No. 22-1676

In the United States Court of Appeals for the Third Circuit

ASTRAZENECA PHARMACEUTICALS LP,

Plaintiff-Appellee,

v.

SECRETARY, UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES, *et al.*,

Defendants-Appellants.

On Appeal from the United States District Court for the District of Delaware, No. 1:21-cv-00027 (Hon. Leonard P. Stark)

BRIEF OF AMICUS CURIAE OTSUKA AMERICA PHARMACEUTICAL, INC.

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INTEREST OF *AMICUS CURIAE* AND SUMMARY OF ARGUMENT[1]

Otsuka America Pharmaceutical, Inc. ("Otsuka") is dedicated to bringing medicines to market that will provide new treatments to patients with no or few treatment options. Otsuka has a focus in areas of particularly acute patient need, including nephrology, kidney disease, and neuroscience. One of its products, JYNARQUE® ("Jynarque"), is approved by the U.S. Food & Drug Administration ("the FDA") to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease ("ADPKD"), a genetic condition that causes cysts to grow in the kidneys and affects between 1 in 400 and 1 in 1,000 people. Many patients with this condition can develop kidney failure by age 60. Patients using Jynarque, however, show a 49% reduction in kidney volume loss after three years of treatment.

Although Jynarque is safe and effective, the FDA has required Otsuka to implement and maintain a risk evaluation and mitigation strategy ("REMS") to address the risk of serious and potentially fatal liver injury associated with the use of Jynarque in a small percentage of patients. Otsuka would face serious potential

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[1] No party's counsel authored this brief in whole or in part, and no party, its counsel, or any other person—other than Otsuka or its counsel—contributed money intended to fund preparation or submission of this brief. *See* Fed. R. App. P. 29(a)(4)(E). The government parties and AstraZeneca have consented to this filing.

consequences if it failed to do so. REMS are imposed by FDA on many other drugs, including whole classes of drugs.

The Jynarque REMS, like many other REMS, includes requirements that restrict the pharmacies that may dispense the medication. A pharmacy dispensing Jynarque must undergo a certification process, specially train its personnel, develop special processes and procedures for dispensing the medication, and otherwise comply with the REMS. These requirements are common elements of REMS.

Like many other manufacturers, Otsuka implemented its REMS by using a restricted pharmacy distribution system involving a small number of specialty pharmacies experienced in dispensing medications that require special procedures. The use of limited distribution systems is common for many specialty drugs, which require special handling, increased patient education, or enhanced safety measures, whether or not the drug is subject to a REMS. This is because, especially with smaller patient populations, it is not possible to certify, train, and ensure REMS compliance or to build safety, special handling, or intensive patient education programs into distribution systems that involve a large network.

Like many manufacturers before it, Otsuka implemented its limited distribution system in 2018 in reliance on years of Health Resources & Services Administration ("HRSA") guidance specifically permitting manufacturers to

implement such systems, whether or not a REMS applied. Importantly, under the Jynarque limited distribution system, all covered entities may secure an unlimited quantity of the medication at the 340B price by using a specialty pharmacy designated by Otsuka, called PANTHERx ("Panther"), which can deliver product to patients anywhere in the United States.

Otsuka has noted, with concern, that HRSA, the U.S. Department of Health and Human Services ("HHS"), and the Department of Justice ("DOJ") have, in this and other on-going cases, taken the position that a manufacturer cannot impose any condition on a covered entity with respect to a 340B purchase. Otsuka's concerns were recently heightened when HRSA sent it a letter on May 19, 2022. In that letter, after asserting that Jynarque is "restricted to a limited distribution network", HRSA took the position that manufacturers cannot employ "restrictive conditions" under the 340B program.

Otsuka writes to make four points: (1) the government's "no conditions" policy will make it impossible for companies like Otsuka to comply with REMS obligations, (2) the "no conditions" policy is a threat to patient safety, (3) the policy is contrary to the plain language of the 340B statute and the "major questions" doctrine, and (4) the policy is an unexplained and unacknowledged departure from prior agency guidance.

BACKGROUND

A. The Importance of Limited Distribution Systems

Limited distribution systems are an extremely important part of ensuring the safe, efficient distribution of many medications. A limited distribution system, as the name indicates, generally involves the use of a small number of pharmacies to ensure the appropriate dispensing of drugs that require special processes or procedures.[2] The pharmacies selected for these systems typically are specialty pharmacies, which have highly specialized expertise and often are able to service patients on a national basis.

As noted above, REMS programs frequently involve the use of limited distribution systems, because the substantial requirements imposed on manufacturers under a REMS necessitate concentrating distribution in a small number of carefully selected and closely monitored pharmacies.[3] Significantly,

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[2] Limited distribution system is also the term used to describe the use of allocation systems in times of drug shortages or threatened shortages, regardless of the size of the pharmacy or other customer base.

[3] *See, e.g.,* Bristol Myers Squibb, *Commitment to Safety and Patients: Risk Evaluation and Mitigation Strategies (REMS)* (2022), https://www.bms.com/patient-and-caregivers/risk-evaluation-and-migration-strategies-rems.html (discussing the REMS for Thalomide, which contains the active ingredient thalidomide, and is used to treat a serious skin disease; because of the safety risks posed by the medication, the company developed "a risk management system that strictly regulates the [drug's] distribution…from beginning to end").

REMS affect many patient populations and medications. FDA recently reported 60 active REMS.[4] A single REMS may apply to an entire class of drugs.[5]

But limited distribution systems are not used only, or even primarily, in connection with REMS programs.[6] Non-REMS manufacturers have imposed limited distribution systems to address a broad array of patient safety and other patient and distribution needs. These conditions on distribution ensure that the providers who care for patients have disease-specific expertise, are knowledgeable about dosing issues, can promote a patient's adherence to an extended course of therapy, fairly allocate drugs in short supply, and permit appropriate scaling of a distribution system and its costs for smaller patient populations, among many other purposes.[7] All of these uses of limited distribution systems are critically important.

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[4] *See* FDA, *FDA Evaluation and Mitigation Strategy (REMS) Public Dashboard*, https://fis.fda.gov/sense/app/ca606d81-3f9b-4480-9e47-8a8649da6470/sheet/dfa2f0ce-4940-40ff-8d90-d01c19ca9c4d/state/analysis (last updated July 11, 2022).

[5] *See* Congressional Research Service, *FDA Risk Evaluation and Mitigation Strategies (REMS): Description and Effect on Generic Drug Development*, at 6 n.38 (Mar. 16, 2018).

[6] *See* HRSA, HHS, *Manufacturer Notices to Covered Entities*, https://www.hrsa.gov/opa/manufacturer-notices (last updated June 2022) (showing dozens of limited distribution systems, where most such programs were not REMS-based).

[7] *Id.*; *see also* Catalyst, *340B Notice Regarding Limited Distribution Plan for FIRDAPSE® (amifampridine) tablets* (Apr. 2, 2019), https://www.hrsa.gov/sites/default/files/hrsa/opa/catalyst-firdapse-340b-notice.pdf

B. Jynarque and ADPKD

ADPKD is a genetic and an "orphan" disease, meaning that it affects a small population of patients.[8] In ADPKD, cysts develop in the kidney and can lead to infections and bleeding. As the cysts grow, they damage the kidney. As a consequence, the progression of ADPKD leads to kidney failure, requiring dialysis or a kidney transplant. Patients with kidney failure almost always have other conditions, such as high blood pressure, and are at increased risk for heart disease and stroke.

Jynarque is the first and only FDA approved drug to slow kidney function decline in adults at risk for rapidly progressing ADPKD. Cyst growth in ADPKD patients is driven by high levels of the hormone vasopressin; Jynarque prevents

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("To ensure that patients being treated with FIRDAPSE receive the best possible care and to ensure optimal drug regimen titration, appropriate drug and clinical counseling, and therapeutic adherence, Catalyst has developed an exclusive distribution plan.…"); Incyte, *Notice to Covered Entities Regarding PEMAZYRE™ Limited Distribution Network* (June 2020), https://www.hrsa.gov/sites/default/files/hrsa/opa/notice-regarding-pemazyre-june-2020.pdf ("In light of the very small patient population anticipated to be treated with PEMAZYRE, PEMAZYRE is available to 340B covered entities through the sole specialty distributor for the product….").

[8] *See* Nat'l Inst. of Diabetes & Digestive & Kidney Diseases, Nat'l Inst. of Health, *Autosomal Dominant Polycystic Kidney Disease*, https://www.niddk.nih.gov/health-information/kidney-disease/polycystic-kidney-disease/autosomal-dominant-pkd (last visited July 26, 2022).

vasopressin from binding to the surface of kidney cyst cells.[9] The medication has been shown to reduce the loss of kidney volume by 49% after three years of treatment with Jynarque.

The FDA-approved labeling for Jynarque reflects that it can, in a small percentage of patients, result in "serious liver problems that can lead to the need for a liver transplant or can lead to death."[10] FDA-approved labeling states that, "[b]ecause of the risk of serious liver problems", Jynarque "is only available through a restricted distribution program."[11]

C. Jynarque's REMS

The REMS required by the FDA for Jynarque, like other REMS for many other products, is a significant, multi-faceted program that carries substantial cost and operational complexity. The Jynarque REMS, like other REMS programs, mandates that only certified pharmacies dispense the product and that it is only "dispensed to patients with evidence or other documentation of safe-use

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[9] Otsuka Am. Pharm., Inc., *How Does JYNARQUE® (tolvaptan) Work?* (Mar. 4, 2021), https://www.youtube.com/watch?v=YuGLmzL87-U.

[10] *See* Otsuka Am. Pharm., Inc., *Medication Guide JYNARQUE® (tolvaptan) Tablets* (Oct. 2020), https://www.otsuka-us.com/sites/g/files/qhldwo5646/files/media/static/JYNARQUE-Medguide.pdf .

[11] *Id*.

conditions."[12] Under the REMS, each patient is required to undergo extensive liver function testing to determine if the patient is experiencing liver toxicity.[13] Otsuka, as the manufacturer, must "monitor, evaluate, and work to improve" all elements of the REMS, including those requiring "pharmacies that dispense the drug be certified [and] document[] safe use conditions."[14]

Outpatient pharmacies are essential to the safe operation of the REMS and to achieving its patient safety objectives. A participating pharmacy must designate an authorized representative to be personally responsible for (1) "carry[ing] out the certification process" and (2) "oversee[ing] implementation and compliance with the REMS Program on behalf of the pharmacy."[15] That authorized representative must thoroughly review the REMS Program Overview,[16] which repeatedly

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[12] *Id*.

[13] *Id.*

[14] *Id*.

[15] *See* Otsuka Am. Pharm., Inc., *Risk Evaluation and Mitigation Strategy (REMS) Document; JYNARQUE (tolvaptan) REMS Program*, at 4 (Nov. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Jynarque_2020_11_25_REMS_Document.pdf ("REMS Document").

[16] *Id*.

emphasizes the role and importance of certified pharmacies in the REMS process.[17]

The authorized representative, informed of the critical role of a pharmacy in the REMS, must then satisfactorily complete the Outpatient Pharmacy Enrollment Form.[18] That FDA-approved form emphasizes that the medication "is available only through…a restricted distribution program" that "is limited to a small number" of pharmacies.[19] The Enrollment Form obligates an enrolling pharmacy to "comply with [all] REMS requirements." Specific commitments are made by an enrolling pharmacy to "[t]rain all relevant staff" involved in dispensing Jynarque. An enrolled pharmacy must also "[e]stablish processes and procedures" specific to dispensing the medication.[20]

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[17] *Id.*

[18] *Id*. at 3.

[19] Otsuka Am. Pharm., Inc., *JYNARQUE® (tolvaptan) REMS Outpatient Pharmacy Enrollment Form*, at 1 (2019), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Jynarque_2020_11_25_Outpatient_Pharmacy_Enrollment_Form.pdf.

[20] Otsuka Am. Pharm., Inc., *JYNARQUE REMS (Risk Evaluation and Mitigation Strategy) Program Overview*, at 3, 7 (2019), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Jynarque_2020_11_25_Program_Overview.pdf ("REMS Program Overview") (requiring the maintenance of "documentation [showing] that all processes and procedures are in place and are being followed").

Critically, the REMS require outpatient pharmacies to "[o]btain *authorization* to dispense *each* prescription."[21] The pharmacy authorization is the means "to verify the prescriber is certified [to prescribe the product] and the patient is enrolled and authorized to receive the drug."[22] Because patients must be properly educated on the safety issues and must have submitted to extensive liver toxicity testing in order to receive a pharmacy "authorization", that pharmacy-dependent mechanism is critical to the ability of the REMS to address the patient safety issues.

In a restriction that has clear 340B contract pharmacy implications, the REMS requirements also state that a certified pharmacy must "[n]ot distribute, transfer, loan, or sell" the medication to others.[23] This restriction is essential to the integrity of the REMS and is reinforced by the obligation on "[w]holesalers that distribute Jynarque" that they "[d]istribute *only* to certified pharmacies."[24]

Certified pharmacies are also critical to achieving the safety objectives of the REMS because they have an obligation to "[r]eport adverse events suggestive of" a

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[21] REMS Document, at 3 (emphases added).

[22] *Id*.

[23] *Id*. at 5.

[24] *Id*. (emphasis added).

liver injury. The reporting of adverse effects can assist FDA in its review of the safety and efficacy of a drug on an on-going basis.[25]

Given the significant pharmacy requirements at the core of the REMS, there is substantial time, effort, and cost to enroll, establish, and maintain oversight over a single pharmacy in the limited network. Accordingly, there is a significant cost to Otsuka for each certified pharmacy added to the network. If Otsuka were to be required to include covered entities or contract pharmacies at their request into the distribution system, the program would be unmanageable. Although only about 9,700 patients have been treated with Jynarque, there are more than 50,000 covered entities and 30,000 contract pharmacies.

There are also significant costs to the certified pharmacies if they wish to join the certified pharmacy network, too. Some 340B covered entities have contacted Otsuka about potentially joining the limited pharmacy network, but, in each case, these covered entities have not pursued enrollment once they were informed of the network requirements.

Regardless, all covered entities have unlimited access to 340B priced Jynarque. In order to ensure access for 340B covered entities, Otsuka has

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[25] *Id.* at 6 (obligating Otsuka to "[e]nsure pharmacies are able to report adverse events"); REMS Program Overview, at 8.

designated Panther as a pharmacy that any covered entity may select as its contract pharmacy. If a covered entity designates Panther as its contract pharmacy, it may ensure delivery of REMS-compliant Jynarque at the 340B price to any patient located anywhere in the United States.

D. HRSA's Recent Correspondence

HRSA recently inquired into Otsuka's REMS-based limited distribution program, stating that it understood, from communications with covered entities, that "this drug is restricted to a limited distribution network of select specialty pharmacies". The letter took the position that manufacturers are prohibited from employing "restrictive conditions" under the 340B program. The letter asked Otsuka about the "[d]etails" regarding its limited distribution plan and, given HRSA's view that manufacturers may not impose restrictive conditions, how the company "ensures compliance with the 340B program". These kinds of letters often precede a "violation" letter.

In its response, Otsuka explained that the use of a single, designated contract pharmacy is necessary, in light of the 30,000 contract pharmacies and 50,000 340B covered entities that could potentially seek to join the pharmacy network. Because it is difficult to ensure adequate oversight over even a limited distribution system, given the complexity of a REMS, opening the network to a potentially unlimited

number of covered entities without being able to direct those orders through Panther would present an overwhelming challenge.[26]

E. REMS Enforcement Risks

Manufacturers are subject to enormous risk if they do not satisfy their REMS obligations. Where REMS requirements are not satisfied, the drug may be deemed "misbranded," such that the drug may not be introduced into interstate commerce.[27] If a manufacturer fails to comply with a requirement of an approved REMS, including the obligation to monitor other REMS participants, the manufacturer is also subject to civil monetary penalties.[28] Civil monetary penalties may run from $250,000 to $1 million per proceeding, and the penalties double for violations that continue for 30 days after FDA notice.[29] REMS compliance issues are also targeted

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[26] Even one covered entity can present an unmanageable REMS challenge. HRSA's letter to Otsuka itself mentioned a California-based disproportionate share hospital that has 288 active child sites and 255 contract pharmacy relationships spanning 22 states as far away as Maine, New Jersey, Massachusetts, Delaware, North Carolina, and Florida. Integrating such a far-flung network with so many components over such a vast geographical scope presents an unacceptable risk of a REMS failure, as well as significant duplicate discount and diversion risks.

[27] *See* 21 U.S.C. § 331(a) (prohibiting introduction of a misbranded drug); A. Walsh, Regulatory Focus, *The Enforcement of Risk Evaluation and Mitigation Strategy (REMS)*, at 2 (Jan. 2019), https://hpm.com/wp-content/uploads/2019/02/RF-2019-01-Enforcement-of-REMS-00521473.pdf.

[28] 21 U.S.C. § 352(y).

[29] Walsh, *supra*, at 3.

under the False Claims Act, 31 U.S.C. § 3729, *et seq*. or pursued as a healthcare fraud issue under 42 U.S.C. § 1320a-7a. Finally, criminal misdemeanor or felony violations may be asserted.[30]

F. Conditions Have Long Been Permitted

For almost two decades, HRSA permitted a wide range of conditions to be imposed by manufacturers. For example, the agency's website, even today, lists upwards of 60 limited distribution systems in which manufacturers restricted the number of 340B pharmacies that can be a part of a limited distribution system.[31] Limited distribution systems listed on HRSA's website include a number which consist of a single designated contract pharmacy for use by all covered entities, like in the Jynarque program.[32] Some of the posted limited distribution systems

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[30] *See* 21 U.S.C. § 333(a).

[31] *See* HRSA, HHS, *Manufacturer Notices to Covered Entities*, https://www.hrsa.gov/opa/manufacturer-notices (last updated June 2022).

[32] Single designated contract pharmacies are, in fact, common in limited distribution systems. *See, e.g.*, Daiichi Sankyo Notice to 340B Covered Entities Regarding Turalio™ (July 2019), https://www.hrsa.gov/sites/default/files/hrsa/opa/daiichi-sankyo-notice-340b.pdf; Bayer, Limited Distribution Notice for Adempas Tablets (Apr. 2020), https://www.hrsa.gov/sites/default/files/hrsa/opa/pdf/Adempas-Limited-Distribution.pdf; Actelion, *Limited Distribution Notice for Opsumit, Tracleer, Uptravi, Veletri, Ventavis, and Zavesca* (June 2020), https://www.hrsa.gov/sites/default/files/hrsa/opa/pdf/limited-distribution-notice-actelion.pdf; Takeda Oncology, *340B Notice Excisive Oncology Distribution Network Update for Iclusig* (Apr. 22, 2021), https://www.hrsa.gov/sites/default/files/hrsa/opa/pdf/notice-takeda-iclusig.pdf;

are REMS-based programs, while the others reflect a range of other important non-REMS goals and purposes.[33]

Those important non-REMS purposes for a limited distribution system include responding to shortages, requiring patients to have access to qualified providers, and ensuring that a distribution system places sufficient experience in a committed group of pharmacies with special expertise.[34] HRSA has also posted limited distribution programs where, because of small patient populations, a wider network would be prohibitively expensive.[35] HRSA has not objected to any of these limited distribution systems.

Nor has HRSA limited the conditions that manufacturers may impose historically to these limited distribution systems. For example, in the 1994 Guidance, HRSA broadly acknowledged manufacturers' ability to assert conditions, such as "request[ing] standard information" and advancing "contract

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Janssen Biotech, *Notice to 340B Covered Entities Regarding Balversa* (Apr. 25, 2019), https://www.hrsa.gov/sites/default/files/hrsa/opa/pdf/notice-340b-balversa-lim-dist.pdf; Eton Pharms., *Exclusive Distribution Network for ALKINDI® SPRINKLE* (Jan. 12, 2021), https://www.hrsa.gov/sites/default/files/hrsa/opa/pdf/notice-alkindi-sprinkle.pdf.

[33] *Id*.

[34] *See id*.

[35] *Id*.

provisions."[36] Even more broadly, HRSA recognized that manufacturers were entitled to adopt "customary business practice" in undertaking 340B transactions.[37]

G. The Litigation to Date and the Use of Conditions

Despite HRSA's long history of permitting manufacturer conditions, HRSA now takes the position that manufacturers cannot impose **any** condition on 340B sales—no matter how necessary or reasonable those conditions are. As a number of HRSA's "violation" letters state:

> [n]othing in the 340B statute grants a manufacturer the right to place conditions on the fulfillment of its statutory obligation to offer 340B pricing on covered outpatient drugs purchased by covered entities.

See, e.g., HRSA, HHS, *HRSA Violation Letter to AstraZeneca*, at 1 (May 17, 2021) ("Violation Letter"), https://www.hrsa.gov/sites/default/files/hrsa/opa/hrsa-letter-astrazeneca-covered-entities.pdf. That statement is unqualified in any way and purports to prohibit any condition of any kind under any circumstances. DOJ echoes this absolutist position in its briefing. *See, e.g.*, Gov't Br. at 27, *Novartis Pharms, Corp. v. Johnson*, No. 21-5299 (D.C. Cir. May 9, 2022) (statute "necessarily precludes manufacturers from imposing their own conditions").

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[36] 59 Fed. Reg. 25,110, 25,114 (May 13, 1994).

[37] *Id*.

The absurd reach of the government's position is perhaps reflected best, however, in the HHS Advisory Opinion. In addressing the question of whether manufacturers can impose any condition whatsoever on the delivery of product, HHS asserted that manufacturers must deliver product as demanded by covered entities. This prohibition against delivery conditions applies, HHS held, regardless of "[t]he situs of delivery, be it the lunar surface, low-earth orbit, or a neighborhood pharmacy".[38]

Unfortunately, some district courts appear to agree with the government's position, regardless of the consequences of adopting that position. *See Sanofi-Aventis U.S., LLC v. HHS*, 570 F. Supp. 3d 129, 202 (D.N.J. 2021) (stating that manufacturers have "[no] discretion…to impose" conditions); *Eli Lilly & Co. v. HHS*, No. 1:21-cv-00081-SEB-MJD, 2021 WL 5039566, at *19 (S.D. Ind. Oct. 29, 2021) (the statute "does not leave room" for manufacturers to "condition or control the availability of their 340B pricing").

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[38] HHS OGC, *Advisory Opinion 20-06 on Contract Pharmacies Under the 340B Program*, at 3 (Dec. 30, 2020), https://www.hhs.gov/guidance/sites/default/files/hhs_guidance-documents/340B-AO-FIVA-12-30-2020_O.pdf. Although the government says that the Advisory Opinion is now "withdrawn," it continues to reflect HHS' and HRSA's actual, on-going policy. *See AstraZeneca Pharms. LP v. Becerra*, No. CV 21-27-LPS, 2022 WL 484587, at *5 (D. Del. Feb. 16, 2022).

Fortunately, other courts, including the court below, have rejected this position based on the plain language of the statute, its purpose, and its structure. *See AstraZeneca Pharms., LP v. Becerra*, 543 F. Supp. 3d 47, 62 (D. Del. 2021) (the statute does not require "manufacturers to deliver 340B drugs to an unlimited number of contract pharmacies as a condition for manufacturers []"); *Novartis Pharms. Corp. v. Espinosa*, No. 21-cv-1479 (DLF), 2021 WL 5161783, at *9 (D.D.C. Nov. 5, 2021) ("[t]he statute's plain language, purpose, and structure do not prohibit drug manufacturers from attaching any conditions to the sales of covered drugs through contract pharmacies") (emphasis omitted).

ARGUMENT

I. THE GOVERNMENT'S NEW "NO CONDITIONS" POLICY PUTS PATIENTS AT RISK.

The government's view that a manufacturer cannot impose any condition—for any reason—is a dangerous threat to patient safety. REMS programs, at their core, involve manufacturers imposing conditions on REMS participants, including pharmacies. FDA, in the interest of patient safety, creates mandates under a REMS that apply to manufacturers, which the manufacturers then impose on pharmacies.

Using Jynarque as an example, FDA mandated that Otsuka take the necessary steps to ensure that: (1) only certified pharmacies dispense the product, (2) those pharmacies have appropriate processes and procedures in place specific

to the medication, (3) they train all of their relevant personnel on the REMS, (4) they only dispense after confirming the dispense is "authorized" (e.g., the patient is appropriately educated and the patient has completed all required liver tests), and (5) the pharmacy completes adverse event reports. Without the ability of a manufacturer to impose these conditions on 340B covered entities, none of these safeguards could be enforced by any manufacturer against any covered entity—leaving patients at risk.

Under the government's position reflected in the Violation Letter, it does not matter if a 340B pharmacy fails to meet one or more REMS requirements; it does not matter if they repeatedly fail to do so. The government's position is that, regardless of the circumstances, no condition can be imposed by any manufacturer on the offer of 340B drugs. According to the government, "must offer" means "must sell", without conditions. That is dangerous—and is not what the plain language of the 340B statute says.

The risk of pharmacies failing to meet the exacting requirements of a REMS is not theoretical. Some pharmacies, in fact, fail to meet REMS requirements and must be disenrolled and prevented from dispensing. Candid assessments acknowledge that well-intentioned pharmacies struggle and sometimes fail to meet

REMS requirements.[39] "While pharmacies are trained in advanced pharmaceutical care, *they cannot always be relied upon to complete these practices*."[40]

One recent report illustrates common issues.[41] Reporting on audits of REMS compliance by a hospital system, "the audit findings revealed 11 missed regularly scheduled training, missed documentation of training, and difficulty in confirming patient enrollment."[42] "This lack of training and inability to gather information when necessary are risks to patient care" and present "challenges to safely dispensing" medication.[43]

A follow-up survey administered to 14 hospitals also showed that "86% of hospitals reported that they do not have processes defined for all the required

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[39] *See, e.g.*, K. Waldman, *Challenges of Integrating REMS Elements Into Pharmacy Systems*, at 4 (May 7, 2016), https://www.jhsph.edu/research/centers-and-institutes/center-of-excellence-in-regulatory-science-and-innovation/training/Waldman_CERSI%20Writing%20Competition_2016.pdf.

[40] *Id*. (emphasis added); *see also* A. Kostrzewa, *Optimization of REMS Program Compliance in a Large Academic Health System*, 12 Innovations in Pharmacy, at 1 (2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8326704/pdf/21550417-12-02-3853.pdf ("[a]nyone who has ever tried to implement a…REMS program in their pharmacy or health system, let alone multiple, knows how challenging it can be").

[41] A. Pemmarju et al., *Challenges in REMS Compliance*, 78 Am. J. Health-Sys. Pharm. 1036, 1036-37 (June 15, 2021).

[42] *Id.*

[43] *Id.*

REMS medications."[44] In addition, 29% reported "[l]ack of pharmacy oversight in the continuum of care," including "storage and handling,…verifying, administering, [and] monitoring."[45] Finally, 36% acknowledged "[l]ack of a responsible person for REMS oversight."[46]

This is not to either criticize pharmacies in general, or 340B pharmacies, in particular. But pharmacy failures occur, and a manufacturer subject to a REMS obligation may need to employ a limited distribution system to ensure compliance. This is why, even under a limited distribution system, mandated reporting by REMS manufacturers to the FDA requires information on pharmacy disenrollments and the reasons for those disenrollments.[47] Disenrollments based on a failure to comply with a REMS requirement is necessarily the enforcement of a condition.

The risk to patients from the government's "no conditions" policy is not limited to REMS programs. As noted above, manufacturers impose conditions on pharmacies to further patient safety and other important goals in many other

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[44] *Id.*

[45] *Id*.

[46] *Id*.

[47] *See, e.g.,* REMS Document, at 6-7.

circumstances, too. *See, supra*, at 7. HRSA has offered no objection, at least historically, to dozens and dozens of non-REMS-based limited distribution systems.

A critically important non-REMS issue, which bears emphasis, is the issue of drug shortages.[48] The government's "no conditions" policy threatens to turn drug shortages into public health disasters. If HRSA, in fact, can mandate that manufacturers impose "no conditions" on 340B covered entities, then, in times of shortage, covered entities—and only covered entities—will be able to make unlimited demands for product. Without the ability to impose allocation systems during a shortage on non-340B and 340B pharmacies alike, some patients will have no access to drugs, even where access to those drugs is a matter of life and death. If manufacturers cannot subject 340B pharmacies to an allocation, 340B covered entities will have disproportionate access to drugs in shortage, while all non-340B purchasers—and their patients—will necessarily have less than a fair, proportionate allocation.

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[48] *See, e.g.*, Am. Hosp. Ass'n, *FDA: 43 New Drug Shortages, 86 Ongoing Shortages in 2020* (June 30, 2021), https://www.aha.org/news/headline/2021-06-30-fda-43-new-drug-shortages-86-ongoing-shortages-2020 ("shortages continue to pose a real challenge to public health").

This goes to the very heart of the government's fundamental misreading of the plain language of the 340B statute. The 2010 "shall offer" language, did not prevent manufacturers from imposing any condition of any kind on 340B covered entities. Instead, that language merely ensured the equitable imposition of conditions during shortages.[49] But the government's "no conditions" policy will result in the exact result that Congress rejected; it will put "340B entities automatically…to the front of the line" during shortages to the detriment of every non-340B patient.[50]

The government's "no conditions" position should be rejected because it will fundamentally prevent manufacturers from addressing a broad range of critically important patient safety and other issues, threatening patient health and the efficient distribution of medicines.

II. THE GOVERNMENT'S NEW "NO CONDITIONS" POSITION PUTS OTSUKA IN AN UNTENABLE POSITION

The government's "no condition" policy will, if permitted, place Otsuka and other manufacturers with REMS obligations in an entirely untenable position. Manufacturers will be forced to choose between complying with their FDA

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[49] *See* Statement of Chairman Waxman, House Energy and Commerce Committee Mark-up of H.R. 3200 (Sept. 23, 2009) (speaking directly to the intent to address shortage situations).

[50] *Id.*

obligations or complying with HRSA's "no conditions" policy. No matter which agency's requirements manufacturers decide to prioritize, they will face potentially devastating consequences from the other agency. This is an absurd result—and the government should not be permitted to create this kind of impossible compliance conundrum.

Under the government's "no conditions" policy, a manufacturer subject to a REMS could not impose any REMS condition on a 340B covered entity. Any 340B covered entity would be able to force its addition to any network, no matter how unwieldly that network then became. 340B pharmacies also could not be required to become certified, name an authorized representative, train all relevant personnel, secure authorizations before dispensing, or any of the other elements of a REMS. According to the government, 340B product must be sold without any such condition. Inevitably, however, a manufacturer that did not impose conditions would face a withering array of potential sanctions, including civil monetary penalties, False Claims Act liability, and even criminal sanctions. *See, supra*, at 13–14.

Alternatively, manufacturers unwilling to risk these sanctions, and that as a consequence impose and enforce REMS requirements on 340B pharmacies, would face a wide range of threats precisely because of their decision to impose conditions on 340B pharmacies. Those risks are readily apparent from the steps

that the government has already taken and has threatened to take against AstraZeneca and the other manufacturers. The AstraZeneca Violation Letter shows the government's willingness to threaten 340B civil monetary penalties, even though AstraZeneca's distribution policy is much broader than the REMS and non-REMS limited distribution systems HRSA has permitted historically. The government has already threatened sanctions against manufacturers, including civil monetary penalties and payment of putative "overcharges," where they employ networks that are broader even than those described in HRSA's 1994 Guidance.[51] The HHS Office of General Counsel Advisory Opinion also threatened False Claim Act liability in such circumstances.[52]

But the risk to any manufacturer that for patient safety or other reasons imposes a limited distribution system is even more fundamental than that. Compliance with 340B program requirements are a condition of Medicaid and Medicare Part B coverage. 42 U.S.C. §§ 256b(a); 1396r-8(a)(1). Accordingly, manufacturers that employ limited distribution systems—regardless of their reasons for doing so—face the loss of both Medicaid and Medicare Part B

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[51] *See, e.g.*, Violation Letter, at 1.

[52] HHS-OGC Advisory Opinion, at 5.

coverage. And that is true not just for a single product that may be the subject of a limited distribution system, but for **all** of their drugs.

The conflict that the government's "no conditions" policy creates for manufacturers subject to a REMS or that otherwise must implement a limited distribution system demonstrates, quite clearly, that the government's new policy cannot be what the text of the statute requires—or what Congress could possibly have intended.

III. THE PLAIN LANGUAGE, PURPOSE, AND STRUCTURE OF THE STATUTE DO NOT SUPPORT THE GOVERNMENT'S NEWLY DISCOVERED "NO CONDITIONS" POLICY.

As AstraZeneca correctly notes in its Brief, at 6, the 340B statute was developed to address the "disincentive" created by the earlier Medicaid Drug Rebate Statute ("MDRS"), which initially penalized manufacturers for offering discounts to safety net providers.[53] Thus, to address that pricing problem, the plain language of the 340B statute imposed an obligation on manufacturers to observe a discounted "ceiling[] on prices" for those entities, while exempting those prices from the calculation of Medicaid rebates.[54] As such, the 340B statute fixed a specific pricing problem with a specific pricing solution. The statute contains no

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[53] *Id*. (citing H.R. Rep. No. 102-384, pt. 2, at 7, 9-10 (1992)).

[54] *Id*., at 7 (citing *PhRMA v. HHS*, 43 F. Supp. 3d 28, 31 (D.D.C. 2014)).

language prohibiting manufacturers from imposing the conditions they had used—long before the 340B statute was passed—to address shortage issues, mitigate patient safety issues, and devise efficient and streamlined distribution systems.

But HRSA has recently come to disagree with the limited program that Congress created to address the MDRS-created price reporting problem. Whatever value the agency may see in giving covered entities the ability to demand delivery and other terms from manufacturers, its authority "does not include a power to revise clear statutory terms."[55] The government's newfound view of the 340B statute goes beyond faithfully interpreting it—it rewrites the statute altogether.

The government's position should also be rejected under the "major questions" doctrine. Courts "expect Congress to speak clearly" when authorizing an agency to exercise powers of "vast 'economic and political significance.'" *Ala. Ass'n of Realtors v. HHS*, 141 S. Ct. 2485, 2489 (2021) (quoting *Util. Air Regulatory Grp.*, 573 U.S. at 324 (2014)). The 340B program, which was designed as a small "fix" to the MDRS price reporting problem, is now the second-largest drug pricing program in the country, larger than the Medicaid program itself.[56] Nothing in the 340B statute's plain text or history hints at the expansive

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[55] *See Util. Air Regulatory Grp. v. EPA*, 573 U.S. 302, 326-27 (2014).

[56] Eleanor Blalock, BRG, *Measuring the Relative Size of the 340B Program; 2020 Update*, at 7 (June 2022), https://media.thinkbrg.com/wp-

approach HRSA has adopted here, under which a manufacturer cannot impose any condition in connection with such a vast program.

The Supreme Court's recent analysis of the "major questions" doctrine reveals the flaw at the heart of the government's position.[57] "[T]he 'history and the breadth of the authority that [an agency] has asserted,' and the 'economic and political significance' of that assertion", may "provide a 'reason to hesitate before concluding that Congress' meant to confer such authority".[58] The major questions doctrine responds to "a particular and recurring problem: agencies asserting highly consequential power beyond what Congress could reasonably be understood to have granted."[59]

That is exactly the situation here. A mandate to ship drugs to an unlimited number of contract pharmacies without any ability to impose any condition—for safety or other reasons—is a decision of the utmost significance. It has vast economic, political, and public health consequences. The transfer of billions of

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content/uploads/2022/06/30124832/BRG-340B-Measuring-Relative-Size-2022.pdf.

[57] *See West Virginia v. EPA*, 142 S. Ct. 2587 (2022).

[58] *See id.* at 2608 (quoting *FDA v Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 159–60 (2000)).

[59] *Id.* at 2609.

dollars' worth of discounted pharmaceutical products without any of the traditional tools being available to address patient safety, shortage, and other important issues would not be made "in so cryptic a fashion." *See West Virginia*, 142 S. Ct. at 2613 (quoting *Brown & Williamson*, 529 U.S. at 160).

Major questions cases arise when a "regulatory assertion[]," given the circumstances, leads to the conclusion, as a matter of "common sense", that Congress did not "actually" delegate that power. *Id.* at 2609 (quoting *Brown & Williamson*, 529 U.S. at 133). HRSA's regulatory actions rely on a single, entirely pricing-focused provision requiring manufacturers to "offer" their products at or below a "ceiling price" to certain covered entities.[60] Yet HRSA reads that provision to enable it to categorically prevent manufacturers from incorporating any other terms in these contracts. But Congress does not "use oblique or elliptical language to empower an agency to make [such] a 'radical or fundamental' change." *Id.* (quoting *MCI Telecomm*, 512 U.S. at 229).[61]

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[60] *See* Violation Letter, at 1 (citing 42 U.S.C. § 256b(a)(1)).

[61] The government may argue that the court need not worry about the consequences of its "no conditions" policy, because HRSA will use regulatory authority to distinguish between reasonable and unreasonable "conditions". But that would be an empty promise. As the government itself concedes, the government's regulatory authority under the 340B program is limited to three distinct areas, not relevant here. *See PhRMA v. HHS*, 43 F. Supp. 3d 28 (D.D.C. 2014). Further, covered entities have repeatedly (and successfully) rejected HRSA's attempts to impose reasonable conditions on them. *See, e.g.*, Amicus

In short, HRSA's newly discovered interpretation has "effected a "fundamental revision of the statute, changing it from [one sort of] scheme of...regulation" into an entirely "different kind." *Id.* at 2610. The Violation Letter should be set aside.

IV. THE GOVERNMENT'S NEW POLICY IS A DRAMATIC AND ENTIRELY UNEXPLAINED REVERSAL OF DECADES OF GUIDANCE AND AGENCY PRACTICE.

Finally, the Court should reject the government's "no conditions" policy as arbitrary and capricious under the Administrative Procedure Act ("the APA"), because the government's recent adoption of this position was an unexplained reversal of HRSA's own long-standing guidance permitting conditions.[62] Indeed,

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Brief of Am. Hosp. Ass'n, Doc. 25, at 15 n.47 (rejecting HRSA's guidance requiring covered entities to maintain title in contract pharmacy relationships); Petition, *Genesis Health Care, Inc. v. Azar*, No. 4:18-mc-00235-RBH (D.S.C. June 28, 2018), Dkt. 1 (covered entity refusing to abide by HRSA diversion finding where the covered entity took the position that HRSA's definition of a patient could not be imposed on it); *see also* Tom Mirga, 340B Report, *Hospital Group: GAO's 340B Duplicate Discount Recommendations "Contrary to Federal Law"* (Feb. 7, 2020), https://340breport.com/your-340b-report-for-tuesday-jan-412/ (taking the position that 340B covered entities have no responsibility whatsoever for Medicaid managed care duplicate discounts).

[62] *See AstraZeneca Pharms.*, 2022 WL 484587, at *7; *see also Nat'l Cable & Telecomms. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967, 981 (2005)("[u]nexplained inconsistency" is a basis for declaring agency action arbitrary and capricious under the APA).

the government fails to even acknowledge its reversal of position in either the AstraZeneca violation letter or the HHS Advisory Opinion.[63]

Otsuka speaks to this issue here because, in implementing its Jynarque limited distribution system in 2018, Otsuka relied on HRSA's long-standing guidance specifically permitting manufacturer conditions in establishing limited distribution systems. It was only after Otsuka had developed its limited distribution system—and committed to a REMS predicated on that system—that HRSA rejected its own long-standing guidance. It did so in the HHS Office of the General Counsel Advisory Opinion and in the various "violation" letters, creating a new "no conditions" policy, and it did so without giving Otsuka or any other stakeholders notice or an opportunity to comment on that change in position.

The district court should be affirmed because it correctly concluded that the government has reversed its prior positions and failed to either acknowledge or explain its change in policy.

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[63] *See Encino Motorcars, LLC v. Navarro*, 579 U.S. 211, 221 (2016) (quoting *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009)) (an agency changing its policy "must at least display awareness that is changing its position").

CONCLUSION

For these reasons, and those stated by Plaintiff-Appellee, AstraZeneca, the judgment of the district court should be affirmed.

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Respectfully submitted,
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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitations of Federal Rules of Appellate Procedure 29(a)(5) and 32(a)(7)(B) and the rules of this Court, because it contains 6,262 words (as determined by the Microsoft Word 2016 word-processing system used to prepare the brief), excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii).

This brief complies with the typeface and type style requirements of Federal Rule of Appellate Procedure 32(a)(5)–(6). The brief was prepared in a proportionally spaced typeface using Microsoft Word 2016 in 14-point Times New Roman font.

Pursuant to Local Rule 31.1(c), the undersigned also certifies that the text of the electronic brief is identical to the text in the paper copies.

Date: July 28, 2022

/s/ William A. Sarraille
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CERTIFICATE OF BAR MEMBERSHIP

Pursuant to Local Rule 28.3(d), I hereby certify that I am a member of the Bar of this Court.

Date: July 28, 2022

/s/ William A. Sarraille
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CERTIFICATE OF SERVICE

I hereby certify that on July 28, 2022, a true and correct copy of the foregoing was timely filed with the Clerk of the Court using the appellate CM/ECF system, which will send notifications to all counsel registered to receive electronic notices.

Date: July 28, 2022

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