24-2092

United States Court of Appeals
for the
Second Circuit

BOEHRINGER INGELHEIM PHARAMACEUTICALS, INC.,

Plaintiff-Appellant,

v.

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, XAVIER BECERRA, IN HIS OFFICIAL CAPACITY AS SECRETARY OF HEALTH AND HUMAN SERVICES, CENTERS FOR MEDICARE AND MEDICAID SERVICES, AND CHIQUITA BROOKS-LASURE, IN HER OFFICIAL CAPACITY AS ADMINISTRATOR OF CENTERS FOR MEDICARE AND MEDICAID SERVICES. ,

Defendants-Appellees.

On Appeal from the United States District Court
for the District of New York, Case Nos. 3:23-cv-01103,
District Judge Micael P. Shea

BRIEF OF DANIEL E. TROY, FORMER CHIEF COUNSEL TO THE U.S. FOOD AND DRUG ADMINISTRATION, AS *AMICUS CURIAE* IN SUPPORT OF PLAINTIFF-APPELLANT AND REVERSAL

LAUREN BERNSTEIN
DLA PIPER LLP (US)
1251 Avenue of the Americas
New York, NY 10020
Telephone: (212) 335-4500
lauren.bernstein@us.dlapiper.com

ILANA H. EISENSTEIN
Counsel of Record
DLA PIPER LLP (US)
1650 Market Street, Suite 4900
Philadelphia, PA 19103
Telephone: (215) 656-3300
ilana.eisenstein@us.dlapiper.com

Attorneys for Amicus Curiae

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RULE 29 STATEMENT OF INTERESTS OF *AMICUS CURIAE* AND INTRODUCTION[1]

Amicus curiae is Daniel E. Troy, former Chief Counsel for the U.S. Food and Drug Administration ("FDA"). As Chief Counsel for nearly four years, Mr. Troy advised the FDA Commissioner, the Department of Health and Human Services, and the White House on litigation and regulatory issues related to drugs, medical devices, biologicals, veterinary drugs, food, and cosmetics. Mr. Troy is also the former general counsel at GlaxoSmithKline and Valo Health, an AI-biotech startup, and a former partner at preeminent law firms. Mr. Troy has more than thirty years of experience in private and governmental sectors. Currently, Mr. Troy regularly testifies as an expert in FDA-related litigation.

As former Chief Counsel to the FDA, and given his positions in the pharmaceutical sector, amicus has direct experience with the agency's thorough review process, as well as the many steps, years, and expenditures that obtaining FDA approval entails. The federal government has a long history of rewarding drug makers who survive FDA review to bring innovative new therapies to patients by enabling them to recoup their investment and thus encouraging them to continue to develop such new drugs for diverse patient populations. Moreover, the federal

[1] No counsel for a party authored this brief in whole or in part. No person other than amicus or his counsel made a monetary contribution to this brief's preparation or submission. The parties have consented to the filing of this amicus brief.

government has made significant changes to the review and approval process that has accelerated approval times, a welcome development now undercut by the Inflation Reduction Act's price negotiation mandate.

Mr. Troy submits this brief to advise the Court of the harms of the Inflation Reduction Act (the "IRA") based on his experience with FDA and in the private sector. First, Mr. Troy describes the rigorous review FDA undertakes before approving drugs as safe and effective, as well as the research, development, and clinical costs associated with bringing a drug from inception through FDA approval and then commercialization. Second, Mr. Troy explains how the IRA reduces pharmaceutical companies' incentives to develop new drugs, including drugs in therapeutic areas with high unmet needs where FDA has successfully implemented review programs or extensions to data exclusivity have been provided to support therapeutic development due to patient need not being addressed by existing market incentives. Third, Mr. Troy illustrates how the IRA discourages pharmaceutical companies from researching additional indications, which could result in much less sound information about drugs becoming available to patients.

ARGUMENT

I. FDA Approval Is Costly and Difficult to Obtain

The process to develop prescription pharmaceuticals and obtain approval from the U.S. Food and Drug Administration ("FDA") is time-consuming and stringent.[2] In fact, ninety percent of clinical drug development efforts fail.[3] As FDA explains on its website:

> Most drugs that undergo preclinical (animal) testing never even make it to human testing and review by the FDA. The drugs that do must undergo the agency's rigorous evaluation process, which scrutinizes everything about the drug—from the design of clinical trials to the severity of side effects to the conditions under which the drug is manufactured.[4]

Meticulous review, and a high bar for approval, are essential to ensure that all marketed drugs are safe and effective. First, drugs must undergo extensive and costly research and development ("R&D"). According to the IQVIA Institute for Human Data Science, R&D expenditure by large pharmaceutical companies totaled a record $161 billion in 2023, more than triple NIH's entire budget.[5] This represents

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[2] FDA, *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective* (Nov. 24, 2017), https://tinyurl.com/mscpydrw; Duxin Sun et al., *Why 90% of Clinical Drug Development Fails and How to Improve It?*, 12 Acta Pharmaceutica Sinica B. 3049, 3050 (2022), https://tinyurl.com/mubk9umh.

[3] Sun, *supra* n.2, at 3050.

[4] FDA, *supra* n.2.

[5] IQVIA Institute for Human Data Sci., *Global Trends in R&D 2024: Activity Productivity & Enablers* 2 (February 22, 2024), https://tinyurl.com/38kyepa5; U.S. Dep't of Health & Human Servs., Nat'l Instits. of Health, *What We Do: Budget* (Oct. 24, 2023), https://www.nih.gov/about-nih/what-we-do/budget (noting that the NIH budget is $48 billion).

a nearly 50% increase from 2018, and constitutes a historic high of nearly one quarter of industry revenues.[6]

R&D costs have nearly doubled since 2000, and pharmaceutical development expenses are higher than costs in other research-intensive industries.[7] Indeed, estimates for average R&D expenditures for pharmaceuticals range from the hundreds of millions to more than $2 billion, with one widely cited study by the Tufts University's Center for the Study of Drug Development placing the R&D costs for new drugs at approximately $2.6 billion per drug.[8] R&D expenditures for major pharmaceutical companies are huge line items in their budgets; for example, GlaxoSmithKline spent about 20% of its revenues on R&D in 2023 and Sanofi about 16%.[9] Even if development is successful, there is no guarantee, even after these expenses, that a drug will be a commercial success. In particular, commercial success is uncertain for medical conditions where few people are affected, such as drugs for orphan diseases or those with an uncertain amount of need, such as infectious diseases medicines. The high cost and extended time for R&D are driven, in substantial part, by the rigorous FDA process for approval of any new drug.

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[6] IQVIA Institute for Human Data, *Global Trends in R&D 2024: Activity Productivity & Enablers* 2.

[7] Cong. Budget Off., *Research & Development in the Pharmaceutical Industry* 1 (2021), https://tinyurl.com/2nv7ue7x.

[8] *Id.* at 14; *see also* Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20, 20 (May 2016), https://tinyurl.com/4c39d99e.

[9] GlaxoSmithKline, *Annual Report 2023* at 81 (Mar. 5, 2024). https://tinyurl.com/35sfef4p; Sanofi, *Half-Year Financial Report* 2023 at 44 (July 28, 2023), https://tinyurl.com/2bhsjdxj.

After a potential new drug has been identified, the drug's sponsor will screen the molecule for pharmacological activity and acute toxicity in animals.[10] FDA becomes involved when, after the drug has passed such preclinical tests, the manufacturer or marketer of the drug is ready to test it on humans.[11] Before human trials can begin, the sponsor of the prospective clinical studies will file an Investigational New Drug Application (an "IND") seeking authorization from FDA to test the drug on humans and ship the drug to clinical investigators across the U.S.[12] The IND must disclose to FDA: (i) preclinical data, to assess whether the drug is safe for human trials; (ii) manufacturing information, to ensure that the manufacturer can produce consistent batches of the drug; and (iii) detailed protocols, to assess the risks involved and qualifications of the investigators.[13] After submission, the IND is reviewed by FDA and a local institutional review board (an "IRB").[14] The IRB, made up of hospitals and research institutions overseeing the clinical research, approves the trial protocols.[15]

Next, Phase 1 trials begin, typically with twenty to eighty healthy volunteers.[16] Phase 1 trials, which take approximately eighteen months, will primarily test the

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[10] U.S. Food & Drug Admin., *Investigational New Drug (IND) Application (2022)*, https://tinyurl.com/2827yn7j.
[11] *Id.*
[12] *Id.*
[13] *Id.*
[14] FDA, *supra* n.2.
[15] *Id.*
[16] *Id.*

drug's safety by assessing its most frequent side effects and how it metabolizes in the body.[17] If unacceptable toxicity levels are found during Phase 1, which occurs approximately 33% of the time, the trial is terminated.[18] Phase 2 assesses the drug's effectiveness to treat a particular disease or condition targeted by the therapy, and usually involves a few dozen to 300 participants.[19] Phase 2 trials often use a control group, who receive a placebo or different drug.[20] Fewer than half of studies make it through Phase 2, and these trials typically take approximately two and a half years.[21] After Phase 2 trials conclude, and if there is evidence of effectiveness, FDA will generally meet with the trial sponsor to determine the scale of Phase 3 trials, which typically range from a few hundred to 3,000 subjects.[22] During Phase 3, more information is gathered about safety and effectiveness, different patient populations and dosages are assessed, and the drug may be studied in combination with other drugs.[23] These trials typically take another two and a half years.[24] Approximately 60% of drug candidates survive Phase 3, meaning 40% do not.[25]

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[17] *Id.*; Sun, *supra* n.2, at 3050 (Figure 1).
[18] Sun, *supra* n.2, at 3050 (Figure 1).
[19] FDA, *supra* n.2.
[20] *Id.*
[21] Sun, *supra* n.2, at 3050 (Figure 1).
[22] FDA, *supra* n.2.
[23] *Id.*
[24] Sun, *supra* n.2, at 3050 (Figure 1).
[25] *Id.*

The costs associated with conducting the trials are substantial, averaging $375 million for approved drugs.[26] Each phase of the study requires, *inter alia*, developing protocols, signing up research centers and investigators, training personnel, gathering more subjects, following up with patients, building manufacturing facilities in compliance with good manufacturing practices, and collecting hundreds of thousands of data points. For example, a 2016 study found that for a typical Phase 3 trial in 2012, 900,000 data points were collected.[27]

For those investigational drugs that are able to successfully complete all three phases of the clinical trials, the drug sponsor will meet with FDA and then prepare a massive New Drug Application ("NDA"), asking FDA to approve the drug for marketing and sale in the United States.[28] The NDA will include all of the animal and human data and analyses, including information about how the drug behaves in the body and how it is manufactured.[29] FDA then has sixty days to decide whether to accept the NDA for filing, and aims to complete review of that NDA within 10 months after receiving the application.[30] During that period, FDA thoroughly

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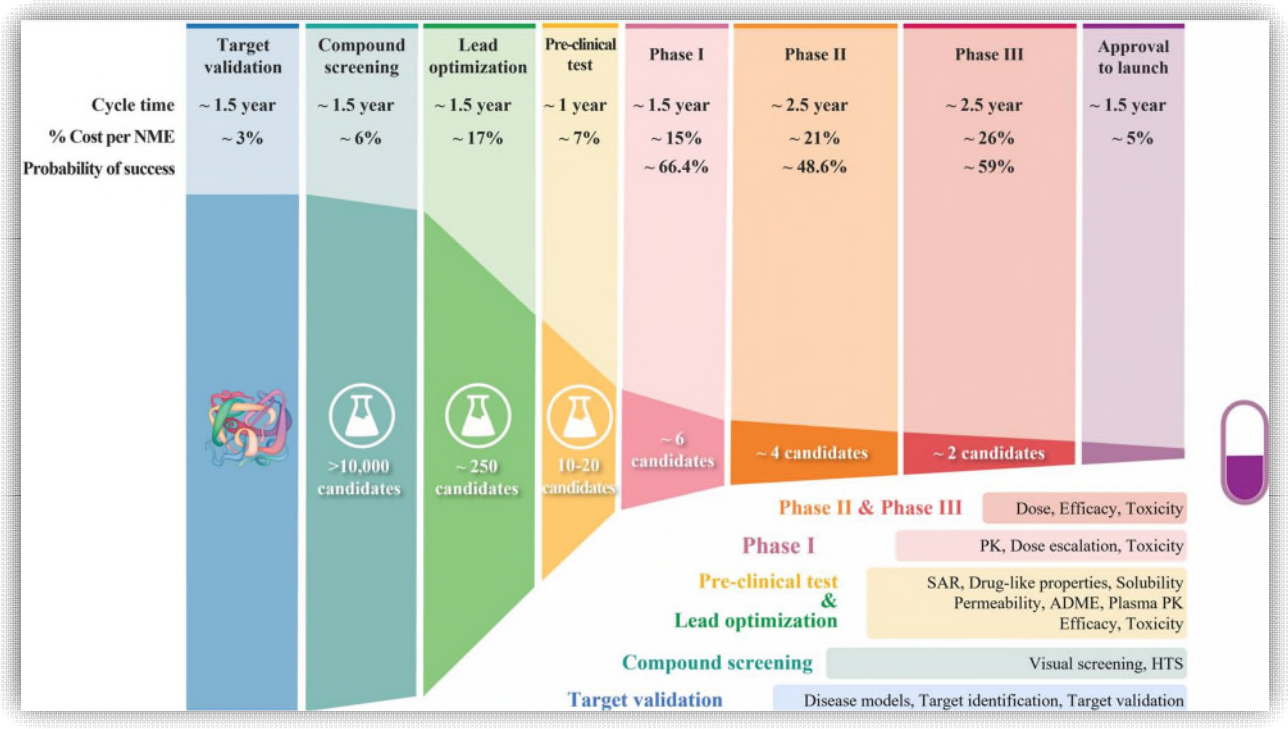
[26] Cong. Budget Off., *supra n.*7, at 15 (citing Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20, 24-25 (May 2016), https://tinyurl.com/2c56fpfy (noting that in 2013, "[s]pending averaged $28 million in phase I, $65 million in phase II, and $282 million in phase III.").
[27] Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. Health Econ. 20, 32 (May 2016), https://tinyurl.com/2c56fpfy.
[28] FDA, *supra* n.2.
[29] *Id.*
[30] *Id.*

reviews the thousands and thousands of pages submitted in and with the NDA, a review that involves medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts to assess potential weaknesses in the trial design or analyses, and determine whether they agree that the drug's benefits outweigh its risks, and that it is safe and effective for the purpose for which it is intended.[31] Depending on FDA's findings, a sponsor may need to conduct additional studies.[32] FDA will also evaluate the drug label to assure that appropriate information is conveyed to healthcare providers and patients.[33] In addition, FDA will inspect the manufacturing facilities to ensure they are employing good manufacturing practices before approving the application.[34]

As shown in the graphic below[35] depicting the process of drug discovery and development, and the failure rate at each step, most drugs do not make it through this costly and time-consuming process:

[31] U.S. Food & Drug Admin., *FDA's Drug Review Process: Continued* (2015), https://tinyurl.com/4hatyx4t.
[32] *Id.*
[33] U.S. Food & Drug Admin., *FDA Drug Approval Process Infographic (Vertical)* (2016), https://tinyurl.com/yj4tdhhz.
[34] FDA, *supra* n.31.
[35] Sun, *supra* n.2, at 3050 (Figure 1).



In recognition of the time and cost involved in developing and obtaining approval for a new drug, there have been special approval pathways established to make drugs available as rapidly as possible. These include: (i) Fast Track designation for drugs in development for a high unmet need, which provides for early and more frequent communication with FDA; (ii) Priority Review, which reduces the time for FDA to review the drug application; and (iii) Accelerated Approval, which allows for drugs for serious conditions with high unmet need to be approved based on a surrogate endpoint. There are also specific data exclusivity extensions, such as for pediatric studies or for "orphan" diseases affecting fewer than 200,000 people in the U.S., or certain types of infectious disease medicines. These programs have a dual aim; they increase the financial benefit to the drug developer,

encouraging investment in therapeutic areas that may otherwise be under-studied, and they accelerate access to new medicines for people who need them.

II. The IRA Slashes Drug Manufacturers' Ability to Recoup Costs

The high costs and high failure rate associated with researching, developing, testing, and obtaining FDA approval for drugs in the United States necessitate charging prices that compensate pharmaceutical companies for taking such risks and which encourage them to continue to invest in new pharmaceuticals in the future, including drugs for serious conditions with high unmet needs. In a study conducted earlier this year, Deloitte found that the average cost of developing new drugs, from discovery through clinical trials and to market, is a staggering $2.3 billion (including the costs associated with failed drugs).[36] R&D costs remain high, while the return on investment continues on a downward trend since 2013.[37] Losses in the development of cancer-treating drugs, for example, are estimated to be between $50 to $60 billion annually.[38] The pharmaceutical business model is built on the concept that the successes subsidize the failures.[39]

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[36] Deloitte, *Deloitte Pharma Study: R&D Returns Are Improving – Regulation Could Stifle Innovation* (May 13, 2024), https://tinyurl.com/4dz3txj9.
[37] *Id.* (Figure).
[38] Valerie Jentzsch et al., *Costs and Causes of Oncology Drug Attrition With the Example of Insulin-Like Growth Factor-1 Receptor Inhibitors*, JAMA Network Open, July 28, 2023; 6(7), at 1, 8, https://tinyurl.com/3pfu5kj2.
[39] Joseph A. Dimasi & Henry G. Grabowski, *R&D Costs & Returns to New Drug Development: A Review of the Evidence*, *in* 2 THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY 21, 23-25 (Patricia M. Danzon and Sean Nicholson eds., 2012), https://tinyurl.com/3xhbn2p9.

The IRA, which compels pharmaceutical companies to sell selected drugs to the government at deep discounts, at the risk of losing their access to the entire Medicare market, deprives pharmaceutical companies of their ability to earn a reasonable return on their massive drug development investments and make up the costs spent on failed research with the profits earned on the successes.

Even before the IRA's passage, rates of return on R&D underperformed relative to alternative investments, with returns for the top twenty drug manufacturers sitting at just 4.1% in 2023.[40] These low rates of return on investment can severely affect a drug manufacturer's ability to raise capital, as demonstrated in recent years by a large rise in biotech bankruptcies following a rise in interest rates after the Covid-19 pandemic.[41] The existing effects of low returns on R&D is evident in the shift away from certain types of therapeutics, including antibiotics, where there has been significant effort to create financial incentives to address the risk of infections and antibiotic resistance.[42] The IRA has the potential to create new vacuums in drug discovery where the financial return is uncertain or small from investments in clinical studies.

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[40] Deloitte, *supra* n.36.

[41] Ana Mulero, *Biotech Bankruptcies Skyrocket*, BioSpace (Oct. 10, 2023), https://tinyurl.com/479dk863.

[42] Milken Inst., *Models for Financing Antibiotic Development to Address Antimicrobial Resistance* 1-2 (March 24, 2022), https://tinyurl.com/3dcfnm8v.

By forcing pharmaceutical companies to provide certain high-revenue drugs to the government at unsustainably low prices, the IRA deeply diminishes investors and pharmaceutical companies' incentives to invest in drug development, particularly in areas where trials are costly and outcomes are uncertain. Pharmaceutical companies simply may not undertake the cost, time, and risk it takes to develop new therapies. Indeed, following the announcement of the IRA's implementation, multiple biopharmaceutical firms announced cancellation of drug development programs due in part to the IRA.[43] That is unsurprising, given the widespread consensus among economists that price controls cause such market distortions.[44]

III. The IRA Disincentivizes Drug Manufacturers from Investing in New Indications and Patient Populations

The IRA also reduces the economic incentives for drug manufacturers to pursue further clinical development in the U.S. for new indications of drugs that have already received FDA approval. Drug manufacturers typically secure patents well before receiving FDA approval, sometimes even before knowing fully what indications for a new drug may be possible. Pembrolizumab (Keytruda), for example, was initially approved for advanced melanoma, but later obtained dozens

[43] Tomas J. Philipson et al., *Policy Brief: The Potentially Larger Than Predicted Impact of the IRA on Small Molecule R&D and Patient Health* §§ 1, 2.2 (Aug. 25, 2023) (The Univ. of Chicago), https://tinyurl.com/ya5hxv5y.

[44] *See, e.g.*, Hugh Rockoff, *Price Controls*, ECONLIB, https://tinyurl.com/229ej2f4 (last visited Nov. 11, 2024).

of other indications over a period of ten years.[45] Similarly, rituximab (Rituxan) was first approved for non-Hodgkin's lymphoma, but subsequently received approval for other indications, such as for the treatment of granulomatosis with polyangiitis, a blood vessel disorder, more than a decade after its first approval.[46] This process is typical of many drugs.[47] Drug manufacturers thus often seek initial approval from FDA to allow them to provide a safe and effective drug to certain groups of patients while they later explore whether other indications are available during the patent life (or the life of later-secured patents), seeking further FDA approval as appropriate. FDA favors this approach, as it allows the agency to consider the safety and efficacy of the drug in narrow subsets, as supported by the manufacturer's research.

The IRA, however, encourages manufacturers to stop R&D on a product altogether after a drug has been approved for the first indication. This is because the IRA imposes mandatory, minimum discounts based on the number of years since a drug was *first* approved for any indication. Therefore, the manufacturer is denied

[45] Judith Stewart, *Keytruda FDA Approval History*, Drugs.com, https://tinyurl.com/4v86x7w9 (last updated Oct. 2, 2024).
[46] Judith Stewart, *Rituxan FDA Approval History*, Drugs.com, https://tinyurl.com/53zysjbp (last updated Jan. 27, 2021).
[47] John M. O'Brien et al., *How The IRA Could Delay Pharmaceutical Launches, Reduce Indications, and Chill Evidence Generation*, Health Affairs Forefront (Nov. 3, 2023), https://tinyurl.com/2cv663c6 (citing rivaroxaban, which received initial FDA approval for the prevention of deep vein thrombosis but later received approval for other indications following subsequent research, and empagliflozin, which was first approved as a diabetes treatment but, following subsequent research, later received FDA approval for other indications more than seven years after the drug was initially approved).

additional profits that would result from R&D expenditures in new indications. *See* 42 U.S.C. § 1320f-3 (mandating discounts of at least 25%, 35%, or 60% from market value depending on the years since receiving FDA approval).

This not only slows the pace of innovation and discovery, but it also adversely affects patients. Depending on internal value projections, the manufacturer will either (a) be incentivized to delay seeking approval until broader, or a larger range of, indications have been realized, postponing access for the initial indication patient group and delaying access to (lawful) off-label prescribing for broader groups; or (b) seek approval of the initial indication and then stop all further R&D into that molecule. Either way, these perverse incentives adversely affect patient outcomes, because manufacturers who think there is a high likelihood of broader indications may wait to delay launch, while those who think there is a lower likelihood of broader indications are discouraged from exploring them. Moreover, as the IRA will reduce the rewards of pursuing new indications, the patients receiving the drugs off-label will not benefit from the information gathered through the clinical development process. Further, insurers can restrict formulary access to on-label uses, limiting patients' ability to obtain treatment.[48] The significant efforts that the federal government and FDA have made to accelerate drug approval are thus eroded by the

[48] C. Joseph Ross Daval & Aaron S. Kesselheim, *Authority of Medicare to Limit Coverage of FDA-Approved Products: Legal and Policy Considerations* 183 JAMA Internal Med. 999, 1002-03 (2023), https://tinyurl.com/hjam36f4.

IRA. The result will be less innovation, fewer patients getting the care they need, and stalling of research-based development involving already-approved drugs. The inevitable effect will be a substantial reduction in the number of Supplemental New Drug Applications filed, as well as a rise in off-label prescribing and uses that might otherwise eventually be approved as on-label – and thus demonstrated to be safe and effective according to FDA's standards.

CONCLUSION

Amicus curiae urges this Court to reverse the judgment of the District Court.

Dated: November 12, 2024

Respectfully submitted,

/s/ *Ilana H. Eisenstein*

Ilana H. Eisenstein

DLA PIPER LLP (US)
One Liberty Place
1650 Market Street, Suite 4900
Philadelphia, PA 19103-7300
Telephone: 215.656.3300
Facsimile: 215.656.3301

Attorney for Amicus Curiae

CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. 32(g), I hereby certify that the foregoing brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7) because it contains 3,318 words, excluding the parts of the document exempted by Fed. R. App. 32(f).

The foregoing document also complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type-style requirements of Fed. R. App. P. 32(a)(6) because this document has been prepared in 14-point Times New Roman proportionally spaced font using Microsoft Word.

Date: November 12, 2024 By: /s/ *Ilana H. Eisenstein*

Ilana H. Eisenstein
DLA PIPER LLP (US)
One Liberty Place
1650 Market Street, Suite 4900
Philadelphia, PA 19103
Telephone: (215) 656-3300
Ilana.Eisenstein@DLAPiper.com

Attorney for Amicus Curiae

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing was filed with the Court electronically on the 12th day of November, 2024. Notice of this filing will be sent by operation of the Court's electronic filing system to all parties indicated on the electronic filing receipt. Parties may access this filing through the Court's system.

Date: November 12, 2024

By: /s/ *Ilana H. Eisenstein*

Ilana H. Eisenstein
DLA PIPER LLP (US)
One Liberty Place
1650 Market Street, Suite 4900
Philadelphia, PA 19103
Telephone: (215) 656-3300
Ilana.Eisenstein@DLAPiper.com

Attorney for Amicus Curiae