No. 22-1219

In the
Supreme Court of the United States

RELENTLESS, INC., ET AL.,
Petitioners,
v.
DEPARTMENT OF COMMERCE, ET AL.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the First Circuit

BRIEF OF DR. RESHMA RAMACHANDRAN AND DR. JOSEPH S. ROSS AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes, Rules, and Regulations

Other Authorities

INTEREST OF AMICI CURIAE[1]

Amici curiae are practicing physicians and leading experts in pharmaceutical and regulatory policy, who have studied and written extensively on the relationship between regulatory standards for drug and medical device approvals and patient safety and medical product efficacy. *Amici* have been published widely in both top-tier medical and public health journals and national media outlets, platforms which they have used to comment on, and sometimes critique, U.S. Food and Drug Administration (FDA) regulatory policy. Nevertheless, they understand that it is vastly preferable, especially for public health and patient safety, if the FDA receives deference from courts when it implements broad or ambiguous statutory authority in a reasonable manner.

Amicus curiae Reshma Ramachandran, MD, MPP, MHS is an Assistant Professor of Medicine at Yale School of Medicine, a practicing board-certified family physician, and the co-director of the Collaboration for Regulatory Rigor, Integrity, and Transparency (CRRIT) at the Yale School of Medicine, which is an interdisciplinary initiative that brings together clinicians, epidemiologists, researchers, legal experts, and others to study how federal agencies evaluate, regulate, and cover drugs and devices and how this impacts patient health outcomes. She has led research projects on FDA regulatory policy and its

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[1] No counsel for any party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *Amici Curiae* or their counsel made a monetary contribution to the preparation or submission of this brief.

impact on patient outcomes and clinical decision-making, as well as around pharmaceutical policy, including on economic and regulatory incentives to foster innovation of novel health technologies. Dr. Ramachandran has testified before Congress multiple times to discuss her research and its implications for regulatory policy. She also serves as the chair of Doctors for America's FDA Task Force, an initiative representing over 27,000 physicians and medical trainees that provides unbiased expertise in evaluating and responding to the FDA regulatory process in a way that maximizes meaningful clinical outcomes for patients.

Amicus Curiae Joseph S. Ross, MD, MHS is a Professor of Medicine and of Public Health at Yale School of Medicine, a practicing board-certified general internist, the Deputy Editor of the Journal of the American Medical Association (*JAMA*), and, along with Dr. Ramachandran, a co-director of CRRIT. He also co-directs the Yale-Mayo Clinic Center for Excellence in Regulatory Science and Innovation (CERSI)—an FDA-funded program that seeks "to foster robust and innovative approaches to advance regulatory science" through collaboration between FDA scientific experts and funding offices, FDA, *Centers of Excellence in Regulatory Science and Innovation (CERSIs)*, https://tinyurl.com/bda95a69—and serves as a member and Chair of the Medicare Evidence Development and Coverage Advisory Committee for the Centers for Medicare and Medicaid Services (CMS), where he provides independent guidance and expert advice to CMS on specific clinical topics including on FDA-regulated medical products. His influential and oft-cited research has illuminated the numerous ways in which FDA policies are

advancing public health and generating evidence to inform clinical decision-making.

Dr. Ramachandran and Dr. Ross are thus well positioned to explain how judicial deference under *Chevron U.S.A., Inc. v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837 (1984) has allowed FDA to exercise its statutory authority in a manner that protects public health and keeps patients safe, and the risks to public health and patient safety if *Chevron* is overruled.

INTRODUCTION AND SUMMARY OF THE ARGUMENT

For nearly 40 years, courts have followed the doctrine set forth in *Chevron* to defer to an agency's reasonable interpretations of ambiguous statutes and those conferring broad authority. As the Court explained, this deferential approach is a matter of respect for Congress's "express delegation of authority" to agencies so that they may "elucidate a specific provision of the statute by regulation." *Id.* at 843-44. The Court further acknowledged that "the principle of deference to administrative interpretations" was long-standing and appropriately applied "'whenever * * * a full understanding of the force of the statutory policy in the given situation has depended upon more than ordinary knowledge respecting the matters subjected to agency regulations." *Id.* at 844 (quoting *United States v. Shimer*, 367 U.S. 374, 382 (1961)).

The FDA's regulatory record demonstrates the wisdom in this doctrine and in continued judicial deference to agencies' interpretations of broad and complicated statutory authority, as well as to their difficult and complex policy judgements, which are

informed by stakeholder engagement, including under the Administrative Procedure Act (APA), 5 U.S.C. § 553, and scientific expertise. Indeed, judicial deference to FDA regulation has contributed significantly to its global status as "the gold standard for health care regulation and evidence-based decision making relating to drugs, devices, and other medical products." Liam Bendicksen et al., *FDA and* Chevron *Deference: A Case Review*, 78 Food & Drug L. J. 371 (2023) (citing Daniel P. Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* 301 (Princeton Univ. Press, 2010)).

The FDA has done this acclaimed and crucial work through its implementation of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301 *et seq.*, a statutory scheme "designed primarily to protect the health and safety of the public at large." *POM Wonderful LLC v. Coca-Cola Co.*, 573 U.S. 102, 108 (2014). "There is no denying the complexity of th[at] statutory regime," or "the FDA's expertise" to administer it. *Mylan Lab'ys, Inc. v. Thompson*, 389 F.3d 1272, 1280 (D.C. Cir. 2004). For instance, to carry out its public health mission, FDA is tasked with approving new drugs, including by evaluating whether drugs seeking approval for market have the necessary indicia of safety and efficacy. 21 U.S.C. § 355. The FDA is also responsible for ensuring that the risks and benefits of the drugs and devices it approves are not then marketed, packaged, or labeled in a way that is confusing or misleading. *See, e.g.*, 21 U.S.C. §§ 352, 353, 355.

The FDA's administration of the FDCA has been remarkably successful. No longer are "Americans * * * inundated with ineffective and dangerous drugs," as

they were prior to the FDCA's enactment. *See* FDA, *80 Years of the Federal Food, Drug, and Cosmetic Act* (July 11, 2018), https://tinyurl.com/ykz8w9v7. And the elimination of toxic drugs and "quack devices," *id.*, has not come at the cost of advancements in science or medicine. To the contrary, the FDA has helped drug companies bring countless numbers of innovative, new therapies to market during this time.

But the FDA's successes have been hard won. Among other constraints, the FDA operates in a setting where hasty process or lack of scientific rigor might expose patients to a dangerous or ineffective drug, but too deliberative of a process could stymie innovation and prevent promising, life-saving therapies from reaching patients in time. *See* Holly Fernandez Lynch et al., *Letter to the Editor: The Limits of Acceptable Political Influence Over the FDA*, 27 Nature Medicine 186, 189 (Feb. 2021) (noting the "dual nature of the FDA's decision-making"). Balancing these statutory priorities cannot be appropriately struck unless the FDA understands and adapts to rapid advancements in science and medicine, which inform whether and when a drug or device is safe and effective. And it must also take care to ensure that regulated parties provide information about approved products in a way that is practically useful to different audiences, both in terms of what is expressed and how it is expressed. In short, every aspect of the work Congress has tasked the FDA with doing demands the exercise of true scientific, medical, and public health expertise.

Amici submit their experience with the FDA's regulatory framework to the Court because a decision overruling *Chevron* threatens to destabilize this framework—which ensures the safety and

effectiveness of drugs and devices upon which virtually everyone relies at some point in their life. *Amici* believe that the broad outcome urged by the Petitioners will lead to "a diminished deference regime," that "could adversely affect public health" through the curtailment of FDA's discretion over drug and medical device regulation. Bendicksen et al., *supra*, at 378.

The FDA's regulatory record underscores the wisdom of continued judicial reluctance to undo by court order regulations developed rigorously and methodically by agencies tasked with making complex policy judgments and based on their scientific or technical expertise. In particular, deference to an agency's reasonable interpretation, in light of its expertise and experience with matters within its purview, is appropriate where the statutory authority at issue broadly delegates policy decisions. *See* Brett M. Kavanaugh, *Fixing Statutory Interpretation*, 129 Harvard L. Rev. 2118, 2152 (Jun. 2016) (concluding that *Chevron* "makes a lot of sense" in this circumstance); *see also Kisor v. Wilkie*, 139 S. Ct. 2400, 2448-49 (2019) (Kavanaugh, J., concurring) (observing that broad "terms afford agencies broad policy discretion"). The FDCA does just this by charging the FDA, among many other complex assignments, with line-drawing as to when drugs are sufficiently safe and effective to be made available to potentially desperate consumers.

Continued deference is also particularly appropriate where the statutory authority at issue, like the Clean Air Act amendments in *Chevron*, is part of "a lengthy, detailed, technical, complex, and comprehensive response to a major social issue." *Chevron*, 467 U.S. at 848; *see also Decker v. Nw. Env't*

Def. Ctr., 568 U.S. 597, 618–19 (2013) (Scalia, J., concurring in part and dissenting in part) (the conclusion that an "agency possesses special expertise in administering its 'complex and highly technical regulatory program' * * * is true enough, and it leads to the conclusion that agencies and not courts should make regulations") (quoting *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994)); Gov't Br. at 16 (collecting examples of cases where "*Chevron* has played a critical role in resolving many interpretive questions in complex and technical areas of federal law," including drug regulation).

The FDCA is a paradigmatic example of "a lengthy, detailed, technical, complex, and comprehensive response to a major social issue." *Chevron*, 467 U.S. at 848. In addition to the complexity of the regime as a whole, arriving at an understanding of individual FDCA provisions often requires an "'evaluation[] of scientific data within [FDA's] area of expertise,'" or a "statutory phrase [to] be read in the context of the kind of drug at issue." *Serono Lab'ys, Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998); *see Kisor*, 139 S. Ct. at 2410 (suggesting that courts are not competent to evaluate if "a company created a new 'active moiety' by joining a previously approved moiety to lysine through a non-ester covalent bond"); *see also Otsuka Pharm. Co. v. Price*, 869 F.3d 987, 993-995 (D.C. Cir. 2017) (examining same question).

Beyond interpreting technically sophisticated terms like "active moiety," *Kisor*, 139 S. Ct. at 2410, the FDCA also requires the FDA to interpret its authority to develop technically sophisticated solutions to complex public health problems, and to do so using their expertise to ensure that their approach

is supported by the best available science, in a landscape where the science may be rapidly changing. *Amici* highlight below some of these programs and authorities, which benefit from the deference afforded to agency experts under *Chevron*.

The Court should avoid the potential for destabilizing a regulatory regime that the FDA has capably used for nearly a century to foster scientific and medical innovation, while also ensuring that dangerous or ineffective drugs and medical devices do not routinely threaten public health, as they once did. The Court should affirm the Court of Appeals.

ARGUMENT

I. The FDA's implementation of the FDCA reinforces the sensibility of *Chevron* deference.

Congress has assigned to the FDA an important and ambitious task: Protect the public health by keeping unsafe or ineffective drugs and devices off the market. Although the FDA's broad mission has remained fixed over time, the landscape around it has shifted dramatically through advances in scientific understanding, the emergence of novel public health threats, and the development of innovative therapies that carry both risk and benefit. Accordingly, through the FDCA, Congress has given the FDA broad authority, to which it has applied its considerable expertise in science, medicine, and public health. For nearly 40 years, that combination has caused courts to defer to an agency's reasonable interpretations of ambiguous statutes and those conferring broad authority under the framework established in

Chevron. As outlined below, the FDA's implementation of the FDCA reinforces the wisdom of that framework.

A. Deference is appropriate for the FDA's regulation of drugs and medical devices as they implement a complex scheme that requires expertise.

Under the *Chevron* framework, deference to an agency's reasonable interpretation of its statutory authority is particularly appropriate where the authority at issue is part of "a lengthy, detailed, technical, complex, and comprehensive response to a major social issue." *Chevron*, 467 U.S. at 848; *see also Decker*, 568 U.S. at 618–19 (Scalia, J., concurring in part and dissenting in part) (the conclusion that an "agency possesses special expertise in administering its 'complex and highly technical regulatory program' * * * is true enough, and it leads to the conclusion that agencies and not courts should make regulations") (quoting *Thomas Jefferson Univ.*, 512 U.S. at 512); Gov't Br. at 16 (collecting examples of cases where "*Chevron* has played a critical role in resolving many interpretive questions in complex and technical areas of federal law," including drug regulation).

The reasons for this sensible approach are severalfold, *see id.* at 7-8, but fundamentally reflect respect for the separation of powers and a sense of judicial humility, which calls on courts to recognize that, often times, "[j]udges are not experts in the field" and are ill-equipped to discern meaning from ambiguously worded and technically complex statutory schemes. *Chevron*, 467 U.S. at 865. Accordingly, where the "traditional tools of statutory

construction," *id.* at 843, are insufficient to answer the interpretive question posed, courts have wisely restricted their role to evaluating the reasonableness of the interpretation offered by the agency possessing the special, technical knowledge necessary to understand the meaning of a statutory provision. *Kisor*, 139 S. Ct. at 2415.[2] The FDCA is a paradigmatic example of the sort of "lengthy, detailed, technical, complex, and comprehensive response to a major social issue," *Chevron*, 467 U.S. at 848, which has provided reason for courts to defer to the FDA's regulatory judgment since long before *Chevron*. *See* Bendicksen et al., *supra*, at 372 n. 9 ("'[T]he twentieth-century FDA received nearly unparalleled judicial deference in its regulation of drugs.'" quoting Carpenter, *supra*, at 729).

Because of the FDCA's undeniable complexity, *Mylan Lab'ys*, 389 F.3d at 1280, understanding the authority it confers often requires an "'evaluation[] of scientific data" or a "statutory phrase [to] be read in the context of the kind of drug at issue." *Serono Lab'ys, Inc.*, 158 F.3d at 1320. These are competencies "within [FDA's] area of expertise,'" *id.*, but will understandably be out of reach for many courts, *see Kisor*, 139 S. Ct. at 2410 (suggesting that courts are not competent to evaluate if "a company created a new 'active moiety' by joining a previously approved

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[2] *Amici* agree, as the Government rightly observes, that *Chevron* deference is sensible even in cases "that do not implicate scientific or technical questions," in light of the "'historical familiarity' and 'expertise' that can yield interpretive insights." Gov't Br. at 17 (describing Petitioners' arguments and quoting *Martin v. OSHRC*, 499 U.S. 144, 153 (1991)).

moiety to lysine through a non-ester covalent bond"); *see also Otsuka Pharm. Co. v. Price*, 869 F.3d 987, 993-995 (D.C. Cir. 2017) (examining same question). The special challenge of understanding the FDCA comes not only from its use of technically sophisticated terms, like "active moiety," *Kisor*, 139 S. Ct. at 2410, but also from its requirement that the FDA develop scientifically sound solutions to complex public health problems, which often arise in an environment where both the scientific understanding and shape of the public health problem are subject to rapid change.

The breadth of the issues addressed by the FDCA adds to its complexity. Giving effect to its ambitious purpose of "protect[ing] the health and safety of the public at large," *POM Wonderful LLC*, 573 U.S. at 108, thus requires the FDA, as the agency charged with executing the FDCA's public health objectives, to exercise expertise that is both deep and wide. *See* 21 U.S.C. §§ 393(b)(2) (directing the FDA to "protect the public health by ensuring" the safety and efficacy of "foods," "human and veterinary drugs," devices intended for human use," "cosmetics," and "electronic product radiation"). Indeed, considering only the FDA's regulation of drugs and devices, the subject of *Amici*'s expertise, is sufficient to appreciate the breadth and complexity of the issues Congress has asked the FDA to regulate.

The FDA, which has been routinely recognized by courts and others "as a scientific decisionmaker and a champion of public health," has historically been up to that task. Bendicksen et al., *supra*, at 372; *see also Mylan Lab'ys, Inc.*, 389 F.3d at 1280 ("There is no denying* * * the FDA's expertise."); *Otsuka Pharm.*

Co. v. Burwell, 302 F. Supp. 3d 375, 403 (D.D.C. 2016) (Jackson, J.) ("[T]he FDA is an expert agency charged with making precisely these sorts of highly technical determinations."), *aff'd sub nom. Otsuka Pharm. Co.*, 869 F.3d at 987.

B. The FDCA confers broad authority to carry out its ambitious public health mission, which warrants deference.

Befitting its ambitious statutory mandate, the FDCA grants the FDA authority sufficient to regulate drugs and medical devices comprehensively and at every point in their lifecycle. From clinical trials and drug development to approval of new drugs, marketing, and labeling, to post-marketing surveillance, FDA regulations set the standards by which the products are regulated, and public health is protected. But while the broad reach of the statutory authority is clear, many provisions are subject to multiple, plausible interpretations. As the several FDA regulations reviewed herein underscore, reasonable and well-supported regulations often interpret statutory language that is amenable to other, plausible interpretations.

i. New drug approvals.

Under the FDCA, no "new drug" can be marketed in the United States unless it has first been approved by the FDA. *See* 21 U.S.C. § 355(a). To gain approval, applicants must provide FDA with, among other things, "*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 thereof." 21 U.S.C. § 355(d) (emphasis added). "[S]ubstantial evidence" means "evidence consisting of *adequate and*

well-controlled investigations, including clinical investigations, by experts qualified by scientific training and expertise to evaluate the effectiveness of the drug involved." *Ibid.* (emphasis added).

At a high level of generality, that authority is clear enough. Congress wants the FDA to make sure only safe and effective drugs are marketed. But, apart from specifying that scientific experts should be involved, Congress did not say what it meant for an investigation to be "adequate and well-controlled." *See ibid.*

The FDA filled in those details, specifying in regulations that an "adequate and well-controlled" study must generally have, at a minimum, "a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect," 21 C.F.R. § 314.126(b)(2); comparisons of at least two dosages, 21 C.F.R. § 314.126(b)(2)(i); minimization of bias to allow for comparability between groups of different ages, sexes, severities of disease, etc., 21 C.F.R. §314.126(b)(4); and that the test drug "be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation," 21 C.F.R. § 314.126(d).

Notwithstanding the reasonableness of the FDA regulations, the breadth of the statutory authority leaves room for other plausible arguments to be advanced in litigation. Placing those arguments on equal footing, as Petitioners hope to do, risks courts acting as policymakers, asserting the final say on whether clinical investigations provide sufficient indicia of the drug's safety and effectiveness to make it available to the public. *See* 21 U.S.C. § 355(d).

That raises cross-cutting concerns because courts, which lack the requisite technical expertise, could be persuaded to allow a potentially dangerous drug into the market just as easily as they might erroneously hold up approval of a drug to which patients desperately need access. Indeed, since the same issue may come before different courts, inconsistent results are likely. *Kisor*, 139 S. Ct. at 2414 (plurality opinion) (observing that courts "are most likely to come to divergent conclusions when they are least likely to know what they are doing"). Divergent outcomes across courts will both increase compliance costs for pharmaceutical companies intent on marketing drugs nationwide and cause manufacturers to hesitate before taking the kinds of risks that lead to real innovation. That will, in turn, increase drug costs and decrease drug access and options for patients, which harms public health, in contravention of the FDCA's core purpose.

ii. Fast Track drug approval.

The traditional drug approval process is not the only way that a drug can be approved for market. Manufacturers may also pursue authorization under the FDCA's "Fast Track" authority, which provides that, "at the request of the sponsor of a drug," the FDA "shall * * * expedite the development and review of [a] drug" if (1) "it is intended, whether alone or in combination with one or more other drugs, for the treatment of a serious or life-threatening disease or condition," and (2) "it demonstrates the potential to address unmet medical needs for such a disease or condition." 21 U.S.C. § 356(b)(1). If these criteria are

met, the FDA may also act on its own initiative to place a drug on this "fast track." 21 U.S.C. § 356(b)(3).

The FDA has interpreted this language in light of the Fast Track program's purpose—spurring innovation and the development of live-saving therapies, 21 U.S.C. § 356(e)(1)—and the context in which the program operates—finding treatments for those with life-threatening diseases and no good treatment options, 21 C.F.R. § 312.80. It has thus recognized that "physicians and patients are generally willing to accept greater risks or side effects" in this situation and that it should, accordingly, evaluate "the benefits of the drug need * * * in light of the severity of the disease being treated." *Id.* Ultimately, FDA has determined that this calls for it to make "a medical risk-benefit judgment in making the final decision on approvability." 21 C.F.R § 312.84.

As with other statutes, that seems reasonable and consistent with the statutory authority. But it nevertheless creates difficult line-drawing problems when the FDA must approve or deny a Fast Track application, which leave ample room for an aggrieved applicant to challenge the FDA's interpretation. Without the deference recognized under *Chevron*, a court that is persuaded, even marginally so, by the applicants' litigation position, will find itself acting as drug policymaker, without any of the requisite expertise to serve in that role. As with drug approval, generally, additional judicial scrutiny of decisions reached under the FDA's Fast Track authority will unleash a host of bad results that undermine Congress's purpose in enacting the FDCA. *See supra* at 12-14.

iii. Drug labeling: setting standards for prescribing information.

Whether a drug is safe and effective is, in many cases, context dependent. For instance, a drug that is safe at one dose might be dangerous if taken at a higher dose. Similarly, a drug that is effective on its own might be rendered ineffective or even dangerous if taken alongside another medication. Accordingly, the FDCA provides that a company selling an approved drug will nevertheless be subject to penalties for marketing a "misbranded" drug:

> [u]nless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users[.]

21 U.S.C. § 352(f).

What constitutes "adequate directions for use" and "adequate warnings against use" are not defined by the statute, *see ibid.*, and, while they can likely be understood as a general matter, a functional definition that serves the FDCA's public health goal must go beyond that and reflect an understanding of the science underlying a drug approval, as well as the clinical setting in which the drugs will be used or prescribed. The FDA regulations demonstrate that greater degree of expertise by setting up a comprehensive and uniform labeling layout, which includes "[h]ighlights of prescribing information," 21 C.F.R. § 201.57(a), a table of contents of the prescribing information, C.F.R. § 201.57(b); and

"[f]ull prescribing information," C.F.R. § 201.57(c). *See* FDA, *How Do I Use Prescription Drug Labeling* (Mar. 29, 2023), http://tinyurl.com/f5hzf555.

As the name suggests, the "highlights" section provides a quick way for a clinician to understand "the most important aspects of a drug," *id.*, such as the drug name, dosage information, indications and contraindications, and "black box" warning, a prominently displayed warning (enclosed in a black box) about any risks of death or serious injury. 21 C.F.R. § 201.57(a). The requirements for full prescribing information go further in depth, such as by describing special considerations for those who are pregnant, and the clinical studies "that support effectiveness * * *, including discussion of study design, population, endpoints, and results[.]" 21 C.F.R. § 201.57.

There are certainly other plausible ways that the FDA could have applied the FDCA's requirement that drugs come with directions and warning labels. The FDA's approach may not even be the very best formulation. But the question under Chevron is whether it is a reasonable application of the FDA's statutory authority, and if it is the product of the FDA's expertise. *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3,922, 3,930-31 (Jan. 24, 2006) (responding to drug manufacturer opposition to highlights section by noting that, in developing the rule, it had used focus groups, surveys, and public meetings to "carefully evaluate[]the drug information needs of physicians and ways to best address those needs in prescription drug labeling").

Like with drug approval decisions, judicial intervention in labeling decisions, without the safeguards of the *Chevron* framework, will produce bad results. A lack of uniformity in labeling requirements across courts will increase compliance costs, to be sure. But ad-hoc judicial disruptions to labeling requirements are also a public health concern. Prescriber information labels, for instance, are critical, carefully constructed documents that allow informed prescribing decisions to happen safely in a clinical setting. They contain, among other things, information about the clinical trial populations on which the drug was first assessed, which will inform the clinician's understanding of whether the drug was shown to be safe and effective for their patient's profile. *See* Tanvee Varma et al., *Metrics, Baseline Scores, and a Tool to Improve Sponsor Performance on Clinical Trial Diversity: Retrospective Cross Sectional Study*, BMJ Medical, Nov. 2022, at 1 (noting that clinical trial populations often exclude those who have other underlying conditions, take multiple other medicines, or are older, female, or racially diverse). Disruption to this authority increases the risk of prescribing errors, which fundamentally undermines the FDCA's public health purpose.

iv. Drug labeling: Medication Guides.

Whereas prescriber information is meant to help healthcare providers, the FDA also uses its labeling authority to require Medication Guides, which enable "patients to use their medications safely and effectively." Prescription Drug Product Labeling; Medication Guide Requirements, 63 Fed. Reg. 66,378 (Dec. 1, 1998). To that end, the FDA has promulgated

detailed regulations prescribing the "[c]ontent and format of a Medication Guide," which require that these guides provide information that the FDA has determined is most necessary to assist consumers in correctly taking their medication. *See* 21 C.F.R. § 208.20. These regulations provide baseline conditions that Medication Guides must include, including headings for things and activities to avoid while taking the medication, and a description of possible side effects. 21 C.F.R. §§ 208.20(b)(6), (7). The regulations also provide the means by which the Medication Guides must be made available to each patient. *See* 21 C.F.R. § 208.24(b).

Although this seems a reasonable exercise of the FDA's authority to regulate against misbranded drugs or misleading labels and packaging, *see* 21 U.S.C. §§ 352, 355, when promulgated, commenters asserted that the FDA lacked authority to require pharmacists to make these Medication Guides available, Prescription Drug Product Labeling; Medication Guide Requirements, 63 Fed. Reg. at 66,382. As with the FDA's authority to dictate the prescribing information that appears on drug labels, patients will be worse off if the contents of Medication Guides are shaped by individual courts instead the FDA's expertise.

* * *

As this discussion shows, the FDA's important work relies to a great extent on broad statutory language, which the FDA has worked diligently to interpret and clarify through regulations that reflect its expert judgment and reasonable approach to implementing the FDCA. Despite its diligence and reasonableness, the FDA's ability to continue fostering drug and

device innovation, while protecting public health, will come rapidly under attack, if *Chevron* falls.

II. Overruling or substantially modifying *Chevron* undermines Congressional intent and is not necessary to resolve Petitioners' stated concerns.

Petitioners would have the Court replace the "stable background rule" provided by the *Chevron* framework, *City of Arlington v. FCC*, 569 U.S. 290, 296 (2013), with a chaotic environment where the reasoned decisions the FDA makes (at nearly every point in the lifecycle of a drug or device) will be subject to challenge and delay. That risks judicial intervention into everything from which drugs are approved to what information appears on a warning label, undermining the FDA's collaborative regulatory process along the way. *Supra* at 12-20.[3] None of that—and particularly not the supplanting of the FDA's expertise—accords with congressional intent. Nor is it necessary. The Court can address Petitioners' concerns about *Chevron* "forcing courts to rubber-stamp" agency decisions, Pet. Br. at 4, by emphasizing, as it has before, that "hard interpretive conundrums, even relating to complex rules, can often

[3] To be clear, *Amici* do not suggest that any particular FDA regulatory authority would necessarily succumb to such litigation. The FDA's authority, while often broad, is typically clear, and good reasons for deference to its expertise and policymaking charge will remain, even if *Chevron* is formally overturned. Nevertheless, a broad ruling for Petitioners will undoubtedly encourage litigation, increase inconsistent lower court applications of any new standard of review, and deliver destabilizing effects.

be solved." *Kisor*, 139 S. Ct. at 2415 (plurality opinion).

A. Deference to the FDA under *Chevron* animates the FDCA's purpose in several ways.

The Court has recognized that the chaotic result Petitioners request should be avoided on separation of powers grounds, given "Congress's frequent 'preference for resolving interpretive issues by uniform administrative decision, rather than piecemeal by litigation,'" a preference that "may be strongest when the interpretive issue arises in the context of a 'complex and highly technical regulatory program'" where "judges are most likely to come to divergent conclusions" because "they are least likely to know what they are doing." *See Kisor*, 139 S. Ct. at 2413–14 (plurality opinion) (first quoting *Ford Motor Credit Co. v. Milhollin*, 444 U.S. 555, 568 (1980), and then quoting *Thomas Jefferson*, 512 U.S. at 512).

Furthermore, any rule the Court adopts that promotes judicial, rather than administrative, regulation will also put distance between regulated parties and the regulatory process in a way that Congress did not intend. That will be a significant loss. Like other agencies, *see* Gov't Br. at 18, FDA's regulations are the product of robust engagement with the many stakeholders with an interest in a regulatory regime that appropriately balances drug safety and effectiveness with enabling life-saving pharmaceutical advances, including regulated entities like pharmaceutical companies and patients and their advocates.

Indeed, stakeholder engagement is legally required in some contexts as various provisions of the FDCA provide expressly that FDA should carry out

its authority "in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products." *See, e.g.*, 21 U.S.C. § 393(b)(4). And, of course, the FDA must also provide the public with notice and an opportunity to comment on proposed regulations, 5 U.S.C. § 553, and must consider and "respond to significant comments." *Perez v. Mortg. Bankers Ass'n*, 575 U.S. 92, 96 (2015).

In addition, the FDA also receives and responds to citizen petitions, meets with stakeholders, conducts informational workshops, and holds open meetings of its various advisory committees. *See, e.g.*, 21 C.F.R. § 10.30 (citizen petitions); FDA, *Stakeholder Engagement Staff* (Nov. 15, 2023), http://tinyurl.com/2p9ahunh; John R. Manthei et al., Latham & Watkins, *Recent FDA Guidance Signals Increased Willingness to Engage Industry Stakeholders* (Oct. 25, 2023), http://tinyurl.com/mrxyb3dn.

The ability of the interested public to engage in the regulatory process is a good thing, and not only in some abstract sense or because it is legally required in some cases. The joinder of stakeholder input and engagement with agency expertise delivers specific benefits for both the public and the FDA. The FDA's public engagement "procedures give the public greater and less costly opportunities to be heard," and "also enable the agency to synthesize various comments and consider more nuanced regulatory approaches than may be possible in piecemeal litigation of the same issues by individual parties in different courts." Gov't Br. at 18. Their ability to undertake extensive information gathering exercises

before reaching a decision is yet another way in which federal agencies have "comparative advantages * * * over courts" in the regulatory context, which has long served to justify the deference they have received. *See Kisor*, 139 S. Ct. at 2413 (plurality opinion).

B. In practice, deference under *Chevron* has allowed the FDA to faithfully and reliably administer the FDCA.

An examination of cases decided by Courts of Appeal at step two of the *Chevron* framework further illustrate that, in practice, *Chevron* has guided courts *toward* outcomes that support the FDCA's public health purpose. *See* Bendicksen et al., *supra*, at 371, 378 (collecting cases since 2000 in which "federal appellate courts have applied the [*Chevron*] framework * * * in litigation involving FDA actions"). *Amici* focus here on three such cases, which involve challenges to the FDA's assertion of its authority to regulate a product as a "drug."

First, in *Pharmanex v. Shalala*, the Tenth Circuit considered a case brought by Pharmanex, a company hoping to "market[] a product, Cholestin, that [wa]s intended to promote healthy cholesterol levels." *Pharmanex v. Shalala*, 221 F.3d 1151 (10th Cir. 2000). Cholestin contained a natural substance that was chemically identical to the active ingredient in a prescription drug, Mevacor. *Id.* at 1153. Pharmanex sought to market Cholestin as a dietary supplement, but the FDA determined that the product qualified as a drug under the FDCA, which subjected it to more rigorous pre-market regulation. *Id.*

As *Chevron* instructs, the Tenth Circuit applied "the traditional tools of statutory construction," *id.* at

1154 (citing *Chevron*, 467 U.S. at 842), concluding that the statute contained ambiguous terms like "article" and "drug," and deferred to the FDA's interpretation, which it found to be reasonable. *Id.* at 1155-56. The court found that Pharmanex's interpretation was "linguistically possible," but would have amounted to "an end-run around the strictures of the new drug approval process," *id.* at 1160, which was a result that would undermine the FDCA's public health purpose, *see id.* at 1158-59.

Second, in *Whitaker v. Thompson*, the D.C. Circuit considered whether the FDA had misinterpreted the FDCA when it refused to allow the marketing of "'saw palmetto,' an extract from the pulp and seed of the dwarf American palm," as a "health claim." *Whitaker v. Thompson*, 353 F.3d 947, 948 (D.C. Cir. 2004). The manufacturer wished to market the saw palmetto as a supplement able to "improve urine flow, reduce nocturia and reduce voiding urgency associated with mild benign prostatic hyperplasia," or an enlarged prostate. *Id.* The FDA argued that claiming a product would help "to maintain health and to 'prevent' disease" constituted a "health claim," whereas "claims that a product could 'treat' a disease" constituted "drug claims." *Id.* at 948-49. In the FDA's view, the claims concerning the saw palmetto extract were "drug claims," meaning that it could not be sold for its stated use unless it first received "approval as a drug." *Id.* at 949.

In a unanimous panel decision, which was joined by then-Judge John G. Roberts, Jr., the D.C. Circuit held that the FDCA's overlapping definitions of "drug claims" and "health claims" created a statutory ambiguity, which "the 'traditional tools of statutory

construction'" could not resolve. *Id.* at 950 (quoting *Chevron*, 467 U.S. at 843 n.9). Accordingly, the court deferred to the FDA's position, which it found reasonable, albeit not "a knock-down argument" or necessarily one that "would be sufficient to overcome a strong textual or structural inference in favor of a different interpretation." *Id.* at 951.

Third, in *United States v. Genendo Pharm., N.V.*, the Seventh Circuit considered a pharmaceutical company's attempt "to import prescription drugs intended for sale in other countries into the United States for repackaging and distribution." *United States v. Genendo Pharm., N.V.*, 485 F.3d 958, 960 (7th Cir. 2007). The FDA seized the drugs, arguing that they were "an 'unapproved new drug,'" *id.* (quoting 21 U.S.C. § 355(a)), because they "deviated from the FDA-approved [new drug application (NDA)] in several important respects," including the manufacturing facility, packaging, labeling, and expiration dates of the imported drugs, *id.* at 961.

Genendo argued that the "deviations from the requirements in the FDA-approved NDA" fell under a statutory "exemption from all labeling and packaging requirements * * *, including the NDA requirements, so long as a drug is en route to or being held at an authorized drug repackager." *Id.* at 961 (citing 21 U.S.C. § 353(a)). The court found both Genendo and the FDA's interpretations "plausible" and, on that basis, "enough ambiguity in the statute" to confine its review to "whether the FDA's interpretation is based on a permissible construction of the statute." *Id.* at 964. The court also observed that adopting Genendo's interpretation of the FDCA would permit drugs to be *repackaged* outside of the FDA approved facilities,

even though approval of such facilities would otherwise be required as part of the comprehensive drug approval process. *Id.*

* * *

What these cases collectively show is that deference under *Chevron* has consistently allowed the FDA to fulfill its public health mission and carry out the FDCA in a faithful way. In each of these cases, the reviewing court found that both parties—FDA and the company seeking to avoid pre-market approval requirements—had put forward plausible interpretations that would have led to opposite outcomes. Had any of those courts applied a lower level of deference, or reviewed the interpretations without any deference, the manufacturers challenging FDA might have been permitted to market drugs to consumers without the protections of FDA's stringent pre-market safety and effectiveness reviews, *Pharmanex*, 221 F.3d at 1158-60; *Whitaker*, 353 F.3d at 948-49, and allowed a loophole for supervision and approvals of packaging facilities, *Genendo Pharm.*, 485 F.3d at 960. The flexibility afforded to the FDA under *Chevron* has benefitted the public health goals of the FDCA greatly, while at the same time, preserving the judiciary's proper role of ensuring the agency is engaged in reasoned decision-making that is within its statutory authority.

C. Overruling or substantially modifying *Chevron* is not necessary to resolve Petitioners' stated concerns.

There is no doubt that the FDA has frequently enjoyed success when courts find ambiguity in the FDCA. But that does not make *Chevron* the

"rubber-stamp" that Petitioners claim it to be. *See* Pet. Br. at 4. Courts are plainly willing and able to strike down unreasonable FDA interpretations, even where the operative FDCA language is ambiguous. *See, e.g.*, *Braeburn Inc. v. FDA*, 389 F. Supp. 3d 1, 27 (D.D.C. 2019) (rejecting FDA interpretation at Step Two because it had "not reasonably interpreted the statute"); *see also Prevor v. FDA*, 67 F. Supp. 3d 125, 137 (D.D.C. 2014) (finding statute clear but noting that, had it found the statute ambiguous, it would have vacated the FDA action as unreasonable); *Stat-Trade Inc. v. FDA*, 869 F. Supp. 2d 95, 107 (D.D.C. 2012) (similar).

Further, any perceived "mismatch," Pet. Br. at 39, between instances in which *Chevron* is appropriately applied to technically complex statutes and those in which courts have rushed to "'wave the ambiguity flag" merely because a statute appears to be 'impenetrable on first read,'" is no reason to throw out the doctrine altogether, Gov't Br. at 14 (quoting *Kisor*, 139 S. Ct. at 2415). That misapplication of *Chevron* is better corrected by the Court emphasizing that "hard interpretive conundrums, even relating to complex rules, can often be solved." *Kisor*, 139 S. Ct. at 2415 (plurality opinion); *see also id.* at 2448 (Kavanaugh, J., concurring in the judgment) ("If a reviewing court employs all of the traditional tools of construction, the court will almost always reach a conclusion about the best interpretation of the regulation at issue.").

Finally, Petitioners cannot reasonably deny that in some cases "the law runs out, and policy-laden choice is what is left over." *Kisor*, 139 S. Ct. at 2415 (plurality opinion). At least in those cases—which, as explained above, are likely to arise when the FDA

gives effect to the FDCA's broad public health mandate—the Court should preserve a mechanism for non-expert courts to give some measure of deference to the expertise of federal agencies, like the FDA.

CONCLUSION

For the foregoing reasons, *Amici* respectfully request that the Court affirm the judgment of the Court of Appeals.

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