bar will display a search box where you can type in and select new products or your search.



Back to top

– Does FAERS include over-the-counter (OTC) or just prescription drugs?

FAERS includes both OTC and prescription drugs.

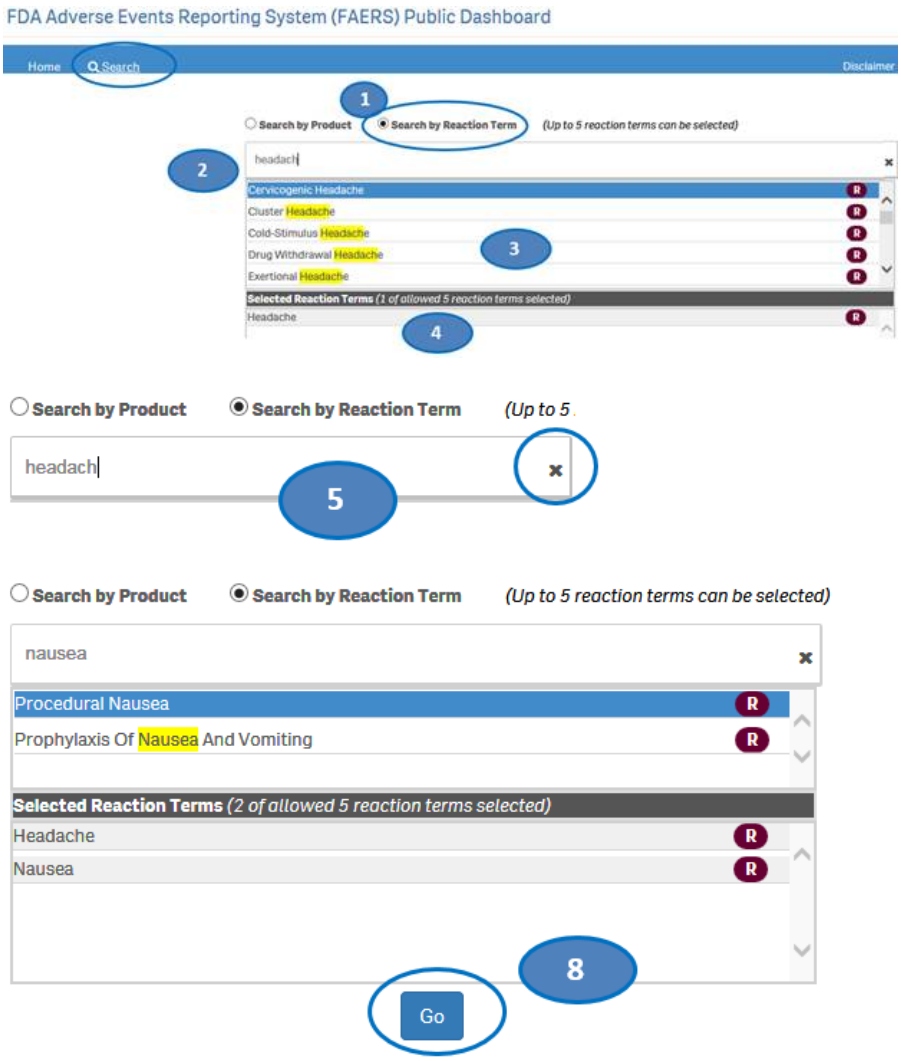
– How can I search for cases for specific side effects/reactions?

From the "Home" sheet, click on the "Search" option and then:

1. Select option "Search by Reaction Term".
2. Type a reaction term value in the search bar.
3. Click or double-click on a desired value from the list of values to select it.
4. The selected reaction term will be displayed under the list "Selected Reactions".
5. To clear the search text, click on the 'X' button in the right corner of the search bar.
6. If you want to add more reactions to your search, repeat the steps above for the reactions you are interested in. You may select up to five reactions for your search.

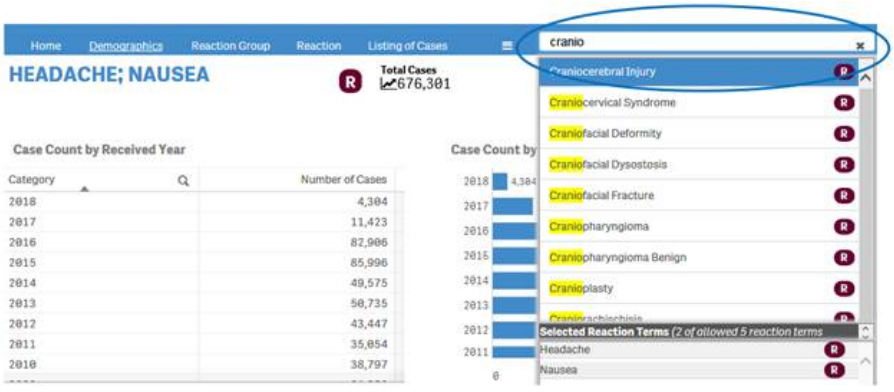
7. If you want to deselect a reaction you have already selected, click or double-click on the reaction you want to deselect from the list "Selected Reaction Terms".
8. Once you have selected all the reactions you want to search for, click on the "Go" button.

Please note that you can select no more than five reaction terms at a time for your search.



How can I change my reaction search?

If you have already done a reaction search, the navigation bar will display a search box where you can type in and select new reactions for your search.



What can I search for using the search box in the navigation bar?

Depending on your initial search, you can use the search box in the navigation to search for either products or reactions terms.

If your initial search in the "Search" sheet was based on product(s), you can only search for products in the search box of the navigation bar.

If your initial search in the “Search” sheet was based on reaction term(s) you can only search for reaction terms in the search box of the navigation bar.

– How many products or reactions can I search for at a time?

You can select up to five products or reactions at a time for a search.

Note: This restriction is applicable for products and reactions only. Multiple value selections can be made for all other data elements such as sex, country, and outcomes.

– Does the “Search” sheet allow selecting products and reactions for the same search?

No, the search sheet allows you to select either products or reactions for your search but not both. For example, if you select specific products using the “Search by Product” option and then choose the “Search by Reaction Term” option, the products you have selected will be removed from the search.

You may, however, filter for products and reactions after your initial search in subsequent sheets.

– How can I view the distribution of report or case counts for different parameters?

To view distribution of counts for different parameters, click on the drop-down menu on the top right corner of a sheet and select the desired option.



– Can I view charts and tables in full screen mode? How do I exit from full screen mode?

When you hover over any chart or table, a  symbol is displayed on the right top corner of the chart or table. Clicking on this icon will enable you to view the chart or table in full screen mode. To exit the full screen mode, click the X on the top right corner of the chart or table.

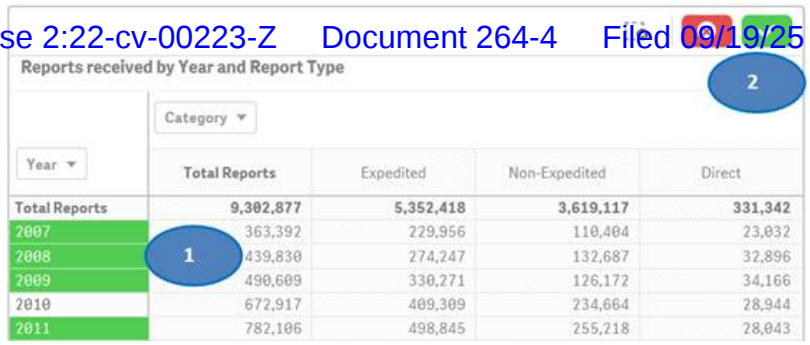
– Can I filter data in charts and tables?

Yes, the dashboard provides extensive filtering capabilities on both charts and tables.

Note: When you apply filters on a table or chart within the “Home” sheet, the filters will be applied only on charts and tables in this sheet. Conversely, when you apply filters on tables or charts in any other sheet, after searching for a product, the filters will be applied on all sheets except for the “Home” sheet.

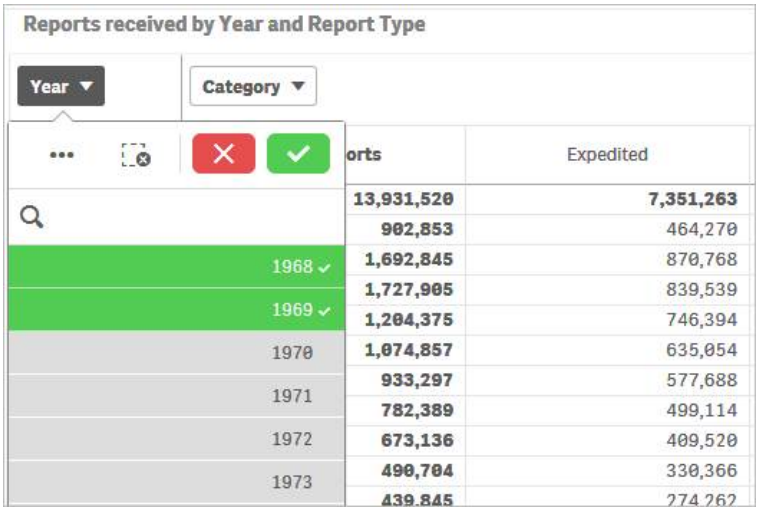
To filter data in a table, for example, filtering by year, there are two options:
Option 1:

1. Click on one or multiple columns or rows. You may also click and drag multiple rows or columns to select them for filtering data.
2. Click on the  icon to confirm your selection.



Option 2:

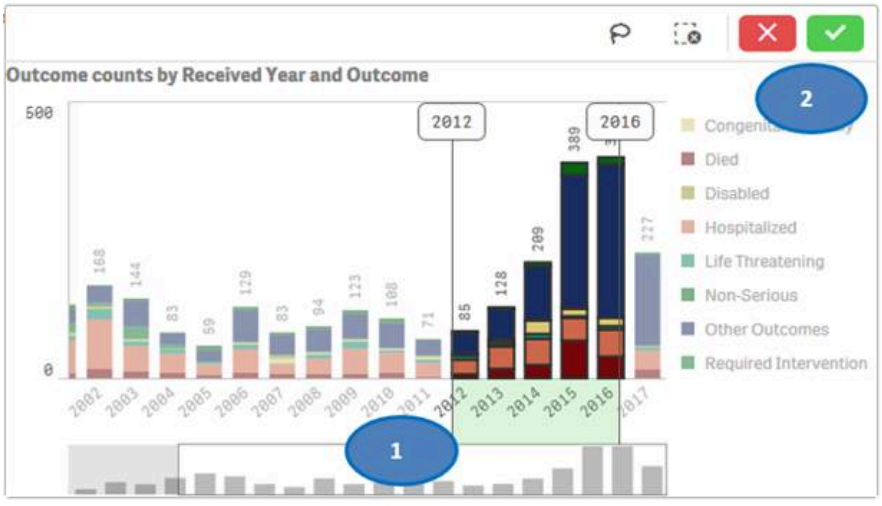
You may also use drop-downs (also known as filter panes) displayed on top of the rows or columns to choose your values for filtering. Please see screenshot below which shows how to select specific years for filtering.



To filter data in a chart, for example, filtering by year, there are two options:

Option 1:

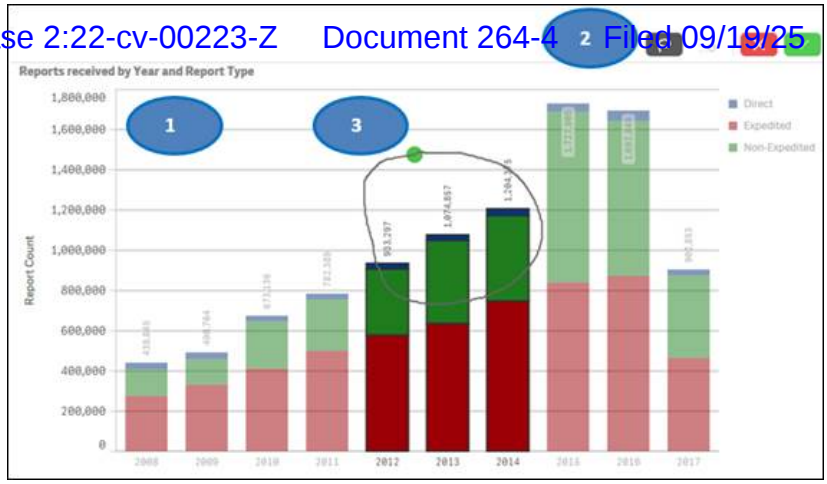
1. Click on one or multiple bars in the chart or items in the chart legend. You may also click and drag multiple bars to select them for filtering data.
2. Click on the ✓ button to confirm your selection.



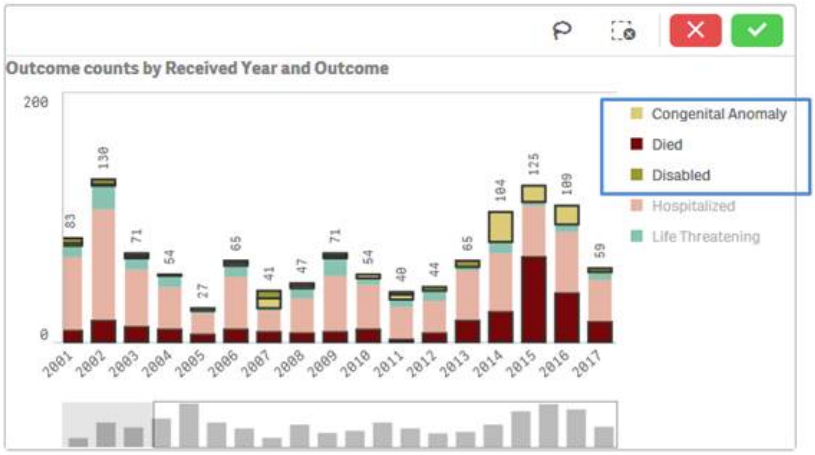
Option 2:

You may also use “lasso selection tool” to select multiple values from the chart. To use this feature:

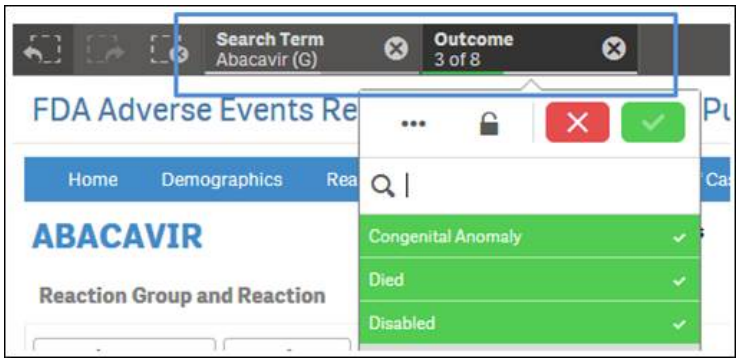
1. Click anywhere on the chart.
2. Click on the lasso icon.
3. Click and drag to draw on the chart and select the bars you want to use for filtering.



You may also select values from a chart's legend for filtering by clicking on the values.

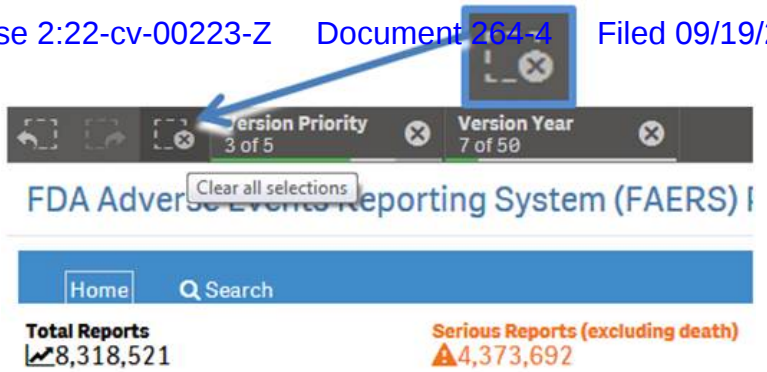


Note that the applied filters show up on the top selection bar.



− How do I reset selected search criteria and remove all filters?

On the top left side of every sheet, you can see the icon shown below, with a dotted lined square with an "X" on it. Click the icon to clear any product you have selected for searching and all selected values used for filtering.



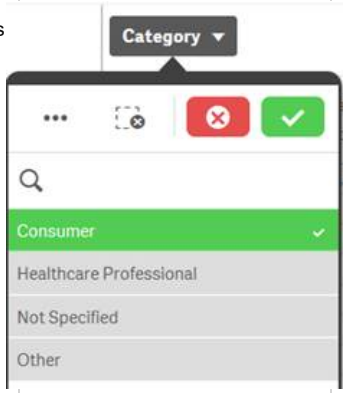
– Can I extract or download dashboard data?

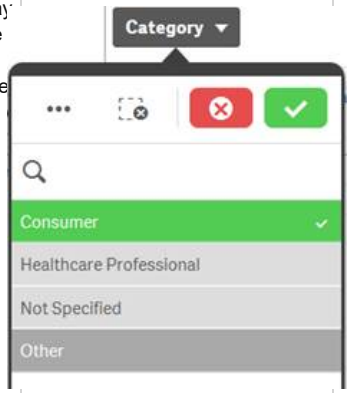
Yes, you may export or download dashboard data. Right-click on any table or chart in the dashboard and click on the “Export” option. You may choose from the following three options for exporting and downloading data:

1. Export as an image: This option will export a snapshot of the table or chart that you are viewing to an image file.
2. Export to PDF: This option will export a snapshot of the table or chart that you are viewing to a PDF file.
3. Export data: This option will export the underlying data of the table or chart that you are viewing to a Microsoft Excel (.xlsx) file. This option is explained in more detail in the final question of the FAQs below.

Back to top

– When using filter panes (or drop-downs) for filtering, I have noticed that different colors are used to highlight different values. What do these colors indicate?

Action	Color Code	Description	Screenshot
Selected	Green, with a check mark as a selection indicator	When you select one or more values in a filter pane and the values turn green, they are in the selected state. In the example screenshot, the value “Consumer” has been selected.	
Possible	White	In the screenshot of the “Category” filter pane for “Reporter Region”, the values “Domestic” and “Foreign” are white (possible), because selecting these values will return data. You could refine your data set by selecting one or more of these possible values.	

Action	Color Code	Description	Screenshot
Alternative	Light gray	Selecting a light gray value will add to the previously selected value to broaden the filtering.	
Excluded	Dark gray	Dark gray value indicates that there is no data for the specific value based on other filters that have already been applied to the data. Caution: Selecting a dark gray value: • May clear some or all other existing filters and apply that value as the new filter. • May cause the selected product to be removed. If that happens, restart your search using the Search for Product option in the navigation bar.	

– Can I use the dashboard without accepting the disclaimer?

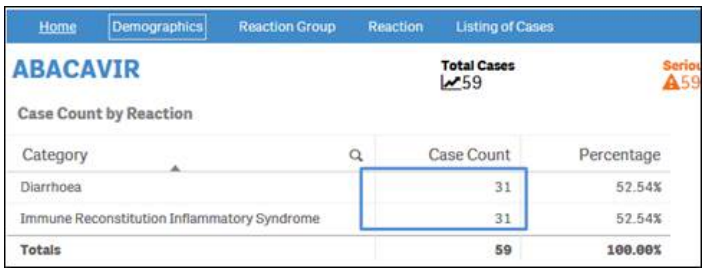
No. You will not be able to view any data in the dashboard without accepting the disclaimer.

– How recent is the data in the dashboard?

Data in the FAERS Public Dashboard is as of March 31, 2025. Data is updated quarterly.

– Why does the sum of case counts for individual reactions not add up to the overall case count for the product?

Each case might have more than one reaction term. Therefore, the sum of the case counts for individual reactions may be same or more than the total count of distinct cases.



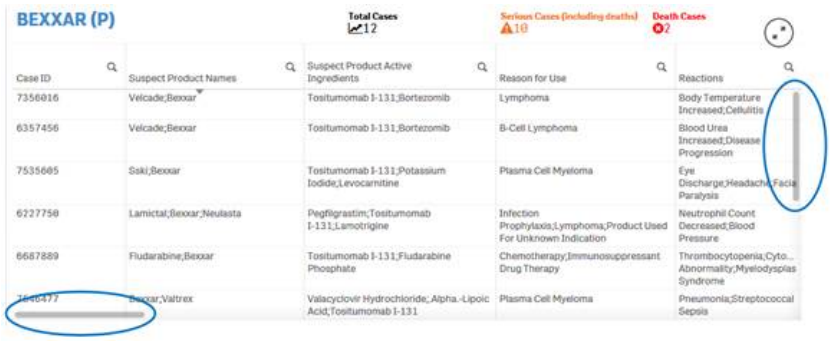
– Why does the sum of individual outcome counts not add up to the overall count for the product?

Each case might have more than one outcome. Therefore, the sum of counts for individual outcomes may not match the total count of distinct cases.

– How do I scroll in the “Listing of Cases” table?

The “Listing of Cases” table allows you to scroll vertically or horizontally using vertical and horizontal scroll bars respectively. To view the scroll bars, hover over the listing of cases table.

- Scroll up or down in the Listing of Cases table using the vertical scroll bar on the right side of the table. This will allow you to see all the rows in the table.
- Scroll to the left or right in the Listing of Cases table using the horizontal scroll bar on the bottom of the table. This will allow you to see all the columns in the table.



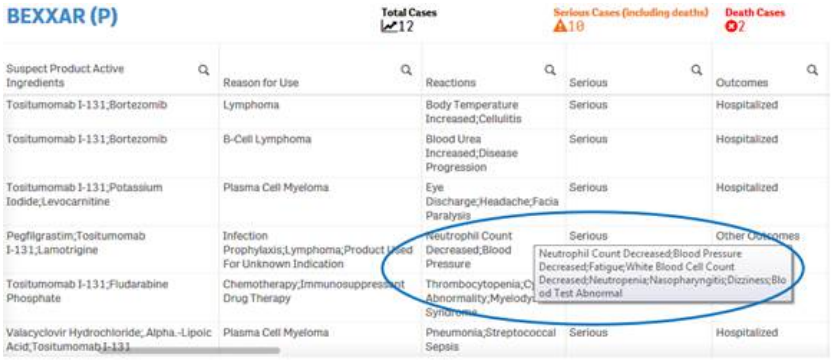
– Can I rearrange columns in the “Listing of Cases” table?

Yes, you may rearrange columns by dragging and dropping column headers anywhere in the table. To move a particular column:

1. Click and hold on the column header.
2. Drag it next to a column you want to move it to and release the click.

– Some of the cells seem to be showing only partial data. How can I see the entire content of such cells?

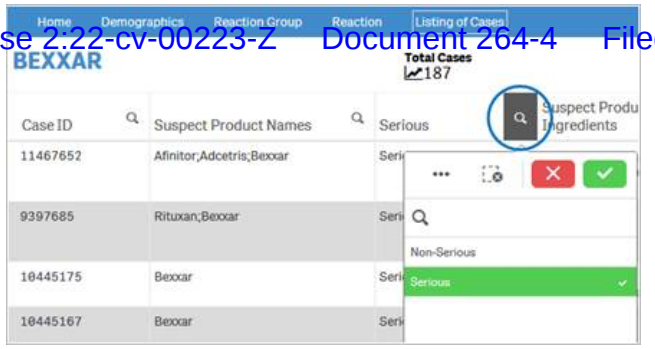
Due to space constraints, some cells display only partial data. To view the entire content of any cell, simply hover over the cell with your mouse. The entire content of the cell appears in a pop-up.



– How do I filter and sort data in the “Listing of Cases” table?

You can filter and sort data in the table using any column or any value in a cell. To filter using a value in cell, simply click on the cell.

The table is refreshed with the filtered data. To filter using a column, click on the 🔍 icon next to the column header, and then select from the list of values for that column.



To sort data using a specific column, simply click on the column header. Click once on the column header to view data in ascending order. Click again on the column heading to sort the values in descending order.

– How do I download data from the “Listing of Cases” table?

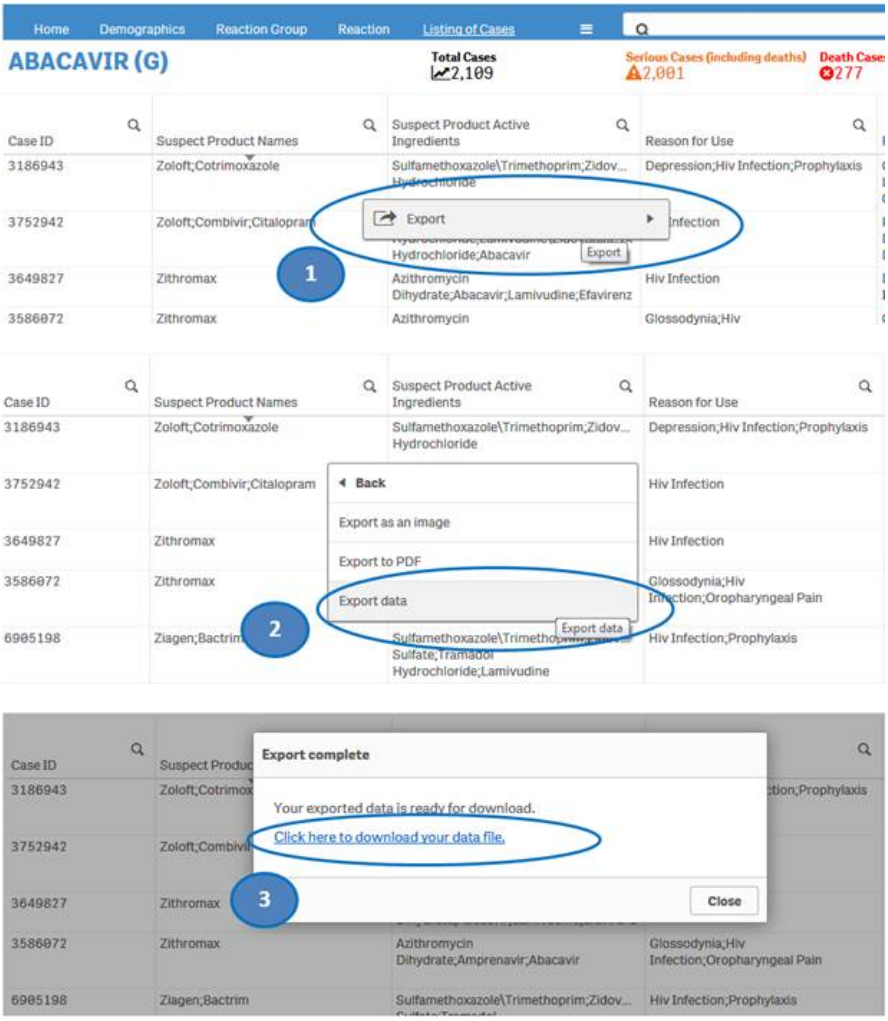
You can download data from the “Listing of Cases” table to a Microsoft Excel (.xlsx) file by using the “Export data” option.

Note: The “Listing of Cases” table provides a limited set of columns for case data. If you require a more comprehensive data set for download, you may download FAERS (FDA Adverse Events Reporting System) Quarterly Data files.

The data displayed in the FAERS Public Dashboard may not be identical to the data in the FAERS Quarterly Data files due to several reasons. Please refer to the Data Questions section for more information.

To download data from the “Listing of Cases” table:

1. Right-click anywhere on the “Listing of Cases” table and click on “Export”.
2. Select “Export data” option.
3. Then click on “Click here to download your data file” to save the file to your machine.



Back to top

EXHIBIT 53

Kathi A. Aultman et al.,
Deaths and Severe Adverse Events After the Use of Mifepristone as an Abortifacient from September 2000 to February 2019,
26 Issues in L. & Med., no. 1,
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Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019

Kathi A. Aultman M.D.,[*] Christina A. Cirucci M.D., Donna J. Harrison M.D.,[**] Benjamin D. Beran M.D.,[***] Michael D. Lockwood D.O.,[****] Sigmund Seiler M.D.[*****]

ABSTRACT: *Objectives:* Primary: Analyze the Adverse Events (AEs) reported to the Food and Drug Administration (FDA) after use of mifepristone as an abortifacient. Secondary: Analyze maternal intent after ongoing pregnancy and investigate hemorrhage after mifepristone alone.

***Methods*: Adverse Event Reports (AERs) for mifepristone used as an abortifacient, submitted to the FDA from September 2000 to February 2019, were analyzed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAEv3).**

***Results*: The FDA provided 6158 pages of AERs. Duplicates, non-US, or AERs previously published (Gary, 2006) were excluded. Of the remaining, there were 3197 unique, US-only AERs of which there were 537 (16.80%) with insufficient information to determine clinical severity, leaving 2660 (83.20%) Codable US AERs (Figure 1). Of these, 20 were Deaths, 529 were Life-threatening, 1957 were Severe, 151 were Moderate, and 3 were Mild.**

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The deaths included: 9 (45.00%) sepsis, 4 (20.00%) drug toxicity/ overdose, 1 (5.00%) ruptured ectopic pregnancy, 1 (5.00%) hemorrhage, 3 (15.00%) possible homicides, 1 (5.00%) suicide, 1 (5.00%) unknown (Table 1).

Retained products of conception and hemorrhage caused most morbidity. There were 75 ectopic pregnancies, including 26 ruptured ectopics (includes one death).

There were 2243 surgeries including 2146 (95.68%) D&Cs of which only 853 (39.75%) were performed by abortion providers.

Of 452 patients with ongoing pregnancies, 102 (22.57%) chose to keep their baby, 148 (32.74%) had terminations, 1 (0.22%) miscarried, and 201 (44.47%) had unknown outcomes.

Hemorrhage occurred more often in those who took mifepristone and misoprostol (51.44%) than in those who took mifepristone alone (22.41%).

***Conclusions*: Significant morbidity and mortality have occurred following the use of mifepristone as an abortifacient. A pre-abortion ultrasound should be required to rule out ectopic pregnancy and confirm gestational age. The FDA AER system is inadequate and significantly underestimates the adverse events from mifepristone.**

A mandatory registry of ongoing pregnancies is essential considering the number of ongoing pregnancies especially considering the known teratogenicity of misoprostol.

At the very least, the FDA should reinstate the original 2011 REMS and strengthen the reporting requirements.

***Conflict of Interest Statement*: The authors did not report any potential conflicts of interest. Authors note that although Dr. Harrison is an associate editor for Issues in Law and Medicine, she recused herself from any involvement in the peer review process for this manuscript.**

***Keywords*: Mifepristone, Mifeprex, RU-486, Misoprostol, Abortifacient, Medical Abortion, Abortion Pill, Medical Abortion Complications, No touch abortion, DIY Abortion, Self-Administered Abortion, Adverse Events, Adverse Event Reports, Post-marketing Surveillance, FAERS, Drug Safety, Emergency Medicine, FDA, REMS, Risk Evaluation Mitigation Strategy.**

Introduction

The application for mifepristone (RU-486, RU-38486, Mifeprex) as an abortifacient was submitted to the Food and Drug Administration (FDA) in 1996 by the Population Council, which was given the manufacturing and distribution rights from Roussel Uclaf. [1] The Population Council partnered with Danco Laboratories, newly created in 1995, and gave them the manufacturing, marketing, and distribution rights. The FDA approved mifepristone in September 2000 under restricted distribution regulations (Subpart H) due to the FDA's conclusion that restrictions "on the distribution and use of mifepristone are needed to ensure safe use of this product."[2]

Included in these restrictions was the requirement that all serious Adverse Events (AEs), after the use of mifepristone as an abortifacient, be reported to the FDA by Danco as part of post-marketing surveillance. According to the FDA,[3] the purpose of such post-marketing surveillance includes identification of potential risks recognized after the time of approval, identification of unexpected deaths, causal attribution of AEs based on the product's known pharmacological action, and AEs for which a Risk Evaluation Mitigation Strategy (REMS) is intended to mitigate the risk.

In 2006, in response to the deaths of 4 women from a rare bacterial sepsis from *Clostridium sordellii (C. sordellii)*, the FDA and CDC convened a workshop, during which mifepristone alteration of the immune system was detailed, and they concluded that such alteration could lead to impaired ability to respond to *C. sordellii* toxin.[4]

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[1] Citizen petition re: Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Day's Gestation Final. Before the Department of Health and Human Services: Food and Drug Administration. AAPLOG. 2002. 7-10. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/Documents/2002%20Aug%2020%20Citizen%20Petition_Mifeprex.pdf

[2] Center for Drug Evaluation and Research. Approval Letter for Mifeprex NDA 20-687. February 18, 2000. Food and Drug Administration. p 5. Accessed November 16, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687approvable00.pdf

[3] US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff. November 2019. p 7-8. Accessed Jan 16 2021. https://www.fda.gov/media/130216/download p7-8

[4] Emerging Clostridial Disease Workshop: May 11, 2006, Atlanta, GA. Department of Health and Human Services, Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health. 2006. p. 109,110. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2006%20CDC%20FDA%20Clostridial%20Disease%20Transcript.pdf

There is evidence that both mifepristone[5,6,7] and misoprostol[8] can suppress immune response to *C. sordellii* in animal models.

In response to the septic deaths, Planned Parenthood changed their off-label protocol from vaginal administration of misoprostol to buccal in 2006.[9,10] Yet, as we found in our analysis, sepsis deaths from *C. sordellii* and other bacteria continued to occur after 2007. All sepsis deaths occurred with either vaginal or buccal misoprostol, which were both off label routes of administration until the buccal route was authorized in 2016.[11]

In 2011, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for Mifepristone incorporating the original restrictions.[12] In May 2015, Mifepristone's sponsor submitted a supplemental new drug application to the FDA to obtain approval to revise the drug's labeling, which the FDA approved in 2016.[13,14] The 2016 changes in the Regimen and Prescriber Agreement extended the original gestational age limit from 49 days to 70 days, changed the mifepristone dose from 600 mg to 200 mg orally, changed the misoprostol dose from 400 mcg orally on Day 3 to 800 mcg buccally on Day 2 or 3, allowed non-physicians to become prescribers, reduced the number of required office visits from 3 to just one initial office visit, and allowed a repeat dose of misoprostol if complete expulsion did not occur.[15] The prescriber agreement was changed so

[5] Emerging Clostridial Disease Workshop: May 11, 2006, Atlanta, GA. Department of Health and Human Services, Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health. 2006. p. 109, 110 Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2006%20CDC%20FDA%20Clostridial%20Disease%20Transcript.pdf

[6] Webster JI, Sternberg EM. Role of the hypothalamic-pituitary-adrenal axis, glucocorticoids and glucocorticoid receptors in toxic sequelae of exposure to bacterial and viral products. J Endocrinol. 2004;181(2):212, 213, 216, 217. doi.org/10.1677/joe.0.1810207

[7] Hawes AS, Rock CS, Keogh CV, Lowry SF, Calvano SE. In vivo effects of the antiglucocorticoid RU 486 on glucocorticoid and cytokine responses to Escherichia coli endotoxin. Infect Immun. 1992;60(7):2645, 2646. doi:10.1128/IAI.60.7.2641-2647.1992

[8] Aronoff DM, Hao Y, Chung J, et al. Misoprostol impairs female reproductive tract innate immunity against Clostridium sordellii. J Immunol. 2008;180(12):8227-8229. https://doi.org/10.4049/jimmunol.180.12.8222

[9] Trussell, J, Nucatola, D, Fjerstad, M, Lichtenberg, ES. Reduction in infection-related mortality since modifications in the regimen of medical abortion. Contraception, 2014;89(3):193-196. https://doi.org/10.1016/j.contraception.2013.11.020

[10] Fjerstad M, Trussell, J, Sivin, I, Lichtenberg, ES, Rates of Serious Infection after Changes in Regimens for Medical Abortion. N Engl J Med. 2009 July 9;361(2):148-149. July 9, 2009 N Engl J Med 2009; 361:145-151. doi:10.1056/NEJMoa0809146

[11] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[12] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2011. 1-11. Reference ID: 2957855. Published June 8, 2011. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2011-06-08_Full.pdf

[13] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 1. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[14] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. 1-8. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf

[15] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p.7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

that instead of being required to "report any hospitalization, transfusion or other serious event to Danco Laboratories,"[16] providers were only required to report deaths.[17] The requirement to report ongoing pregnancies that are not terminated was also eliminated. "The FDA approved GenBioPro, Inc.'s abbreviated new drug application (ANDA) for generic Mifeprex on April 11, 2019" and "established a single, shared system REMS for mifepristone products" without substantially changing the REMS.[18]

During the COVID-19 pandemic the Maryland District Court issued a preliminary injunction prohibiting the FDA from enforcing the in-person dispensing and signature requirements contained in the mifepristone REMS.[19] This decision eliminated the need for an initial office visit for dispensing the medication and opened the door for dispensing of the drug via telehealth with no actual clinician contact. On January 12, 2021, the Supreme Court enabled the FDA to enforce the mifepristone REMS.[20] These requirements are essential for the safety of women and must be kept in place.

The first systematic analysis of these Adverse Event Reports (AERs) obtained by the Freedom of Information Act (FOIA), was published by Gary and Harrison in 2006.[21] This paper extends that analysis to AERs not previously published and augments the scant published literature on mifepristone safety.

Objectives

Primary: To analyze and codify the significant adverse events and their treatment after the use of mifepristone as an abortifacient, extending the previously published analysis by Gary in 2006.[22] Secondary: To examine maternal decisions in the case of ongoing pregnancy after attempted mifepristone termination, and to determine if failing to take misoprostol after mifepristone increased the risk of hemorrhage.

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[16] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2011. p. 7. Reference ID: 2957855. Published June 8, 2011. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2011-06-08_Full.pdf

[17] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. p. 6. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf

[18] Questions and Answers on Mifeprex. Food and Drug Administration. March 28, 2018. Updated 4-12-2019. Accessed November 13, 2020. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifeprex

[19] American College of Obstetricians and Gynecologists, et al., v. Food and Drug Administration, et al., No. 20-1320, 2020 WL 3960625 (D. Md. July 13, 2020). Accessed November 16th, 2020. https://www.courthousenews.com/wp-content/uploads/2020/07/093111166803.pdf

[20] FDA v ACOG. SCOTUS. 20a34_3f14. Accessed January 20, 2021. https://www.supremecourt.gov/opinions/20pdf/20a34_3f14.pdf

[21] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[22] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

Materials and Methods

FDA AERs related to the use of mifepristone from September 2000 to February 2019 were obtained through the Freedom of Information Act (FOIA) from the FDA, and a comparison was made with FDA reports available online on the FDA Adverse Events Reporting System (FAERS) Dashboard.[23] Duplicate AERs were identified by comparing FDA case identification numbers, manufacturer identification numbers, dates of treatment, patient age, and descriptions of case scenarios to ensure that each case was included only once in this analysis. The authors excluded duplicates, cases originating outside of the United States, and cases previously published in the Gary analysis[24] (Figure 1).

One of the concerns in looking at AEs is the risk of falsely assigning causality. The FDA does not give guidance for determining causality for AEs in the AERs but does give guidance for selecting AEs for inclusion in the Adverse Reaction section of the Drug Label.[25] They recommend that, "Decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on factors such as" the "frequency of reporting," "the extent to which the adverse event is consistent with the pharmacology of the drug," "the timing of the event relative to the time of drug exposure," and other factors. Although a causal relationship cannot be attributed with certainty to all reported AEs for a drug, a causal relationship seems probable for each of the categories of AEs we chose to analyze based on these factors, except for ectopic pregnancies and some of the deaths. Ectopic pregnancies were included in our analysis not because there is a causal relationship, but because ectopic pregnancy is a contraindication to the use of mifepristone and the diagnosis was missed, putting women's lives at risk. The deaths must be evaluated individually to determine causality.

Because reporting is often voluntary and sporadic, there is no denominator for how many mifepristone abortions are performed in the U.S. It was therefore impossible to calculate complication rates for mifepristone and misoprostol abortions based on AER data. For clarity, we specified the denominator used in each case. Coding for severity was done using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAEv3),[26] since this was

[23] FDA Adverse Events Reporting System (FAERS) Public Dashboard. Food and Drug Administration. Accessed November 13, 2020. https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis

[24] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[25] Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); January 2006. P. 8. Accessed January 8, 2021. https://www.fda.gov/media/72139/download

[26] Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Cancer Center Therapy Evaluation Program (CTEP); 2003. 1-77. Published December 12, 2003. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/CTCAEv3.pdf

the methodology used in the original analysis of the first 607 Adverse Events.[27] The five levels of coding are: Mild, Moderate, Severe, Life-threatening, and Death.

Overall severity (Figure 1) for each unique AER was determined independently by two board-certified physicians (Obstetrics and Gynecology or Family Medicine). Since within each AER, a patient may have experienced several Adverse Events (AEs), the overall severity of the AER was based on the highest severity of its AEs. For the diagnoses we analyzed (Table 1), each AE was coded in the same manner and stratified according to type, severity, and treatment. Disagreements were resolved by discussion or review by a third board-certified Obstetrician-Gynecologist who also reviewed coding for uniformity. Surgeries, transfusions, providers, and location of treatment were analyzed and tabulated.

Ruptured ectopic pregnancies were coded as Life-threatening and unruptured ectopic pregnancies as Severe.

Infections were coded as Life-threatening when evidence of sepsis was present, or ICU-level treatment was required. They were coded as Severe if parenteral/IV antibiotics were given and Moderate if oral antibiotics were prescribed.

Life-threatening hemorrhage was defined, as in the previous analysis, to be transfusion of two or more units of packed red blood cells (PRBCs), hemoglobin less than 7, or documented large volume, rapid blood loss with clinical symptomatology of acute blood loss anemia (e.g., syncope, tachycardia, hypotension). Severe hemorrhage was defined as requiring surgical intervention and/or less than 2 U PRBCs. Moderate hemorrhage was defined as management with fluids/medication alone.

Retained Products of Conception (RPOC) was coded as Severe if a dilatation and curettage/evacuation (D&C) was performed. Ongoing viable intrauterine pregnancy was considered equivalent in severity to RPOC requiring curettage and thus Severe. When the ultimate outcome was unknown, the pregnancy was considered ongoing if "ongoing pregnancy" was noted or ultrasound showed cardiac motion or significant growth.

AEs which did not contain sufficient information to assign an accurate severity code were deemed "Uncodable." AERs lacking any codable information were deemed overall Uncodable.

The percent of women with significant hemorrhage after mifepristone alone was compared to those who took both mifepristone and misoprostol, to investigate the validity of the assertion that lack of subsequent misoprostol administration was a causative factor in hemorrhage after mifepristone use.[28]

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[27] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[28] Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progester-one to Prevent Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2020;135(1):158-165. doi:10.1097/AOG.0000000000003620

Results

Adverse Event Report Overall Severity

Figure 1 summarizes the handling of the AERs provided by the FDA and their severity coding. The FDA provided 6158 pages of AERs. Of these, any duplicates, non-US, or AERs previously published in the Gary paper were excluded from the analysis. There were 3197 unique, US-only AERs of which 537 had insufficient information to determine clinical severity, leaving 2660 Codable US-only AERs. Of these, 20 were Deaths, 529 were Life-threatening, 1957 were Severe, 151 were Moderate, and 3 were Mild.

Deaths (Table 1)

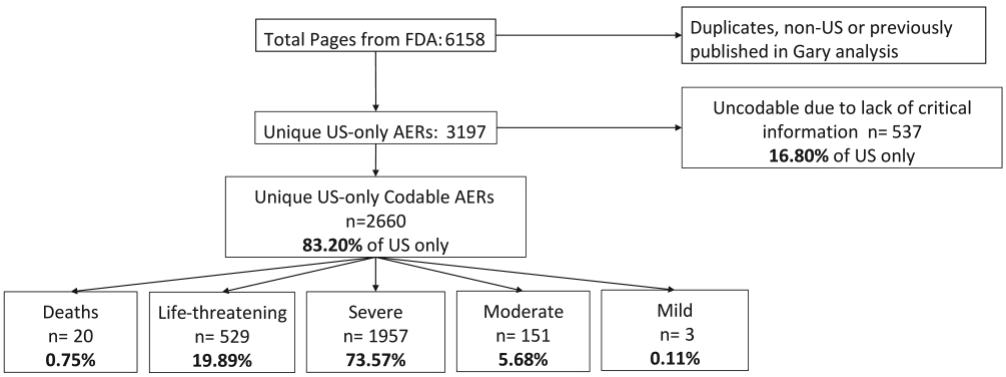
Our analysis identified 23 of the 24 deaths reported by the FDA as of 2018.[29] Three of those deaths were previously published in the Gary paper[30] leaving 20 deaths (Table 1). Our analysis yielded a total of 7 sepsis deaths. These included five cases of *C. sordellii* and one case of *Clostridium perfringens*, all consistent with those reported by the FDA. There was an additional death which we categorized as a sepsis death whereas the FDA labeled this case as "delayed onset toxic shock-like syndrome" but did not include it as a sepsis death. The patient had an exploratory laparotomy revealing green pus, which was culture positive for *prevotella* and *peptostreptococcus,* and she died intraoperatively.[31]

[29] RCM # 2007-525 NDA 20-687 Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2018. FDA. 1-2. Reference ID: 4401215. Accessed November 13, 2020. https://www.fda.gov/media/112118/download

[30] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[31] Individual Case Safety Report number 4734082-4-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received August 4, 2005. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/Peptostreptococcus%20death%209.10277-8.pdf

Figure 1. AER Distribution



Note: From 2000 to 2016 FDA only required the manufacturer to report AEs which were severe, life-threatening or had fatal outcomes. Since 2016, FDA only requires the manufacturer to report fatal outcomes.

We categorized two deaths as suspicious for infectious death. One case was labeled by the FDA as "undetermined natural causes," however, the AER reported the cause of death as "acute visceral and pulmonary (1420 grams) congestion and edema," [32] which is consistent with the clinical findings for sepsis/Acute Respiratory Distress Syndrome (ARDS). This patient had autopsy-proven retained products of conception and blood cultures which grew *Strep viridans* isolated at less than 24 hours incubation. One additional case which the FDA labeled "methadone overdose"[33,34] we considered suspicious for sepsis. Prior to her death, this patient had fever and chills and was treated by an outside physician with cephalexin, which would have been ineffective against infections from *C. sordellii* or anaerobic gram-negative bacilli. There was no autopsy report or toxicology report in the AER.

Non-infectious deaths include one death that the FDA listed as "natural," caused by "pulmonary emphysema."[35] This patient was a 40-year-old chronic smoker who died within hours of misoprostol ingestion and had a contusion on her head consistent with a fall, a scenario possibly related to a cardiac event or acute respiratory reaction to misoprostol. She had an intact fetus at the time of

[32] Individual Case Safety Report number 9587011-03-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received May 21, 2014. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/death%20Visc%20pul%20cong.pdf

[33] Individual Case Safety Report number 4970303-0-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received April 21, 2014. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/death%2023%20yo%20meth%20overdose%20fever%20and%20chills.pdf

[34] Individual Case Safety Report number 5063156-8-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received July 27, 2006. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/methadone%20AER%20(1).pdf

[35] Individual Case Safety Report number 11283049-02-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received December 8, 2015. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/emphysema.pdf

autopsy. Other non-infectious deaths included one death from a ruptured ectopic pregnancy, one from hemorrhage, 3 possible homicides, one suicide, and 4 deaths from drug toxicity/overdose. It is unknown whether the 8 women who died by homicide, suicide, or drug toxicity/overdose were screened for domestic violence, drug addiction, or depression prior to the abortion.

Infection (Table 1)

Infection was the leading cause of mortality. There were 502 cases of infection, which included 9 Deaths, 39 had Life-threatening sepsis, 249 were Severe infections, 132 Moderate infections, and 73 infections which were Uncodable.

Ectopic Pregnancy (Table 1)

There were 75 ectopic pregnancies. Of these, 26 were ruptured, including 1 death. Twenty-four were unruptured, and there were 25 for which the rupture status was not given. Fifty-six ectopic pregnancies were treated surgically and 11 were treated with methotrexate. The management was not documented in 7 cases. The patient who died received no treatment as she died on the way to the hospital.

Retained Products of Conception (RPOC) (Tables 1 and 2)

RPOC was the leading cause of morbidity. There were 977 confirmed cases of RPOC, including 2 molar pregnancies, and 1506 likely cases of RPOC (documentation was inadequate for confirmation). Of the 2146 total D&Cs, most were for RPOC, including 897 for confirmed RPOC, 1058 for bleeding or presumed RPOC, but no pathology was provided, and 2 for molar pregnancy. A small percentage of RPOC had medical treatment or no treatment.

Hemorrhage/Bleeding (Table 1)

There were 1639 bleeding events including one death. These included 466 Life-threatening and 642 Severe events. There were also 106 events coded as Moderate, while 424 reports of bleeding were Uncodable given the information in the database.

Ongoing Pregnancy (Table 1)

There were 452 ongoing pregnancies. Of these 102 chose to keep their baby, 148 chose termination, 1 miscarried, and 201 had an unknown outcome. Of those with an unknown outcome, there were 44 patients referred or scheduled for termination, who did not follow through (39 no-showed, 3 canceled, 2 did not schedule).

Surgeries (Table 2)

There were 2243 surgeries including 2146 D&Cs, 76 laparoscopies/laparotomies without hysterectomy, 7 hysterectomies, and 14 other surgeries. Of the hysterectomies, 3 were performed for sepsis, 2 for hemorrhage, 1 for a cervical ectopic, and 1 for placenta accreta. There were 1291 surgeries performed in the hospital or ER and 952 in an outpatient setting. Of the 2146 D&Cs, 1194 were performed in the hospital or ER, and 952 in an outpatient setting. Of the 2146 D&Cs, 1194 were provided by the Hospital or ER, 853 by the abortion provider, and 99 by another outpatient provider.

Transfusions (Table 2)

Four hundred and eighty-one patients required blood transfusion following medical abortions. Of these, 365 received 1 to 10 units packed red blood cells (PRBCs) alone, 1 received fresh frozen plasma (FFP) alone, 8 received a combination of PRBCs and FFP, and 107 received an unknown amount of blood product.

Relationship of Misoprostol Use to Hemorrhage (Table 3)

The use of mifepristone with misoprostol was associated with a higher incidence of hemorrhage than the use of mifepristone alone. Of the 3056 women who took both mifepristone and misoprostol, 1572 (51.44%) hemorrhaged, whereas, among the 58 women who did not take misoprostol, only 13 (22.41%) hemorrhaged. It was unclear whether 84 patients took misoprostol or not. Fifty-four (64.29%) of them hemorrhaged. The hemorrhage rate was higher for the mifepristone with misoprostol group as compared to the mifepristone alone group even if all the unknowns were assigned to the mifepristone alone group or vice versa.

Table 1 - Diagnoses[a]

Deaths	Deaths (n)	Deaths (%)	Deaths: % of (3197) Unique US AERs (%)	Organism (%)
Sepsis	9	45.00%	0.28%	
Sepsis confirmed	7	35.00%	0.22%	100%
Clostridium sordellii	*5*	*25.00%*	*0.16%*	*71.43%*
Clostridium perfringens / Peptostreptococcus	*1*	*5.00%*	*0.03%*	*14.29%*
Peptostreptococcus	*1*	*5.00%*	*0.03%*	*14.29%*
Sepsis Likely, Unknown Organism	2	10.00%	0.06%	
Visceral and Pulmonary Congestion consistent with ARDS / sepsis	1	5.00%	0.03%	
Fever / chills treated with cephalexin, found dead[b]	1	5.00%	0.03%	
Ruptured Ectopic Pregnancy	1	5.00%	0.03%	
Hemorrhage	1	5.00%	0.03%	
Possible Homicide	3	15.00%	0.09%	
Suicide	1	5.00%	0.03%	
Drug Toxicity/Overdose	4	20.00%	0.13%	
Unknown[c]	1	5.00%	0.03%	
Total Deaths	**20**	**100%**	**0.63%**	
Infections, Level of Severity	**Infections (n)**	**Infections (%)**	**Infections: % of (3197) Unique US AERs (%)**	
Death	9	1.79%	0.28%	
Life threatening infection/sepsis	39	7.77%	1.22%	
Severe infection (IV anitbiotics)	249	49.60%	7.79%	
Moderate infection (oral antibiotics)	132	26.29%	4.13%	
Uncodable[d]	73	14.54%	2.28%	
Total Infections	**502**	**100%**	**15.70%**	

Table 1 – Diagnoses (Continued)

Ectopic Pregnancies, Rupture Status	Ectopic Pregnancies (n)	Ectopic Pregnancies (%)	Ectopic Pregnancies: % of (3197) Unique US AERs (%)
Ruptured[e]	26	34.67%	0.81%
Unruptured[f]	24	32.00%	0.75%
Surgical Treatment	13	17.33%	0.41%
Methotrexate Treatment	11	14.67%	0.34%
Unknown Rupture Status[g]	25	33.33%	0.78%
Surgical Treatment	18	24.00%	0.56%
Unknown Treatment	7	9.33%	0.22%
Total Ectopic Pregnancies	**75**	**100%**	**2.35%**
Ectopic Pregnancies, Level of Severity	**Ectopic Pregnancies (n)**	**Ectopic Pregnancies (%)**	**Ectopic Pregnancies: % of (3197) Unique US AERs**
Death	1	1.33%	0.03%
Life Threatening (Ruptured, survived)	25	33.33%	0.78%
Severe (Not Ruptured)	24	32.00%	0.75%
Uncodable	25	33.33%	0.78%
Total Ectopic Pregnancies	**75**	**100%**	**2.35%**

Table 1 – Diagnoses (Continued)

Retained Products of Conception (RPOC)	RPOC (n)	RPOC (%)	RPOC: % of (3197) Unique US AERs (%)
RPOC confirmed	977	39.35%	30.56%
RPOC confirmed (by pathology or ultrasound); Had D&C	891	35.88%	27.87%
RPOC confirmed by U/S but D&C not documented	29	1.17%	0.91%
RPOC treated medically	27	1.09%	0.84%
Tissue at os (no D&C)[h]	27	1.09%	0.84%
Molar Pregnancy	2	0.08%	0.06%
No Treatment, RPOC on autopsy	1	0.04%	0.03%
RPOC Likely	1506	60.65%	47.11%
Had D&C, no pathology provided	1056	42.53%	33.03%
Unknown[i]	450	18.12%	14.08%
Total RPOCs	**2483**	**100%**	**77.67%**
Bleeding Events, Level of Severity	**Bleeding Events (n)**	**Bleeding Events (%)**	**Bleeding Events: % of (3197) Unique US AERs**
Death	1	0.06%	0.03%
Life threatening or Disabling: 2U or more transfusion or Hgb<7 or witnessed massive blood loss	466	28.43%	14.58%
Severe: surgical intervention and/or 1 U transfusion	642	39.17%	20.08%
Moderate: medical intervention	106	6.47%	3.32%
Uncodable[j]	424	25.87%	13.26%
Total Bleeding Events	**1639**	**100%**	**51.27%**

Table 1 – Diagnoses (Continued)

Ongoing Pregnancies, Outcome	Ongoing Pregnancies (n)	Ongoing Pregnancies	Ongoing Pregnancies: % of (3197) Unique US AERs (%)	Ongoing Pregnancies with Unknown Outcome (%)
Desired to Keep Pregnancy	102	22.57%	3.19%	
Kept Pregnancy	101	22.35%	3.16%	
Kept Pregnancy but baby died in-utero	1	0.22%	0.03%	
Terminated Pregnancy	148	32.74%	4.63%	
Surgical Termination[k]	139	30.75%	4.35%	
Medical Termination	9	1.99%	0.28%	
Unknown Intent, miscarried[l]	1	0.22%	0.03%	
Unknown Outcome	201	44.47%	6.29%	100%
Referred D&C but did not show	39	8.63%	1.22%	19.40%
Referred D&C but cancelled	3	0.66%	0.09%	1.49%
Told to schedule/referred D&C did not go	2	0.44%	0.06%	1.00%
Unknown outcome, no other information[m]	157	34.73%	4.91%	78.11%
Total	**452**	**100%**	**14.14%**	

[a] Because of rounding, percentages may not appear to add up exactly.
[b] FDA attributed to methadone overdose.
[c] 40 year old smoker died within hours of misoprostol ingestion. Per FDA, "natural causes due to severe pulmonary emphysema."
[d] Patients with documented infection but inadequate information to determine severity.
[e] One of the ruptured ectopics died on the way to the hospital. The other 25 were treated surgically.
[f] The unruptured ectopics include two cornual ectopics, one treated surgically and one treated medically.
[g] Includes two cervical ectopics, one treated with D&C/Hysterectomy/massive transfusion and one with unknown treatment.
[h] Either with path provided, or described as RPOC, placental fragments, fetus, or tissue.
[i] Suspected RPOC indicating D&C needed, but not documented as being done.
[j] Patients with documented bleeding but inadequate information to determine severity.
[k] Includes one hysterotomy for pregnancy in non-communicating horn.
[l] After no show for surgical termination.
[m] Includes 10 with known gestational age 20-29 weeks.

Table 2 – Treatment[a]

Type of Surgery	Type of surgery (n)	Type of surgery (%)	Surgery: % of (3197) Unique US AERs (%)
D&C[b]	**2146**	**95.68%**	**67.13%**
Hysterectomy	**7**	**0.31%**	**0.22%**
Sepsis (includes 2 deaths)	3	0.13%	0.09%
Hemorrhage after uterine perforation	2	0.09%	0.06%
Hemorrhage - Cervical Ectopic	1	0.04%	0.03%
Placenta accreta	1	0.04%	0.03%
Laparoscopy/Laparotomy without hysterectomy	**76**	**3.39%**	**2.38%**
Ectopic (Actual or Suspected)	66	2.94%	2.06%
Infection	7	0.31%	0.22%
Uterine Perforation	1	0.04%	0.03%
Salpingo oophorectomy for Torsion	1	0.04%	0.03%
Hysterotomy for pregnancy in non-communicating horn	1	0.04%	0.03%
Other Surgeries	**14**	**0.62%**	**0.44%**
Uterine Artery Embolization	1	0.04%	0.03%
Vaginal sutures (after 15 week surgical termination for ongoing pregnancy)	1	0.04%	0.03%
Paracenteses (multiple, same patient, death)	1	0.04%	0.03%
Necrotozing fasciitis debridement and below knee amputation	1	0.04%	0.03%
Upper and lower endoscopy for bright red bleeding	1	0.04%	0.03%
Unknown surgery for deep venous thrombosis	1	0.04%	0.03%
Angioplasty	1	0.04%	0.03%
Cholecystectomy	2	0.09%	0.06%
Appendectomy	1	0.04%	0.03%
Laceration repair (scalp, chin)	2	0.09%	0.06%
Unknown Surgery	2	0.09%	0.06%
Total	**2243**	**100%**	**70.16%**

Table 2 – Treatment (Continued)

Location of Surgery	Location of Surgery (n)	Location of Surgery (%)
All Surgeries	**2243**	**100.00%**
Hospital or ER	1291	57.56%
Outpatient	952	42.44%
D&C	**2146**	**100.00%**
Hospital or ER	1194	55.64%
Outpatient	952	44.36%
Surgical Provider for D&C	**Surgical Provider (n)**	**Surgical Provider (%)**
Hospital/ER	1194	55.64%
Abortion Provider	853	39.75%
Other Provider	99	4.61%
Total	**2146**	**100%**
Indication for D&Cs	**Indication for D&C (n)**	**Indication for D&C (%)**
Confirmed D&C[c]	**2146**	**100%**
RPOC (confirmed by pathology or ultrasound)	897	41.80%
RPOC/Bleeding (no pathology provided)	1058	49.30%
Ongoing pregnancy, surgical termination by D&C	139	6.48%
RPOC ruled out	34	1.58%
Ectopic evaluation	12	0.56%
Molar pregnancy	2	0.09%
Not able to take misoprostol	4	0.19%
Possible D&C	**680**	
Possible RPOC, unknown treatment, possible D&C	450	
RPOC confirmed by U/S but D&C not documented	29	
Ongoing pregnancy Unknown outcome, possible D&C	201	
TOTAL (Confirmed and Possible)	**2826**	

Table 2 – Treatment (Continued)

Transfusions	Transfusions (n)	Transfusions (%)	Transfusion: % of (3197) Unique US AERs (%)
PRBC alone	**365**	**75.88%**	**11.42%**
1U	32	6.65%	1.00%
1-2U	1	0.21%	0.03%
2U	246	51.14%	7.69%
2.5U	1	0.21%	0.03%
3U	45	9.36%	1.41%
4U	27	5.61%	0.84%
5U	5	1.04%	0.16%
6U	5	1.04%	0.16%
7U	2	0.42%	0.06%
10U	1	0.21%	0.03%
Other Blood products	**9**	**1.87%**	**0.28%**
1 U FFP	1	0.21%	0.03%
2 U PRBC/1 U FFP	1	0.21%	0.03%
2 U PRBC/ 4 U FFP	1	0.21%	0.03%
3 U PRBC/ 1 U FFP	1	0.21%	0.03%
4 U PRBC/ 1 U FFP	1	0.21%	0.03%
4 U PRBC/ 2 U FFP	1	0.21%	0.03%
5 U PRBC/ 4 U FFP	1	0.21%	0.03%
6 U PRBC/ 2 U FFP	1	0.21%	0.03%
7 U PRBC/ FFP and Platelets unknown amount	1	0.21%	0.03%
Unknown amount (documented as given, units not recorded)	**107**	**22.25%**	**3.35%**
Total[d]	**481**	**100%**	**15.05%**

[a] Because of rounding, percentages may not appear to add up exactly.
[b] With or without suction, one with hysteroscopy.
[c] There were 8 patients who had 2 D&Cs and one who required uterine artery embolization. There were 4 perforations: two had resultant hysterectomies, one had a laparoscopy, and one received 2 U PRBCs but no documented surgery.
[d] Additionally there were 7 patients who likely received transfusion, but was not recorded, 3 patients who refused transfusion, and 1 patient for whom transfusion was considered but not given.

Table 3 – Relationship of Misoprostol to Hemorrhage[a]

	Mifepristone + Misoprostol		Mifepristone alone		Unknown		Mifepristone + Misoprostol + unknown [b]		Mifepristone alone + unknown [c]	
	n	%	n	%	n	%	n	%	n	%
No Hemorrhage	**1484**	**48.56%**	**45**	**77.59%**	**30**	**35.71%**	**1514**	**48.23%**	**75**	**52.82%**
Hemorrhage	**1572**	**51.44%**	**13**	**22.41%**	**54**	**64.29%**	**1625**	**51.77%**	**67**	**47.18%**
Death	1	0.03%	0	0.00%	0	0.00%	1	0.03%	0	0.00%
Life threatening	441	14.43%	5	8.62%	20	23.81%	461	14.69%	25	17.61%
Severe	633	20.71%	3	5.17%	6	7.14%	639	20.36%	9	6.34%
Moderate	101	3.30%	1	1.72%	4	4.76%	105	3.35%	5	3.52%
Uncodable	396	12.96%	4	6.90%	24	28.57%	420	13.38%	28	19.72%
Total US AERs	**3056**	**100%**	**58**	**100%**	**84**	**100%**	**3139**	**100%**	**142**	**100%**

[a] Because of rounding, percentages may not appear to add up exactly.
[b] Assumes all unknowns took both mifepristone and misoprostol.
[c] Assumes all unknowns took mifepristone, but not misoprostol.

Discussion

This article is critically important considering the paucity of published literature on mifepristone safety and the minimal analysis done on the AERs by the FDA.

Ectopic Pregnancies

Although reported as AEs, ectopic pregnancies are not a direct adverse event from the medication, but rather a contraindication to its administration. They were reported as adverse events because the ectopic pregnancies were missed.

The American College of Obstetricians and Gynecologists (ACOG) notes that "According to the Centers for Disease Control and Prevention, ectopic pregnancy accounts for approximately 2% of all reported pregnancies. However, the true current incidence of ectopic pregnancy is difficult to estimate because many patients are treated in an outpatient setting where events are not tracked, and national surveillance data on ectopic pregnancy have not been updated since 1992. Despite improvements in diagnosis and management, ruptured ectopic pregnancy continues to be a significant cause of pregnancy-related mortality and morbidity. In 2011–2013, ruptured ectopic pregnancy accounted for 2.7% of all pregnancy-related deaths and was the leading cause of hemorrhage-related mortality."[36]

[36] ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy, Obstet Gynecol: March 2018; 131(3): e91-e103. doi:10.1097/AOG.0000000000002560

Confirmed/suspected ectopic pregnancy and undiagnosed adnexal mass are contraindications to mifepristone use under current prescribing requirements. The label warnings state: "Ectopic pregnancy: exclude before treatment." [37] Unfortunately, it is difficult to rule out ectopic pregnancy by history alone because, "half of all women who receive a diagnosis of an ectopic pregnancy do not have any known risk factors."[38] According to ACOG Practice Bulletin No. 193, "The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy." Of the 75 reported ectopic pregnancies in the FDA AERs we analyzed, over a third were known to be ruptured including one death. Clearly, an ultrasound should be required prior to the administration of mifepristone to document that the pregnancy is located within the uterus. Although not 100% effective, this will screen for ectopic pregnancy, confirm gestational age, which can be inaccurate based on menstrual history alone,[39] and screen for adnexal masses, another contraindication to mifepristone use.[40]

Ongoing pregnancies

Of the women with an ongoing pregnancy, less than a third were known to have proceeded with termination of the pregnancy, and almost a quarter were known to have kept their pregnancy; in almost half, the outcome was unknown. The significant percentage of women with ongoing pregnancy who changed their mind and chose to keep their pregnancy, after initially choosing termination, raises concerns regarding the pre-abortion counseling and informed consent they received. Women undergoing abortion should receive the same quality of informed consent and pre-procedural counseling that is standard of care prior to other medical treatment or surgery. It is imperative that women considering abortion be provided adequate and complete information and counseling on risks, advantages, disadvantages, and alternative options.

Additionally, the high percentage of women with ongoing pregnancies for whom there is no follow up or known outcome is concerning. As health care providers we are to continue to care for our patients and manage any complications, yet in the AERs we reviewed this was not typically the case for the abortion provider. Furthermore, a federal registry of known outcomes and birth defects is imperative. One of the initial FDA post-marketing requirements for

[37] MIFEPREX. Package insert. Danco; 2016. Approved March 2016. p. 1. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf

[38] ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy, Obstet Gynecol: March 2018; 131(3): e91-e103. doi: 10.1097/AOG.0000000000002560

[39] Shipp, Thomas D. 2020. Overview of ultrasound examination in obstetrics and gynecology. Lit Rev current through Dec 2020. UpToDate. Edited by Barss A Vanessa. Wolters Kluwer. June 10, 2020. Accessed January 11, 2021. https://www.uptodate.com/contents/ectopic-pregnancy-clinical-manifestations-and-diagnosis/print?source=history_widget.

[40] MIFEPREX. Package insert. Danco; 2016. Approved March 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf

Danco was a surveillance study of outcomes of ongoing pregnancies.[41] The FDA released them from this post-marketing commitment in January 2008 because Danco reported that only one or two ongoing pregnancies per year were followed for final outcomes in part because of consent requirements.[42] This is disturbing in light of the percentage of women in our analysis who kept their pregnancies, as well as those with ongoing pregnancy and unknown outcomes, all of whom could have been followed for final outcomes. The significant lack of follow-up of ongoing pregnancies (44.47% with unknown outcomes) and the very minimal information on those who chose to keep the pregnancy, highlights the need for a national registry especially considering the teratogenicity of misoprostol.[43]

Relationship of Misoprostol to Hemorrhage

The Creinin study of abortion pill reversal was stopped for safety concerns due to hemorrhage in 3 of the 12 study participants.[44] One of the conclusions of that study was that "Patients who use mifepristone for a medical abortion should be advised that not using misoprostol could result in severe hemorrhage, even with progesterone treatment."[45] The authors hypothesized that the absence of misoprostol caused these women to hemorrhage. The women who had documented use of misoprostol in our database hemorrhaged at a higher rate than those documented not to have taken misoprostol.

Reporting of Adverse Events

Although not the initial goal of this study, the analysis of the AERs revealed glaring deficiencies in the AE reporting system making it difficult to properly evaluate adverse events. When mifepristone was approved in 2000, FDA required that providers "must report any hospitalization, transfusion or other serious event to Danco Laboratories."[46] This created an inherent conflict of interest as it is not in the best interest of the entities or providers to report adverse events to those regulating them. Because only severe events were reportable, this requirement likely resulted in an underestimation of moderate and mild AEs. It

[41] Center for Drug Evaluation and Research. NDA 20-687. Approval Letter for MIFEPREX (mifepristone) Tablets, 200 mg to Population Council. Food and Drug Administration. Written September 28, 2000. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.htm

[42] 2016 03 20 FDA resp to Cit Pet.pdf. Docket No. FDA-2002-P-0364. FDA. March 29, 2016. p. 31. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2016%2003%2020%20%20FDA%20resp%20to%20Cit%20Pet.pdf

[43] Cytotec (misoprostol tablets). Package insert. G.D. Searle; Revised November 2012. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019268s047lbl.pdf

[44] Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2020;135(1):158-165. doi:10.1097/AOG.0000000000003620

[45] Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2020;135(1):5. doi:10.1097/AOG.0000000000003620

[46] M I F E P R E X™(Mifepristone) Tablets, 200 mg Prescriber's agreement. Food and Drug Administration. September 28, 2000, 1-2. Accessed November 16, 2020. http://wayback.archive-it.org/7993/20170113112742/http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111364.pdf

is also likely that some of the AEs that we coded as Mild or Moderate were actually Severe but there was not enough information in the AER for us to justify coding them as Severe. In March 2016, the FDA substantially reduced the prescribing requirements and changed the drug protocol [47] and yet at the same time eliminated reporting requirements except for deaths.[48] With the relaxation of reporting requirements, the ability to perform any relevant post-marketing evaluation of mifepristone was lost. It is imperative for the safety of women that the FDA restore and strengthen the 2011 REMS requirements.

The information in the AERs is almost exclusively obtained from abortion providers, rather than the physician treating the complication, yet in this analysis, abortion providers managed only 39.75% of surgical complications (a number which is likely much lower since these are only the cases which are known to the abortion provider). Throughout the reports, there was also a lack of detail and many patients who were simply "lost to follow-up." This resulted in 16.80% of the AERs being Uncodable as to severity and likely under-coding of many AERs and AEs, as coding could only be assigned based on the scant information provided. Many of the AEs experienced by women were unknown to the abortion provider until the follow-up examination, which is troubling considering the poor follow-up rate and elimination of the requirement for an in-office follow up visit. Some of the patient deaths were not known to the abortion provider until they saw the death in an obituary or were contacted by an outside source. Because of this, in addition to abortion providers, hospitals, emergency departments, and private practitioners should be required to report AEs.

Complications occur in the best of hands in all areas of medicine, but as physicians, we are responsible to manage those complications and follow our patients through to resolution. The findings that: 1. the most common outcome of ongoing pregnancy was unknown outcome, 2. abortion providers performed less than half the D&Cs done for complications, and 3. a third of ectopic pregnancies (missed prior to administering the abortifacient) had unknown rupture status, leave us deeply concerned regarding the care these women received. A post-marketing requirement was that there be a "cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention."[49] The applicant was released from this requirement because they stated that because there were so few providers

[47] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[48] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. p. 3, 6. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf

[49] Center for Drug Evaluation and Research. NDA 20-687. Approval Letter for MIFEPREX (mifepristone) Tablets, 200 mg to Population Council. Food and Drug Administration. Written September 28, 2000. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.htm

without surgical intervention skills, no meaningful study could be done.[50] Yet, that same year the FDA changed the provider agreement to allow non-physicians to become prescribers.[51] These findings highlight the importance of follow-up and management of complications by the abortion provider. Allowing any further relaxation of mifepristone prescribing requirements will put women at an even higher risk of adverse events

Limitations and Strengths

It was not possible to calculate complication rates for mifepristone and misoprostol abortions based on AER data because there is no denominator for how many mifepristone abortions are performed in the U.S. since reporting is often voluntary and sporadic. For clarity, we specified the denominators we used.

Our analysis was limited by the fact that the number of AEs for which we received reports is likely a gross underestimation of the actual number of AEs that occurred. In our analysis, the surgical management of over half the complications was performed by someone other than the abortion provider, yet treating physicians are not required to report complications. Few reports were generated by those in Emergency Departments and hospitals who treated the complications.

Our analysis was also limited by the lack of information in the AERs, including redaction of critical dates, a paucity of diagnosis and treatment information, and lack of follow up.

Our study has several strengths. Our data comes from information provided to the FDA and is the largest analysis of AERs for mifepristone abortions. This data is publicly available under the Freedom of Information Act so that anyone can verify the data for themselves. This analysis reviews all AERs not reported in the first study by Gary.[52] Although heavily redacted, there was sufficient information in over 80% of the AERs to evaluate severity. An objective standardized system, CTCAEv3, was used to code for severity, and each AER was coded by at least two board-certified obstetrician-gynecologists or family medicine physicians.

Conclusions and Relevance

This article is important because it augments the scant published literature on mifepristone safety.

Due to the lack of adequate reporting of adverse events, especially by those treating them, these unique AERs represent a fraction of the actual adverse events occurring in American women.

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[50] 2016 03 20 FDA resp to Cit Pet.pdf. Docket No. FDA-2002-P-0364. FDA. March 29, 2016. p. 31. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2016%2003%2020%20%20FDA%20resp%20to%20Cit%20Pet.pdf

[51] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[52] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

Significant morbidity and mortality have occurred with the use of mifepristone as an abortifacient, including at least 24 US deaths reported by the FDA from September 2000 to December 2018. Because of this and the significant morbidity associated with this drug, the FDA should consider at a minimum reinstating the original 2011 REMS and strengthening the reporting requirements. The reporting of transfusions, hospitalizations, and other serious adverse events are essential.

Given the morbidity and mortality of undiagnosed ectopic pregnancy, a clear contraindication to the use of mifepristone, an ultrasound to confirm pregnancy location is essential before mifepristone is dispensed.

Considering the significant percentage of women with ongoing pregnancies who chose to continue their pregnancy, there must be reasonable waiting periods, parental involvement, and adequate pre-abortion counseling on all pregnancy options. It is also critical that a pregnancy registry be established.

In our analysis, the patients who used mifepristone alone had a lower rate of hemorrhage than those using mifepristone followed by misoprostol.

The FDA Adverse Event Reporting System is woefully inadequate to determine the post-marketing safety of mifepristone due to its inability to adequately assess the frequency or severity of adverse events. The reliance solely on interested parties to report, the large percentage of uncodable events, the redaction of critical clinical information unrelated to personally identifiable information, and the inadequacy of the reports highlight the need to overhaul the current AER System.

This analysis evaluated 3197 adverse events resulting from the use of mifepristone as an abortifacient and brought to light serious concerns about the safety requirements and care of women undergoing mifepristone abortion. Although complications may occur in the best of hands, and no medical procedure is without risks, safety measures must be employed to minimize these adverse outcomes. Women undergoing abortion should receive the same quality of informed consent and pre-procedural counseling that is standard of care prior to other medical treatment or surgery. It is imperative that women considering abortion be provided adequate and complete information and counseling on risks, advantages, disadvantages, and alternative options. Although there may be disagreements about the ethics of abortion, there must be total agreement that our patients—whether undergoing a medical abortion or otherwise—deserve the highest standard of medical care.

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EXHIBIT 54

Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

(Apr. 2021)

Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

Technical Specifications Document

Associated Guidance Documents and Conformance Guide:

Draft Guidance for Industry: Providing Submissions in Electronic Format – Postmarketing Safety Reports (June 2014)

Guidance for Industry and FDA Staff: Postmarketing Safety Reporting for Combination Products (July 2019)

Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format: IND Safety Reports (October 2019)

Electronic Submissions of IND Safety Reports Technical Conformance Guide (October 2019)

For questions regarding this technical specifications document, contact the Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, at FAERSESUB@fda.hhs.gov; or Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, at CBERICSRSubmissions@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2021

Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

Revision History Table

Date	Version	Summary of Changes
2008-06-11	1.0	Initial Version
2008-08-06	1.1	Added Filename format information
2008-10-10	1.2	Updated UTF-8 to ISO-8859-1 encoding; indicated simultaneous acceptance of ICSR and ICSR attachments; provided another acceptable file extension for SGML files; and clarified use of abbreviations (NDA, ANDA, and STN)
2008-10-22	1.3	Provided clarification in Section II; updated footnote 3; and added new paragraph to Section V.C.
2013-07-05	1.4	Updated AERS to FAERS migration changes, removed references to SGML file formatting, incorporated updates from CBER
2018-02-06	1.5	Added a new section to highlight data fields for reporting ICSRs on Combination Products
2019-09-30	1.6	Added two new sections to provide regional data elements for electronic submissions of certain IND safety reports (section I) and IND-exempt Bioavailability (BA)/Bioequivalence (BE) studies (section J). Added an appendix (II) highlighting various case scenarios for electronic submissions of IND safety reports to FAERS.

2020-02-11	1.7	Added a new value to the data element B.4.k.1 for drug characterization to accommodate a similar device. Updated the data element B.4.k.18.2 to specify values. Updated the data element B.4.k.18.3 to use default value.
2020-12-18	1.8	Added a new regional data element A.1.FDA.16 (FDA Safety Report Type) in Table 2 Detailed Description of Administrative Tags Added section Submission Rules Added a new value to the data element B.4.k.1 and B.4.k.19 in section J. IND-exempt BA/BE Studies
2021-03-26	1.9	Updated section XML Header to include DTD 3.0 for premarketing reporting Updated the reference description to data element A.1.FDA.16 in Table 2 Detailed Description of Administrative Tags Updated section ICSR Message Header Information to include information in premarketing reporting Updated section AS2 Headers and Routing IDs for Premarketing Safety Report Submissions Updated section Submission Rules

Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

Table of Contents

I. ELECTRONIC SUBMISSIONS OF ICSRS AND ICSR ATTACHMENTS 6

II. SUBMISSION FILE NAME 7

III. ICSR ACKNOWLEDGEMENTS 7

A. ESG ACKNOWLEDGEMENT 7
B. FAERS ACKNOWLEDGMENT 7

IV. ELECTRONIC TRANSPORT FORMAT: XML FILES 7

A. AS2 HEADERS AND ROUTING IDS FOR POSTMARKETING SAFETY REPORT SUBMISSIONS 8
B. AS2 HEADERS AND ROUTING IDS FOR PREMARKETING SAFETY REPORT SUBMISSIONS 8
C. XML HEADER 9
D. ICSR MESSAGE HEADER INFORMATION 10
E. ICSR FILE EXTENSION 10

V. DATA ELEMENTS FOR ELECTRONIC SUBMISSIONS 10

A. MINIMUM DATA ELEMENTS REQUIREMENTS 10
B. ADMINISTRATIVE AND IDENTIFICATION ELEMENTS 11
C. AUTHORIZATION/ APPLICATION NUMBER FORMAT 12
D. UNIQUE CASE IDENTIFICATION NUMBERS FOR INITIAL AND FOLLOW-UP ICSRS 13
E. MEDDRA SPECIFIC ELEMENTS 13
1. Reaction/Event 14
2. Other E2B Elements 14
F. DRUG DESCRIPTION AND CASE NARRATIVE ELEMENTS 15
1. Recording Multiple Drugs 15
2. Medicinal Product Name and Active Drug Substance Name 15
3. Case Narrative 16
G. OTHER DATA ELEMENTS 16
1. Dosage Information Field 16
2. Pharmaceutical Form Field 16
3. Route of Administration Field 16
4. Receiver Field (A.3.2) 16
5. Message Receiver Field (M.1.6) 17
H. DATA ELEMENTS FOR ELECTRONIC SUBMISSIONS OF SAFETY REPORTS FOR POSTMARKETING COMBINATION PRODUCTS 17

I. DATA ELEMENTS FOR ELECTRONIC SUBMISSIONS OF IND SAFETY REPORTS 28
J. DATA ELEMENTS FOR ELECTRONIC SUBMISSIONS OF ICSRS FROM IND-EXEMPT BIOAVAILABILITY (BA)/ BIOEQUIVALENCE (BE) STUDIES 35

VI. ELECTRONIC FORMAT FOR ICSR ATTACHMENTS 38

A. CONVERTING THE ICSR ATTACHMENT TO PDF 38
B. IDENTIFICATION INFORMATION IN THE PDF DOCUMENT INFORMATION FIELDS 38

VII. SUBMISSION RULES 39

APPENDIX I. EXAMPLES OF CORRECT AND INCORRECT APPLICATION NUMBER AND DRUG ELEMENT FORMATS 41

APPENDIX II. CASE SCENARIOS FOR IND SAFETY REPORTS SUBMITTED TO FAERS 43

APPENDIX III. CASE SCENARIOS FOR SAFETY REPORTS FROM IND-EXEMPT BA/BE STUDIES TO FAERS 47

List of Tables

Table 1. Minimum Data Elements 11
Table 2. Detailed Description of Administrative Tags* 12
Table 3. Detailed Description of Application Number Formats 13
Table 4. Additional E2B Elements for Preferred MedDRA Coding 14
Table 5. Detailed Description of Drug(s) and Narrative Elements*† 15
Table 6. Receiver Information 17
Table 7. Combination Product Data Elements 18
Table 8. Investigational New Drug Clinical Data Elements 28
Table 9. Data Elements for IND-Exempt BA/BE Studies 35
Table 10. Document Information Fields in ICSR Attachments 39
Table 11. Submission Rules and Acknowledgement Status 40
Table 12. Examples of Application Number Formats and Drug Element Formats 41
Table 13. Case Scenario 1. For IND Safety Reports Submitted to FAERS 43
Table 14. Case Scenario 2. For IND Safety Reports Submitted to FAERS 45
Table 15. ICH E2B Data Element & Value Selections for IND-Exempt BA/BE Study Exposures 48

Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

This document provides current specifications for submitting individual case safety reports (ICSRs) and ICSR attachments in electronic form. The specifications apply to electronic submission of ICSRs for drug and biological products studied under an investigational new drug application (IND) (including bioequivalence studies conducted under IND), ICSRs from IND-exempt bioavailability (BA)/bioequivalence (BE) studies, and ICSRs for marketed drug and biological products and combination products to the FDA Adverse Event Reporting System (FAERS). The specifications do not apply to the following marketed biological products: prophylactic vaccines, whole blood or components of whole blood, human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated by FDA.

This document discusses the technical specifications for electronic submission of ICSRs and ICSR attachments through the FDA Electronic Submissions Gateway (ESG).[1] ICSRs (and any ICSR attachments) are to be prepared in accordance with the International Council for Harmonisation (ICH) E2B(R2) data elements in extensible markup language (XML) file format for compatibility with the FAERS database. ICSRs for marketed products should not be submitted to the electronic Common Technical Document (eCTD).[2]

If you have not previously submitted an ICSR in electronic format to FAERS, you should contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov and they will assist you with submission of a test file.

I. ELECTRONIC SUBMISSIONS OF ICSRS AND ICSR ATTACHMENTS

Each initial ICSR or follow-up ICSR may consist of structured information and non-structured information, such as ICSR attachments.

For the FDA to process, review, and archive the ICSRs, prepare your ICSRs for electronic submission by following these steps:

- Provide a unique filename for the submission; see section II of this document.
- Add a file header and file extension; see section IV of this document.
- Populate the elements of the ICSR file; see section V of this document.

[1] For information on providing submissions using the ESG, refer to https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm.

[2] See FAERS Electronic Submissions at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm.

- If applicable, add ICSR attachments to ICSRs; see section VI of this document.

II. SUBMISSION FILE NAME

Each electronic submission of ICSRs or attachments to ICSRs must have a unique filename (e.g., your named file + date and time stamp down to the second: filenameYYYYMMDDHHMMSS). You may choose your own format to maintain uniqueness.

III. ICSR ACKNOWLEDGEMENTS

A. ESG Acknowledgement

After submitting an ICSR or ICSR attachment, you should receive an ESG message delivery notice (MDN) notifying the sender of the receipt of their submission, but not acknowledging the acceptance of the submission. If the MDN is not received within 2 hours, go to the ESG System Status web page. If the ESG web page is non-operational, go to the ESG Home Page for further information.

B. FAERS Acknowledgment

The MDN is then followed by a FAERS acknowledgment within 2 hours of the ESG acknowledgement. The FAERS acknowledgement notifies the sender whether their submission has been processed. If you do not receive the FAERS acknowledgement, resubmit the ICSRs without changing the filename.

If you receive a report acknowledgement code 02, indicating that your submission did not process due to file error/s that are specified in the acknowledgment, then proceed as follows:

- For submission with a single ICSR, resubmit the corrected ICSR with a new unique filename.
- For a submission consisting of multiple ICSRs, if one or more ICSRs in the submission failed to process, separate those ICSRs from the processed ICSRs, correct them and resubmit only the corrected ICSRs as a new submission with a unique filename. For example, if there were 50 ICSRs in an original submission and 15 of them failed to process, then only those 15 ICSRs must be separated, corrected appropriately, and resubmitted with a new unique filename. The resubmission should not contain any of the previously processed ICSRs.

IV. ELECTRONIC TRANSPORT FORMAT: XML FILES

FDA accepts the data elements defined in the "Guidance for Industry E2BM Data Elements for

Transmission of Individual Case Safety Reports (April 2002)."[3] The ICH E2B(R2) guidance provides additional information and clarification of the previously issued guidances.[4]

The electronic transport format also known as the Document Type Definition (DTD) for XML files is described in the associated document "XML Formatted DTD" (DTD Version 2.1, DTD Version 2.2 and DTD Version 3.0) (see links to the documents below in section C).

A. AS2 Headers and Routing IDs for Postmarketing Safety Report Submissions

For postmarketing safety report submissions, the sponsors should include the unique AS2 headers or routing IDs for safety reports and attachments in one of the two ways listed below.

- AS2 Headers
  - Destination: "CDER"
  - XML files: AERS
  - PDF's: AERS_ATTACHMENTS

or

- Routing IDs
  - XML files: FDA_AERS
  - PDF's: FDA_AERS_ATTACHMENTS

B. AS2 Headers and Routing IDs for Premarketing[5] Safety Report Submissions

For premarketing safety report submissions, the sponsors should include the unique AS2 headers or routing IDs for premarketing safety reports and attachments, as listed below, to differentiate these reports between CDER and CBER, and from postmarketing ICSRs.

---

[3] For information on Guidance for Industry on E2BM Data Elements for Transmission of Individual Case Safety Reports, please refer to the following:

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073092.pdf.

[4] See the guidance for industry entitled *E2B Data Elements for Transmission of Individual Case Safety Reports* (January 1998) (E2B). FDA currently supports use of E2B data elements in addition to the E2BM data elements. However, it is preferred that ICSRs be submitted with E2BM data elements to allow for the most efficient processing of the submissions. For those who wish to use E2B data elements and the corresponding electronic transport format (ICH M2 Electronic Transmission of Individual Case Safety Reports Message Specification Final Version 2.3 Document Revision February 1, 2001 (ICH ICSR DTD Version 2.1)), please refer to documentation provided at https://www.fda.gov/downloads/drugs/ucm149932.pdf

[5] The term premarketing safety report refers to IND safety reports and IND-exempt BA/BE studies safety reports.

1. Submitting premarketing safety reports for CDER IND and IND-Exempt BA/BE

- AS2 Headers
  - Destination: "CDER"
  - XML files: AERS_PREMKT_CDER
  - PDF's: AERS_ATTACHMENTS_PREMKT_CDER

or

- Routing IDs
  - XML files: FDA_AERS_PREMKT_CDER
  - PDF's: FDA_AERS_ATTACHMENTS_PREMKT_CDER

2. Submitting premarketing safety reports for CBER IND

- AS2 Headers
  - Destination: "CBER"
  - XML files: AERS_PREMKT_CBER
  - PDF's: AERS_ATTACHMENTS_PREMKT_CBER

or

- Routing IDs
  - XML files: FDA_AERS_PREMKT_CBER
  - PDF's: FDA_AERS_ATTACHMENTS_PREMKT_CBER

C. XML Header

The addition of an XML header enables FDA to process ICSRs in an XML format successfully. FDA supports only the ISO-8859-1 character set for encoding the submissions.

1. For submissions of postmarketing safety reports for drug and biological products, add the following XML header to the ICSR file:

<?xml version="1.0" encoding="ISO-8859-1"?>

<!DOCTYPE ichicsr SYSTEM "https://www.accessdata.fda.gov/xml/icsr-xml-v2.1.dtd">

2. For submissions of postmarketing safety reports for combination products, add the following XML header to the ICSR file:

<?xml version="1.0" encoding="ISO-8859-1"?>

<!DOCTYPE ichicsr SYSTEM "https://www.accessdata.fda.gov/xml/icsr-xml-

v2.2.dtd">

3. For submissions of premarketing safety reports, add the following XML header to the ICSR file:

<?xml version="1.0" encoding="ISO-8859-1"?>

<!DOCTYPE ichicsr SYSTEM "https://www.accessdata.fda.gov/xml/icsr-xml-v3.0.dtd">

D. ICSR Message Header Information

1. For submissions of postmarketing drug and biological product safety reports, use the value "2.1" for the DTD Descriptor <messageformatversion>:

<messageformatversion>2.1</messageformatversion>

2. For submissions of postmarketing combination product safety reports, use the value "2.2" for the DTD Descriptor <messageformatversion>:

<messageformatversion>2.2</messageformatversion>

3. For submissions of premarketing safety reports, use the value "3.0" for the DTD Descriptor <messageformatversion>:

<messageformatversion>3.0</messageformatversion>

E. ICSR File Extension

Use "xml" as the file extension for ICSRs in XML format. The name of the file should be 200 characters or less, excluding the three-digit extension. FDA does not support file names with multiple periods "." or the use of any special or foreign characters except underscore "_" and dash "-".

V. DATA ELEMENTS FOR ELECTRONIC SUBMISSIONS

A. Minimum Data Elements Requirements

For a submission to be successfully processed, submit an ICSR with the minimum data elements for reporting that are appropriate for the product type. If a sponsor submits an ICSR without the minimum data elements, they will receive a FAERS acknowledgement code 02 stating that the submission was not processed (see section III.B above). The minimum data elements for reporting are provided in Table 1 and the bullets that follow list the data elements to include in an ICSR by product type.

Table 1. Minimum Data Elements

Element	Data
B.1	Identifiable Patient
A.2	Identifiable Reporter
B.2	Reaction or Event
B.4	Suspect Drug Product

- Adverse event reports submitted for unapproved prescription drug products, unapproved nonprescription drug products and products approved for marketing under an abbreviated new drug application (ANDA), biologics license application (BLA), or new drug application (NDA), including combination products should have, at a minimum, the four data elements listed in Table 1.

- Adverse event reports for compounded drugs submitted by registered outsourcing facilities should have at a minimum, a suspect product and an adverse event.

- IND safety reports should include, at a minimum, the four data elements listed in Table 1 and the IND number under which the clinical trial where the event occurred is conducted.

- Serious adverse event reports from IND-exempt BA/BE studies should include, at a minimum, the four data elements listed in Table 1 and the pre-assigned ANDA number (hereafter referred as, Pre-ANDA number).

B. Administrative and Identification Elements

For FDA to successfully process your electronic ICSR submissions, populate the administrative and identification elements as indicated in Table 2.

Table 2. Detailed Description of Administrative Tags*

Element	DTD Descriptor 2.1	Length	Element Values for DTD 2.1
A.1.9	<fulfillexpeditecriteria>	1N	1= Yes (15-Day expedited) 2= No (non-expedited) 4= 5-Day 5= 30-Day 6= 7-Day expedited
A.1.0.1	<safetyreportid>	100AN	Sender's (Case) Safety Report Unique Identifier†
A.1.10.1	<authoritynumb>	100AN	Regulatory authority's case report number
A.1.10.2	<companynumb>	100AN	Other sender's case report number
A.3.1.2	<senderorganization>	60AN	Sender identifier
A.2.3.2^	<sponsorstudynumb>	35AN	IND or Pre-ANDA number under which the clinical trial where the event occurred is conducted
A.1.FDA.16††	<fdasafetyreporttype>	1N	1=IND Safety Report 2=IND-Exempt BA/BE Safety Report 3=Postmarketing Safety Report

* Include either <companynumb> or <authoritynumb> values. FDA cannot process the ICSR without one of these element values.
† The Sender's Safety Report Unique Identifier is comparable to the Manufacturer Report Number (also referred to as the Manufacturer Control Number (MCN)) provided on paper in FDA Form 3500A. This number is the company's unique case identification number, which is used for the life of the case.
^ For IND and IND-exempt BA/BE study safety reports only. An IND-exempt BA/BE study refers to a BA/BE study not conducted under IND.
†† The FDA Safety Report Type data element distinguishes premarketing (IND and IND-Exempt BA/BE) safety reports from postmarketing safety reports and is used to determine which reports are posted publicly. The FDA Safety Report Type data element is optional when using DTD 2.1 and 2.2 for postmarketing safety report submission but is mandatory when using DTD 3.0 for premarketing safety report submission.

C. Authorization/ Application Number Format

In the section designated for drug and biological products information, use the following format for the "Authorization/ Application Number" element (B.4.k.4.1) <drugauthorizationnumb> as indicated in Table 3 and described below.

- For approved drug and biological products marketed under an approved application, include the acronym "NDA" or "ANDA," followed by a space and then the number for the application (e.g., NDA 012345, ANDA 012345). For prescription drug products marketed without an approved application (Rx No Application), use "000000." For a nonprescription drug product marketed without an approved application (Non-Rx No

Application), use "999999." For adverse event reports for compounded drug products submitted by registered outsourcing facilities, use "COMP99."

- For marketed biological products, include the appropriate acronym "BLA," "STN," or "PLA" followed by a space and the primary six-digit number (e.g., STN 123456).

Table 3. Detailed Description of Application Number Formats

Type of Application	Recommended Format
NDA/ ANDA	NDA, ANDA 012345
STN/ BLA/ PLA	STN or BLA or PLA 123456
Rx No Application	000000
Non-Rx No Application	999999
Compounded Products	COMP99

D. Unique Case Identification Numbers for Initial and Follow-Up ICSRs

For the follow-up ICSR safety reports to be correctly linked to your initial ICSR report, follow these steps:

- Use the same <safetyreportid> for the E2BM elements in section A.1.0.1 for the initial ICSR and any of its follow-up ICSRs; this allows the follow-up report to be linked to the initial report in the FAERS database.

- If the initial ICSR was submitted on paper but its follow-up ICSR is submitted electronically, include the Manufacturer Control Number (MCN) listed in Box G9 of the FDA paper Form 3500A from the initial report in both A.1.0.1 <safetyreportid> and in A.1.10.2 <companynumb> field in the follow-up electronic submission.

- Always use the <safetyreportid> that was assigned to the initial ICSR when submitting follow-up reports. If you need to change the <safetyreportid> internally, note the internally reassigned <safetyreportid> in the narrative section of the follow-up report (i.e., element B.5.1) (e.g., "This ICSR has been reassigned to the Company ID number COA12345"). Do not use the internally reassigned <safetyreportid> for any follow-up reports.

- In the event that an incorrect <safetyreportid> has been used in a follow-up report, contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov so that the follow-up ICSR can be matched to the initial ICSR.

E. MedDRA Specific Elements

Use the ICH Medical Dictionary for Regulatory Activities (MedDRA) to code medical

terminology.[6] When possible, use the Lowest Level Term (LLT), and record the LLT as the MedDRA numeric code rather than the LLT name (e.g., the LLT name is Rash; the MedDRA numeric code for LLT Rash is 10378444).

1. Reaction/Event

a) Reaction/Event as reported by the primary source field

Record the original reporter's words verbatim and/or use short phrases to describe the reaction/event in element (B.2.i.0).

b) Reaction/Event MedDRA Term LLT numeric code or text field

Record the MedDRA LLT that most closely corresponds to the term reported by the original reporter in element (B.2.i.1).

c) Reaction/Event MedDRA Preferred Term (PT) numeric code or text field

Record the MedDRA PT that most closely corresponds to the term reported by the original reporter in element (B.2.i.2).

2. Other E2B Elements

For the E2B elements listed in Table 4, use either MedDRA text or, preferably, the corresponding numeric code.

Table 4. Additional E2B Elements for Preferred MedDRA Coding

Element	DTD Descriptor 2.1	Length
B.1.7.1a.2	<patientepisodename>	250 AN
B.1.8f.2	<patientdrugindication>	250 AN
B.1.8g.2	<patientdrugreaction>	250 AN
B.1.9.2b	<patientdeathreport>	250 AN
B.1.9.4b	<patientdetermineautopsy>	250 AN
B.1.10.7.1a.2	<parentmedicalepisodename>	250 AN
B.1.10.8f.2	<parentdrugindication>	250 AN
B.1.10.8g.2	<parentdrugreaction>	250 AN
B.3.1c	<testname>	100 AN
B.4.k.11b	<drugindication>	250 AN
B.4.k.17.2b	<drugrecuraction>	250 AN
B.4.k.18.1b	<drugreactionasses>	250 AN
B.5.3b	<senderdiagnosis>	250 AN

[6] Companies can license MedDRA from an international maintenance and support services organization (MSSO) (toll free number 877-258-8280; Direct 571-313-2574; fax 571-313-2345; e-mail MSSOhelp@mssotools.com).

F. Drug Description and Case Narrative Elements

To ensure the successful processing of your electronic ICSR submission, applicants are advised to populate the drug description and narrative elements as indicated in Table 5.

Table 5. Detailed Description of Drug(s) and Narrative Elements*†

Element	DTD Descriptor 2.1	Length	Element Values for DTD 2.1
B.4.k.1	<drugcharacterization>	1N	1=Suspect 2=Concomitant 3=Interacting 4=Drug not administered
B.4.k.2.1	<medicinalproduct>	70AN	Proprietary Medicinal Product Name
B.4.k.2.2	<activesubstancename>	100AN	Drug Substance Name
B.5.1	<narrativeincludeclinical>	20000AN	Case Narrative

*Include <medicinalproduct> and/or <activesubstancename>. FDA cannot process the ICSR without at least one of these elements.
†Appendix I lists various examples of correct drug element formats.

1. Recording Multiple Drugs

If you are submitting safety reports for products containing multiple drugs, you should follow these steps:

- List the proprietary drug product name in element (B.4.k.2.1) and/or list the drug substance name in element (B.4.k.2.2).
- List the characterization of each reported drug's role, such as suspect, concomitant, interacting, drug not administered, or similar device in element (B.4.k.1).

2. Medicinal Product Name and Active Drug Substance Name

FDA validates medicinal product names to the available Structured Product Labeling (SPL)[7], the submitted label (as ICSR attachment), and the Substance Registration System (SRS). These are further described below:

- When the product has an SPL, use the same naming convention as it appears in the SPL when submitting the ICSR.

[7] The SPL is a document markup standard approved by Health Level Seven (HL7) and adopted by FDA as a mechanism for exchanging product and facility information. See https://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

- When submitting a product label as an attachment to an ICSR, use the name as it appears on the submitted product label.

- If no medicinal product is named and only the active substance is named, use the name of the active substance as it appears in the SRS.[8]

3. Case Narrative

a) Initial ICSR

Record all case narrative information including clinical course, therapeutic measures, outcome, and all additional relevant information in element (B.5.1). If the information exceeds the field length, consider describing the information using fewer words. Although the use of only the most widely used medical abbreviations is permissible if necessary, their use should be limited when possible.

b) Follow-up ICSR

Record both new information and corrections to previously submitted ICSRs in element (B.5.1).

G. Other Data Elements

1. Dosage Information Field

If dosage information cannot be captured in the structured fields in B.4.k.5, then use the element (B.4.k.6) <drugdosagetext>.

2. Pharmaceutical Form Field

Record the pharmaceutical form in element (B.4.k.7) <drugdosageform>. FDA accepts the European Medicines Agency (EMA) dosage codes or text.[9]

3. Route of Administration Field

Code the route of administration in element (B.4.k.8) <drugadministrationroute> as described in the ICH E2B(R2) guidance.

4. Receiver Field (A.3.2)

Complete the receiver using the code or text listed in Table 6.

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[8] https://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/default.htm.

[9] For a complete list of EMA dosage form codes and text, please refer to https://www.ema.europa.eu/documents/other/list-pharmaceutical-dosage-forms_en.xls

Table 6. Receiver Information

Element	DTD Descriptor 2.1	Code or Text
A.3.2.1	<receivertype>	2
A.3.2.2a	<receiverorganization>	FDA
A.3.2.2b	<receiverdepartment>	Office of Surveillance and Epidemiology
A.3.2.2d	<receivergivename>	FAERS
A.3.2.3a	<receiverstreetaddress>	10903 New Hampshire Avenue
A.3.2.3b	<receivercity>	Silver Spring
A.3.2.3c	<receiverstate>	MD
A.3.2.3d	<receiverpostcode>	20993
A.3.2.3e	<receivercountrycode>	US
A.3.2.3l	<receiveremailaddress>	faersesub@fda.hhs.gov

5. Message Receiver Field (M.1.6)

The following two message receiver identifiers are used by FDA to distinguish between test and production submissions:

- Test ICSRs: <messagereceiveridentifier>ZZFDATST</messagereceiveridentifier>
- Production ICSRs: <messagereceiveridentifier>ZZFDA</messagereceiveridentifier>

H. Data Elements for Electronic Submissions of Safety Reports for Postmarketing Combination Products

To ensure the successful processing of your electronic ICSR submission for a marketed drug- or therapeutic biologic led- combination product (e.g., a combination product containing a drug/biologic and device and marketed under an NDA or a BLA), you should populate the data elements indicated in Table 7.

Note: Some of the DTD descriptors listed in Table 7 are under existing E2B(R2) header elements, and some DTD descriptors are under new data elements. Those data element numbers that are new, have the word "FDA" incorporated into the number and are U.S.-specific regional elements related to reporting on combination products.

Table 7. Combination Product Data Elements

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
M.1.2	<messageformatversion>	Message Format Version	Version number of Message Format	3AN	2.2	Use value 2.2 if using icsr-xml-v2.2.dtd Use value 2.1 if using icsr-xml-v2.1.dtd
A.1	<safetyreport>	Header/ Entity	Identification of the case safety report			
A.1.9	<fulfillexpeditecriteria>	Does this case fulfill the local criteria for an expedited report		1N	1=Yes 2=No 4=5-Day 5=30-Day	Element values= 1 for 15-Day Expedited* and 2 for periodic non-expedited† Element value= 4 for remedial action to prevent an unreasonable risk of substantial harm to the public health Element value= 5 for malfunction with no associated adverse event Do not use element value of 3.
A.1.FDA.15	<combinationproductreport>	Combination Product Report Flag	Combination Product Report Flag	1N	1=Yes 2=No	
A.2	<primarysource>	Primary source(s) of information	Header/ Entity		Area below should be a repeatable block	

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
A.2.1		Primary source(s)	Header			
A.2.1.3.FDA.4	<reporteremailaddress>	Reporter's Email Address		100AN		
B.1.1	<patientinitial>	Patient	Patient Identifier	10AN		If a single report is reported for a malfunction with no adverse event, the element value should be "NONE." If there are multiple malfunction reports with no adverse event, then the element value should be "SUMMARY."
B.4	<drug>	Drug(s) Information	Header/ Entity		Area below should be a repeatable block	
B.4.k.1	<drugcharacterization>	Characterization of drug role		1N	1=Suspect 2=Concomitant 3=Interacting 5=Similar Device	If the product in the report is about a similar device, the element value should be 5=Similar Device.
B.4.k.2		Drug Identification	Header			
B.4.k.2.4.FDA.1a	<expirationdateformat>	Expiration date format	Product Expiration date	3N	102=CCYYMMDD 610=CCYYMM 602=CCYY	
B.4.k.2.4.FDA.1b	<expirationdate>	Expiration date	Product Expiration date	8N		

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
B.4.k.2.FDA.5	<productavailableforevaluation>	Product available for evaluation	Indicate whether product is available for evaluation	1N	1=Yes 2=No 3=Return	
B.4.k.2.6.FDA.1a	<productreturndateformat>	Product return date format	Date Format	3N	102=CCYYMMDD 610=CCYYMM 602=CCYY	
B.4.k.2.6.FDA.1b	<productreturndate>	Product return date	Date when Product was returned	8N		
B.4.k.20.FDA.1	<brandname>	Brand Name	The trade or proprietary name of the device constituent part of the suspect combination product as used in product labeling or in the catalog	80AN		At least one of the 3 must be reported <brandname> or <commondevicename> or <productcode> for the device constituent part
B.4.k.20.FDA.2	<commondevicename>	Common Device Name	Generic or common name of the device constituent part of the suspect combination product or a generally descriptive name	80AN		At least one of the 3 must be reported <brandname> or <commondevicename> or <productcode> for device constituent part
B.4.k.20.FDA.3	<productcode>	Product Code	Product code	3AN	http://www.acce	At least one of the 3 must be

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
			assigned to the device constituent part based upon the medical device product classification		ssdata.fda.gov/premarket/ftparea/foiclass.zip	reported <brandname> or <commondevicename> or <productcode> for device constituent part
B.4.k.20.FDA.4	<manufacturer>	Manufacturer	Header/ Entity			
B.4.k.20.FDA.4a	<manufacturername>	Device Manufacturer Name	Manufacturer name of the device constituent part of the suspect combination product	100AN		
B.4.k.20.FDA.4b	<manufactureraddress>	Manufacturer Address	Manufacturer address of the device constituent part of the suspect combination product	100AN		
B.4.k.20.FDA.4c	<manufacturercity>	Manufacturer City	Manufacturer city of the device constituent part of the suspect combination product	35AN		
B.4.k.20.FDA.4d	<manufacturerstate>	Manufacturer State	Manufacturer state of the device	40AN		

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
			constituent part of the suspect combination product			
B.4.k.20.FDA.4e	<manufacturercountry>	Manufacturer Country	Manufacturer country of the device constituent part of the suspect combination product	2AN	ISO3166	
B.4.k.20.FDA.5	<modelnumber>	Model Number	Model number of the device constituent part	30AN		
B.4.k.20.FDA.6	<catalognumber>	Catalog Number	Catalog number of the device constituent part	30AN		
B.4.k.20.FDA.7	<serialnumber>	Serial Number	Serial number of the device constituent part	30AN		
B.4.k.20.FDA.8	<udinumber>	Unique Identifier UDI#	Unique identifier of the device constituent part	50AN		
B.4.k.20.FDA.9a	<dateimplantedformat>	Device Implant Date Format	Date format of device implant in the patient	3N	102=CCYYMMDD 610=CCYYMM 602=CCYY	For medical devices that are implanted in the patient, provide the implant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
B.4.k.20.FDA.9b	<dateimplanted>	Device Implant Date	Date of device implant in the patient	8N		For medical devices that are implanted in the patient, provide the implant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable
B.4.k.20.FDA.10a	<dateexplantedformat>	Device Explant Date Format	Date format of device explant from the patient	3N	102=CCYYMMDD 610=CCYYMM 602=CCYY	If an implanted device was removed from the patient, provide the explant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable
B.4.k.20.FDA.10b	<dateexplanted>	Device Explant Date	Date of device explant from the patient	8N		If an implanted device was removed from the patient, provide the explant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable
B.4.k.20.FDA.11a	<deviceage>	Approximate age of device/ product	Age of device constituent part	5N		
B.4.k.20.FDA.11b	<deviceageunit>	Approximate age unit of device/	Age unit of device constituent part	3N	800=Decade 801=Year 802=Month	

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
		product			803=Week 804=Day 805=Hour	
B.4.k.20.FDA.12	<labeledsingleusedevice>	Single Use Device	Indicate whether the device constituent part was labeled for single use or not	1N	1=Yes 2=No	
B.4.k.20.FDA.13a	<devicemanufacturedateformat>	Device Manufacture Date Format	Device Manufacture Date format	3N	102=CCYYMMDD 610=CCYYMM 602=CCYY	
B.4.k.20.FDA.13b	<devicemanufacturedate>	Device Manufacture Date	Device Manufacture Date	8N		
B.4.k.20.FDA.14		Remedial action initiated/ Remedial action taken for the product	Header			
B.4.k.20.FDA.14.1a	<remedialactionrecall>	Recall	Recall initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1b	<remedialactionrepair>	Repair	Repair initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1c	<remedialactionreplace>	Replace	Replace initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1d	<remedialactionrelabel>	Relabeling	Relabeling initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1	<remedialactionnotify>	Notification	Notification	1N	1=Yes	

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
e			initiated		2=No	
B.4.k.20.FDA.14.1f	<remedialactioninspection>	Inspection	Inspection initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1g	<remedialactionpatientmonitor>	Patient monitoring	Patient monitoring	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1h	<remedialactionmodifyadjust>	Modification/ Adjustment	Modification/ Adjustment initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1i	<remedialactionother>	Other	Other Remedial Action initiated	75AN		
B.4.k.20.FDA.15	<deviceusage>	Device Usage	Indicate the use of the device constituent part of the suspect combination product	1N	1=Initial Use of Device 2=Reuse 3=Unknown	
B.4.k.20.FDA.16	<devicelotnumber>	Device Lot Number	Lot number of the device constituent part of the suspect combination product	35AN		
B.4.k.20.FDA.17	<malfunction>	Malfunction	Malfunction of product	1N	1=Yes 2=No	
B.4.k.20.FDA.18		Follow-up type	Header			
B.4.k.20.FDA.18.1a	<followupcorrection>	Correction	Correction	1N	1=Yes 2=No	
B.4.k.20.FDA.18.1b	<followupadditionalinfo>	Additional information	Additional information	1N	1=Yes 2=No	
B.4.k.20.FDA.18.1	<followupresponsetoFDA>	Response to	Response to FDA	1N	1=Yes	

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
c		FDA request	request		2=No	
B.4.k.20.FDA.18.1d	<followupdeviceevaluation>	Device Evaluation	Device Evaluation	1N	1=Yes 2=No	
B.4.k.20.FDA.19	<deviceproblemandevaluation>	Device Problem and evaluation codes	Header/ Entity		Area Below Should be a Repeatable Block	
B.4.k.20.FDA.19.1a	<evaluationtype>	Evaluation Type	Type of problem and/or the evaluation	2N	01=Device Problem 02=Method 03=Result 04=Conclusion	
B.4.k.20.FDA.19.1b	<evaluationvalue>	Evaluation Value	The FDA code value based on the respective evaluation type	6N		The value depends on the respective <evaluationtype> If <evaluationtype> = 01 --> https://www.fda.gov/media/146825/download If <evaluationtype> = 02 --> https://www.fda.gov/media/146827/download If <evaluationtype> = 03 --> https://www.fda.gov/media/146828/download If <evaluationtype> = 04 --> https://www.fda.gov/media/146829/download
B.4.k.20.FDA.20	<operatorofdevice>	Operator of	Operator of the	100AN		Use the value “Health

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
		the Device	Device			Professional" or "Lay User/Patient." If none applicable, then specify the "Other" value

* 21 CFR 314.80(c)(1) and 600.80(c)(1) use the term "15-day Alert reports." In the combination product PMSR final rule (21 CFR 4.101), these reports are defined as "Fifteen-day reports."

† Periodic non-expedited ICSRs are the reports required under 21 CFR 314.80(c)(2)(ii)(B) and 21 CFR 600.80(c)(2)(ii)(B) for serious, expected and nonserious adverse drug experiences.

I. Data Elements for Electronic Submissions of IND Safety Reports

To ensure the successful processing of your electronic IND ICSR submission, you should populate the following data elements as described in Table 8.

Table 8. Investigational New Drug Clinical Data Elements

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
A.1.4	<reporttype>	Type of Report		1N	1=Spontaneous 2=Report from Study 3=Other 4=Not Available to Sender (unknown)	Element value= 2 for Report from Study
A.1.9	<fulfillexpeditecriteria>	Does this case fulfill the local criteria for an expedited report?		1N	1=Yes 2=No 4=5-Day 5=30-Day 6=7-Day	Element value=1 for 15-Day Expedited Element value= 6 for 7-Day Expedited
A.1.12	<linkreportnumb>	Identification Number of the report which is linked to this report		100AN		Used to link all individual cases (safetyreportid) that make up an IND Safety Report submitted as a result of an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
						submitted as per (312.32(c)(1)(i)(B)) when a Narrative Summary Report is provided, this field should be populated in the IND Safety Report that contains the Narrative Summary Report.
A.2.3.1	<studyname>	Study Name		100AN	Study ID_$Abbreviated Trial Name	The Study ID should be the same value used in the study tagging file format of the eCTD submission.
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number		35AN	IND number under which the clinical trial where the event occurred is conducted Use the "Parent" IND number* for reports submitted from an Aggregate Analysis as per (312.32(c)(1)(i)(C)) or for several events	Populate this field with the Primary IND in the first block and repeat block A.2 with elements A.2.3.2 and A.2.3.3.as noted below with element value= 5 for sponsor's other INDs evaluating suspect product (where applicable) Include the acronym "IND" followed by a space and then the IND

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
					submitted as per (312.32(c)(1)(i)(B)), from trials conducted under more than one IND	number for the application (e.g. IND 123456) See Appendix II (Case Scenarios) for additional information on how to submit reports from sponsor's other INDs (Cross-reporting).
A.2.3.3	<observestudytype>	Study type in which the Reaction(s)/ Event(s) were observed		1N	1= Clinical Trials 2= Individual Patient Use (e.g., 'Compassionate Use' or 'Named Patient Basis') 3= Other Studies (e.g., Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring) 4= Report from	Required if element value for A.1.4 is 2=Report from Study Repeat this field as needed with element value= 5 for each Cross-reported IND. The first block of this element in the report must not be 5. If element value 4 is chosen, then A.1.9= 1. See Appendix II (Case

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
					Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is provided 5= Cross-reported IND Safety Report	Scenarios) for additional information on how to submit reports from an Aggregate Analysis.
B.1.1	<patientinitial>	Patient Identifier		10AN		For a report from an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is provided, the element value should be "AGGREGATE"
B.4.k.2.1	<medicinalproduct>	Proprietary Medicinal Product Name		70AN		For investigational drug and biological products without an established name (i.e. INN or USAN

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
						name), prior to submitting IND safety reports to FAERS, the sponsor should submit a clinical information amendment to the IND, listing the names of the active drug substance/s and the medicinal product as they will be reported in E2B file submissions. The names should fit within the established E2B character length limits. Use company product code if no established name, for multi-ingredient products, or if name exceeds character length
B.4.k.2.2	<activesubstancename>	Active Drug Substance Names		100AN		
B.4.k.18	<drugreactionrelatedness>	Relatedness of Drug to				For IND Safety Reports, at least one suspect

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
		Reaction/ Event				product should have relatedness of drug to reaction/ event
B.4.k.18.1a	<drugreactionassesmeddra version>	MedDRA Version for Reaction Assessed		8AN		
B.4.k.18.1b	<drugreactionasses>	Reaction Assessed		250AN		
B.4.k.18.2	<drugassessmentsource>	Source of Assessment		60AN		Use the value "Sponsor" or "Investigator". Include sponsor and investigator assessment when reporting both in separate blocks
B.4.k.18.3	<drugassessmentmethod>	Method of Assessment		35AN		Use the value "FDA".
B.4.k.18.4	<drugresult>	Result		35AN	1=Suspected 2=Not suspected	For IND Safety Reports, at least one suspect product should have relatedness of drug to reaction/ event
B.5.1	<narrativeincludeclinical>	Case Narrative Including Clinical		20,000 AN		FDA strongly encourages sponsors to construct narratives that fit within the ICH E2B character

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
		Course, Therapeutic Measures, Outcome, and Additional Relevant Information				limit of 20,000 AN. If your narrative exceeds this limit, sponsors should include as much of the narrative as possible in this field and submit an ICSR attachment for any text that exceeds the character limit. Sponsors should not submit an ICSR attachment containing the entire narrative and leave the case narrative field empty. For reports from Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) where PDF is attached, put "see attached Narrative Summary Report" in this field.

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
B.5.4	<sendercomment>	Sender's Comments		2000 AN		Identification and analysis of previously submitted events (as required by 312.32(c)(1)) should be reported in this field.

* The "parent IND" is the IND under which clinical investigations were initiated in the United States. (If the drug is being evaluated in multiple INDs, this is generally the IND with the lowest number.) NOTE: This may not be the same as the first A.2.3.2 block if the drug is being evaluated under multiple INDs.

NOTE: See FAERS Webpage for case scenario examples for reporting IND safety reports (e.g., IND safety reports where the sponsor is evaluating suspect product under more than one IND, IND safety reports that are a result of an aggregate analysis, and IND safety reports with unapproved and approved drugs listed as suspect products).

J. Data Elements for Electronic Submissions of ICSRs from IND-Exempt Bioavailability (BA)/ Bioequivalence (BE) Studies

For successful processing of your electronic ICSRs submissions for a BA/BE study not conducted under an IND, you should populate the following data elements as described in Table 9.

Table 9. Data Elements for IND-Exempt BA/BE Studies

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
A.1.4	<reporttype>	Type of Report		1N	1=Spontaneous 2=Report from Study 3=Other 4=Not Available to Sender (unknown)	Element value= 2 for Report from Study

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
A.1.9	<fulfillexpeditecriteria>	Does this Case Fulfill the Local Criteria for an Expedited Report?		1N	1=Yes 2=No 4=5-Day 5=30-Day 6=7-Day	Element value=1 for 15-Day Expedited Or Element value= 6 for 7-Day Expedited
A.2.3.1	<studyname>	Study Name		100AN	Abbreviated Trial Name	
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number		35AN	Pre-ANDA number for the IND-Exempt BA/BE Studies	Include the acronym "Pre-ANDA" followed by a space and then the Pre-ANDA number for the application (e.g. Pre-ANDA 123456)
A.2.3.3	<observestudytype>	Study Type in Which the Reaction(s)/ Event(s) were Observed		1N	1= Clinical Trials 2= Individual Patient Use (*e.g., 'Compassionate Use' or 'Named Patient Basis'*) 3= Other Studies (*e.g., Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*) 4= Report from Aggregate Analysis as per 312.32(c)(1)(i)(C) or for	Element value="1" for Clinical Trials.

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
					Several Events Submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is Provided 5= Cross-Reported IND Safety Report	
B.4.k.2.1	<medicinalproduct>	Proprietary Medicinal Product Name		70AN		
B.4.k.1	<drugcharacterization>	Characterization of drug role		1N	1 = Suspect 2 = Concomitant 3 = Interacting 4 = Drug not administered	For no exposure to a study drug use 4=Drug not administered
B.4.k.2.2	<activesubstancename>	Active Drug Substance Name		100AN		
B.4.k.19	<drugadditional>	Additional Information on Drug		100AN	1 = Test drug 2 = Reference drug 3 = Placebo/Vehicle 4 = Control (negative or positive) 5 = Other drug	Specify whether the product exposed is the Test drug, Reference drug, Placebo, Vehicle, Control or Other drug

VI. ELECTRONIC FORMAT FOR ICSR ATTACHMENTS

FDA can accept and archive ICSR attachments in PDF format. Currently approved formats for the non-structured component of an ICSR, such as ICSR attachments, are PDF versions 1.4 (current ICH standard) or 1.6 (current version in use at FDA). An ICSR attachment should be electronically submitted to FAERS after the associated ICSR has been submitted and accepted by FAERS.

A. Converting the ICSR Attachment to PDF

Applicants should provide an individual PDF file for each ICSR attachment. If you are submitting multiple ICSR attachments for a particular ICSR, include each attachment in the same PDF file and provide a PDF bookmark to distinguish each attachment. For example, if you are submitting a hospital discharge summary and an autopsy report for a single ICSR, include both in a single PDF file with a bookmark to the hospital discharge summary and a bookmark to the autopsy report.

B. Identification Information in the PDF Document Information Fields

Each PDF file contains fields to be completed by the author of the document. FAERS uses these fields to locate and retrieve the attachments to specific ICSRs. To enable FDA to match the attachment(s) to the correct ICSR, applicants should fill in the PDF document information fields with the appropriate E2B(R2) data elements for the ICSR as indicated in Table 10.

Table 10. Document Information Fields in ICSR Attachments

PDF Document Information Field	Include/ Optional	Document Information*	Length
Title	Include	A.1.0.1 <safetyreportid> Sender's (Case) Safety Report Unique Identifier	100AN
Subject	Include	A.1.10.1 <authoritynumb> Regulatory Authority's Case Report Number OR A.1.10.2 <companynumb> Other Sender's Case Report Number	100AN
Author	Optional	A.1.11.2 <duplicatenumb> Other Identification Number	100AN
Keywords	Optional	A.1.7b <receiptdate> Date of Receipt of the Most Recent Information for this ICSR	8N

* The information refers to the data elements in E2B(R2)

In addition:

- Use the ISO-8859-1 character set for the information fields.
- Do not exceed the character length indicated above for each information field.
- Avoid creating any custom fields with names identical to the information fields listed in Table 10.

If you need assistance, you can contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov.

VII. SUBMISSION RULES

The submission rules define the condition that shall result in a negative acknowledgement and not be accepted by FAERS.

Table 111. Submission Rules and Acknowledgement Status

Data Element	DTD Descriptor 2.1/2.2/3.0	Rejection Rule Description	Acknowledgement
NA	NA	ICSR submitted via AS2 Header where XML file: AERS or Routing ID where XML file: FDA_AERS and using DTD 3.0	reportacknowledgmentcode (B.1.8) = 02
NA	NA	ICSR submitted via AS2 Header where XML file: AERS_PREMKT or Routing ID where XML file: FDA_AERS_PREMKT and using DTD 2.1 or 2.2	reportacknowledgmentcode (B.1.8) = 02
A.1.FDA.16	<fdasafetyreporttype>	ICSR submitted via AS2 Header where XML file: AERS_PREMKT or Routing ID where XML file: FDA_AERS_PREMKT using DTD 3.0 and data value is empty	reportacknowledgmentcode (B.1.8) = 02
A.2.3.2	<sponsorstudynumb>	ICSR submitted via AS2 Header where XML file: AERS_PREMKT or Routing ID where XML file: FDA_AERS_PREMKT using DTD 3.0 and data value is empty or not prefixed with 'IND' or 'Pre-ANDA'	reportacknowledgmentcode (B.1.8) = 02

APPENDIX I. EXAMPLES OF CORRECT AND INCORRECT APPLICATION NUMBER AND DRUG ELEMENT FORMATS

Table 122. Examples of Application Number Formats and Drug Element Formats

Examples of Application Number Format		Comment
Correct	<drugauthorizationnumb>NDA 012345</drugauthorizationnumb>	
Correct	<drugauthorizationnumb>BLA 123456</drugauthorizationnumb>	
Correct	<drugauthorizationnumb>NDA 012345</drugauthorizationnumb> <drugauthorizationholder>COMPANYX</drugauthorizationholder>	
Incorrect	<drugauthorizationnumb>123456/**10300**</drugauthorizationnumb>	Use the appropriate prefix for the NDA/ ANDA/ STN/ BLA/ PLA. Do not include additional data after the application number
Incorrect	<drugauthorizationnumb>NDA **12-345;IND12,345** </drugauthorizationnumb>	Omit hyphens and commas in the application number. Do not populate the tag with two application numbers
Incorrect	<drugauthorizationnumb>**OTC Product**</drugauthorizationnumb>	For a non-prescription drug product marketed without an approved application (Non-Rx No Application), use “999999"
Incorrect	<drugauthorizationnumb>NDA 012345**(COMPANYX)**</drugauthorizationnumb> <drugauthorizationholder></></drugauthorizationholder>	Do not populate the company name in the <drugauthorizationnumb> tag

Examples of Application Number Format		Comment
Correct	<medicinalproduct>TYLENOL</medicinalproduct> <activesubstancename>ACETAMINOPHEN</activesubstancename>	
Correct	<medicinalproduct>MIRACLE WONDER DRUG</medicinalproduct> <activesubstancename>ACETAMINOPHEN</activesubstancename>	
Incorrect	<medicinalproduct>AMAZING DRUG **OTC®**</medicinalproduct> <activesubstancename>ACETAMINOPHEN **500 mg**</activesubstancename>	
Incorrect	<medicinalproduct>NEW DRUG **40 mcg/mL**</medicinalproduct> <activesubstancename>NEWSUBSTANCE **Inj** </activesubstancename>	
Incorrect	<medicinalproduct>**MWD**</medicinalproduct> <activesubstancename>**APAP**</activesubstancename>	Do not use abbreviations for the brand name or active substance in the <medicinalproduct> and <activesubstance> tags

APPENDIX II. CASE SCENARIOS FOR IND SAFETY REPORTS SUBMITTED TO FAERS

The following case scenarios are intended to provide examples to sponsors on the use of ICH E2B data standard elements for submission of IND safety reports to FAERS that may differ from postmarketing safety reports.

1. For any IND safety report where the sponsor is evaluating the suspect product under more than one IND (i.e. "Cross-reporting")
    a. Repeat block A.2 for each IND
        i. Use first block A.2 to designate IND where the event occurred = "primary IND"
            1. A.2.3.2 = primary IND
            2. A.2.3.3 = data value could either be 1, 2, 3, or 4
            3. Other relevant information for the report to be populated in block A.2
        ii. Repeat block A.2 as many times as needed with only the following data elements for each IND that the sponsor holds where that suspect product is being evaluated:
            1. A.2.3.2 = IND number for each cross-reported IND

            and

            2. A.2.3.3 = 5

Table 133. Case Scenario 1. For IND Safety Reports Submitted to FAERS

Data Element	DTD Descriptor 3.0	Title	Element Values for DTD
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	IND number under which the Clinical Trial where the event occurred is conducted

Data Element	DTD Descriptor 3.0	Title	Element Values for DTD
A.2.3.3	<observestudytype>	Study Type in Which the Reaction(s) were observed	1= Clinical Trial 2= Individual Patient Use (*e.g. 'Compassionate Use' or 'Named Patient Basis'*) 3= Other Studies (*e.g. Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*) 4= Report from Aggregate Analysis 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary report is provided. 5=Cross-reported IND safety report

2. For an IND safety report that is a result of an aggregate analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided:

    a. Submit one IND safety report with the IND where the event occurred in A.2.3.2 <sponsorstudynumb> (or the "parent" IND if the events occurred in multiple INDs).

    For this IND safety report, populate the data elements below in addition to other relevant information regarding the event and suspect product.

        i. Use data element = 4 in A.2.3.3<observestudytype>

        ii. Use the term "AGGREGATE" in B.1.1 <patientinitial>

    b. Section VII.A.2. of the *FDA Guidance for Industry – "Safety Reporting Requirements for INDs and BA/BE Studies" (December 2012)* discusses several submission requirements for IND safety reports that are a result of an aggregate analysis. The following two sections describe these submission elements and how they are accomplished with electronic submission to FAERS.

        1. The guidance states that IND safety reports that are a result of an aggregate analysis should contain a narrative description of the event and the results of the analysis (hereafter referred to as a "narrative

summary report"). For IND reports submitted to FAERS, attach the narrative summary report to the IND safety report as a PDF attachment (do not put the narrative summary report in the E2B narrative field).

a. These instructions also apply to several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided.

2. The guidance states that all the individual cases that were analyzed in the aggregate analysis should be submitted. Use the repeatable block A.1.12 to link all the safety report numbers for the individual supportive ICSRs (i.e. the numbers in A.1.0.1 for all the individual cases that are summarized in the narrative summary report).

a. These instructions also apply to several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided.

b. IND safety reports previously submitted as ICSRs to FAERS do not have to be resubmitted (place the safety report numbers for these previously submitted reports in A.1.12).

c. For IND safety reports previously submitted in eCTD format, the sponsor should list the eCTD sequence number and date of submission in the narrative summary report. (The eCTD sequence number is the unique four-digit number for each IND submission the sponsor submits in the us-regional.xml file for the eCTD submission.)

d. IND safety reports previously submitted on paper should be attached to the IND safety report as PDF attachments.

Table 144. Case Scenario 2. For IND Safety Reports Submitted to FAERS

Data Element	DTD Descriptor 3.0	Title	Element Values for DTD
A.1.12	<linkreportnumb>	Identification number of the report(s) which are linked to this report	Used to link all individual cases (safetyreportid) that make up an IND Safety Report submitted as a result of an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	IND number under which the Clinical Trial where the event occurred is conducted

Data Element	DTD Descriptor 3.0	Title	Element Values for DTD
A.2.3.3	<observestudytype>	Study Type in Which the Reaction(s) were Observed	1= Clinical Trials 2= Individual Patient Use (*e.g. 'Compassionate Use' or 'Named Patient Basis'*) 3= Other Studies (*e.g. Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*) 4= Report from Aggregate Analysis 312.32(c)(1)(i)(C) 5=Cross-reported IND safety report
B.1.1	<patientinitial>	Patient Identifier	For a Report from an Aggregate Analysis, the element value should be "AGGREGATE"

3. For adverse events that occur with a marketed drug being evaluated under an IND that meets both IND and post-marketing safety reporting requirements (21 CFR 312.32 and 314.80, 600.80, or 310.305), sponsors must submit two separate ICSRs:

    a. for the marketed drug for the NDA/BLA

    and

    b. for the study drug for the IND (IND number in A.2.3.2)

APPENDIX III. CASE SCENARIOS FOR SAFETY REPORTS FROM IND-EXEMPT BA/BE STUDIES TO FAERS

Table 15 illustrates the ICH E2B data elements and element values for each IND-exempt BA/BE study exposure scenario described below:

Scenario 1: Exposure to a *study drug*:

This scenario applies to all drugs specified in the study protocol. For example, if a BA/BE study protocol for a generic opiate includes administration of naltrexone to each study subject prior to administration of a test or reference drug, naltrexone is a *study drug*, although it is not the test or reference drug. Similarly, a selective 5-HT3 receptor antagonist to prevent nausea and vomiting is considered a *study drug* if the BA/BE study protocol states that the drug is administered to each study subject prior to administration of a test or reference drug.

Scenario 2: Exposure to an *other drug*:

Other drugs are drugs taken by or administered to a subject that are not part of study conduct per protocol. For example, a subject with a diagnosis of hypertension has normal blood pressure while treated with a beta blocker. The subject meets study enrollment criteria and continues to take his beta blocker during study participation. In this situation, the beta blocker is an *other drug*. Similarly, if a subject develops symptoms of heartburn during participation in a BA/BE study and is permitted, by the investigator, to use a nonprescription antacid or H2 blocker for symptomatic relief, the nonprescription drug taken by the subject is an *other drug*.

Scenario 3: No exposure to a study drug:

A serious adverse event a subject experiences after enrollment to the study, but prior to exposure to a study drug, is subject to the expedited safety reporting requirement. To report a serious adverse event with no study drug exposure, the submitter should select values as shown in the Table 15, Scenario 3.

Table 155. ICH E2B Data Element & Value Selections for IND-Exempt BA/BE Study Exposures

Drug Exposure Scenario	Data Element	Element Values
Scenario 1: Exposure to a *study drug*	B.4.k.1	Select one element value
	B.4.k.2.1	Proprietary medicinal product name
	B.4.k.2.2	Drug substance name
	B.4.k.19	Select one from the following: 1 = Test drug 2 = Reference drug 3 = Placebo/Vehicle 4 = Control (negative or positive)
Scenario 2: Exposure to an *other drug*	B.4.k.1	Select one element value
	B.4.k.2.1	Proprietary medicinal product name
	B.4.k.2.2	Drug substance name
	B.4.k.19	5 = Other drug
Scenario 3: No exposure to a *study drug*	B.4.k.1	4 = Drug not administered
	B.4.k.2.1	Proprietary medicinal product name
	B.4.k.2.2	Drug substance name
	B.4.k.19	1 = Test drug