THE END OF FDA EXCEPTIONALISM? DISSECTING DEFERENCE TO THE FDA IN DRUG DISPUTES

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On April 7, 2023, a federal judge issued a nationwide stay on the United States Food and Drug Administration (FDA) approval of the abortifacient medication mifepristone. It was instantly a landmark case, decried as the first time in over one-hundred years that a federal court nullified an FDA drug approval. A few hours later, a second federal district court enjoined FDA restrictions on mifepristone. Two federal courts substantively evaluating FDA drug approval data in one day is unprecedented. It begs the question: will courts overturn FDA drug approvals again?

Conventional wisdom says no. Abortion exceptionalism, the trend of legislatures and courts subjecting abortion to unique and burdensome rules, suggests that aggressive judicial review of FDA approvals in non-abortion contexts will continue to be limited. Yet this Article analyzes pharmaceutical litigation involving the FDA across the last decade to offer an alternative narrative on whether and when challenges to FDA drug determinations might occur. Between 2019 and 2023, courts have overturned multiple longstanding FDA policies by challenging science-based

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policy decisions. Viewed in this light, the mifepristone cases could be one piece of a concerning emerging trend.

This Article also explores why litigants have been more successful than usual. It argues that the emerging new norm of scrutinizing science-based policy choices may also be connected to growing public skepticism of the FDA in the wake of multiple concurrent pharmaceutical-approval crises including COVID-19 treatments, opioids, and the controversial Alzheimer's drug aducanumab. Judicial deference to agencies has also been declining for decades. After the 2023 Supreme Court Term, longstanding FDA policies deciding drug approvals might be successfully challenged more often. While there are other reasons to suspect that challenges to FDA drug approval decisions may not increase, it is more important than ever to restore trust in the FDA and consider where judicial review of pharmaceutical determinations is beneficial.

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INTRODUCTION

On April 7, 2023, a Texas district court decided on substantive grounds that a drug, mifepristone, approved by the United States Food and Drug Administration (FDA) could no longer be sold in the United States.[1] This case overturned twenty years of FDA evaluations justifying approval.[2] Within hours, a second court reversed decisions on the same abortifacient, this time requiring fewer restrictions on access to mifepristone.[3] The threat of a court removing an FDA-approved drug that remains an integral part of women's reproductive healthcare from the market sent shockwaves through patients, physicians, legal scholars, political activists, and pharmaceutical companies alike. Interdisciplinary scholars have critiqued the Texas court from a variety of perspectives. Among them, the consequences of removing safe and legal abortion access from patients,[4] the implications for preemption[5] and federalism,[6] the unusual standing argument (upon which the Supreme Court

1 All. for Hippocratic Med. v. FDA, 668 F. Supp. 3d 507, 543–57 (N.D. Tex. 2023), *aff'd in part, vacated in part*, 78 F.4th 210 (5th Cir. 2023), *cert. granted*, 144 S. Ct. 537 (2023) (mem.), *rev'd and remanded*, 602 U.S. 367 (2024), *vacated and remanded*, 117 F.4th 336 (5th Cir. 2024).

2 *See id.*; Abbe R. Gluck, *The Mifepristone Case and the Legitimacy of the FDA*, 329 JAMA 2121, 2121 (2023).

3 Washington v. FDA, 668 F. Supp. 3d 1125 (E.D. Wash. 2023).

4 *See* David S. Cohen, Greer Donley & Rachel Rebouché, *Abortion Pills*, 76 STAN. L. REV. 317, 380–94 (2024); *see also* Bria Peacock, *A Black Abortion Provider's Perspective on Post*-Roe *America*, 386 NEW ENG. J. MED. 1, 2 (2022) ("Forced births and reproductive exploitation of Black bodies are historical facts, and history often repeats itself. When it does, marginalized people usually suffer the most.").

5 *See* Patricia J. Zettler, Annamarie Beckmeyer, Beatrice L. Brown & Ameet Sarpatwari, *Mifepristone, Preemption, and Public Health Federalism*, J.L. & BIOSCIENCES, Dec. 2022, at 1, 2; *id.* at 4 ("[T]here are compelling legal arguments that support courts concluding many state laws limiting or banning access to mifepristone are preempted by FDA regulation."). For an insightful discussion of preemption and health law, see Elizabeth Y. McCuskey, *Body of Preemption: Health Law Traditions and the Presumption Against Preemption*, 89 TEMP. L. REV. 95 (2016).

6 *See* Louise Aronson, *A New Year's Wish—Learning to See Racism in Health Care Through a Child's Eyes*, 386 NEW ENG. J. MED. 1 (2022); *see also* Peter Grossi & Daphne O'Connor, *FDA Preemption of Conflicting State Drug Regulation and the Looming Battle over Abortion Medications*, J.L. & BIOSCIENCES, Jan.–June 2024, at 1; James M. Beck, Philip W. Danziger, Sarah B. Johansen & Andrew R. Hayes, *Federal Preemption and the Post*-Dobbs *Reproductive Freedom Frontier*, 78 FOOD & DRUG L.J. 109 (2023). For an excellent discussion of federalism and health law, see Myrisha S. Lewis, *Innovating Federalism in the Life Sciences*, 92 TEMP. L. REV. 383, 391 (2020).

overturned the case[7]), and proper deference to a scientific administrative agency.[8] Many of the nation's leading FDA law professors argued in an amicus brief that this might be the first time a court has ever substantively evaluated data supporting a drug approval decision and reversed the FDA's determination.[9] However, there is an important yet unexplored question lurking: *will courts continue to overturn FDA drug approval decisions outside of the abortion context?*

At first glance, these 2023 judicial opinions reevaluating an FDA pharmaceutical approval appear to be an anomaly.[10] This may be yet another example of abortion exceptionalism, the well-documented trend of courts and legislatures singling out abortion care.[11] Judges and scholars agree substantive challenges to FDA drug approvals are unusual, if not completely unprecedented.[12] Challenges to the FDA's broad authority on

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7 The Supreme Court of the United States held that the plaintiffs lacked standing to challenge the FDA's actions regarding the regulation of mifepristone. FDA v. All. for Hippocratic Med., 602 U.S. 367 (2024); Joel Zivot, *The Mifepristone Ruling Lacks Both Standing and Merit—Will SCOTUS Preserve Our Rights or Quash Them?*, HILL (Apr. 21, 2023, 5:00 PM), https://thehill.com/opinion/civil-rights/3963320-the-mifepristone-ruling-lacks-both-standing-and-merit-will-scotus-preserve-our-rights-or-quash-them [https://perma.cc/B24C-MUJK]; CONG. RSCH. SERV., LSB11183, MEDICATION ABORTION ACCESS REMAINS UNCHANGED AS SUPREME COURT REJECTS LEGAL CHALLENGE ON STANDING GROUNDS (2023). Standing is beyond the scope of this Article.

8 *See* Anne Zimmerman, *Politicizing Deference to the FDA Considering the Alliance for Hippocratic Medicine Cases*, YALE J. ON REGUL. (Apr. 17, 2023), https://www.yalejreg.com/nc/politicizing-deference-to-the-fda-considering-the-alliance-for-hippocratic-medicine-cases-by-anne-zimmerman [https://perma.cc/DN2K-A7P9].

9 Brief of Food and Drug Law Scholars as Amicus Curiae in Support of Defendants' Opposition to Plaintiffs' Motion for Preliminary Injunction at 19, All. for Hippocratic Med. v. FDA, 668 F. Supp. 3d 507 (N.D. Tex. 2023) (No. 22-cv-223), 2023 WL 2974513; *see also* Lars Noah, *Listening to Mifepristone*, 80 N.Y.U. ANN. SURV. AM. L. 33, 49–50 (2023); Greer Donley & Patricia J. Zettler, Response to *Listening to Mifepristone*, 80 N.Y.U. ANN. SURV. AM. L. 63 (2023); Daniel G. Aaron, Teneille R. Brown & Michael S. Sinha, *Court Intrusion into Science and Medicine—The Mifepristone Decisions*, 329 JAMA 1735, 1735 (2023).

10 Nicholas R. Parrillo, Administrative Law as a Choice of Business Strategy: Comparing the Industries Who Have Routinely Sued Their Regulators With the Industries Who Rarely Have 44 (unpublished manuscript) (on file with author) ("Drugmakers' reluctance to sue to overcome FDA safety-and-effectiveness constraints appears to go far back, to the 1980s at the latest. The brand-name manufacturers' association PhRMA has not been a plaintiff or petitioner in *any* suit against FDA (or against HHS on an FDA matter) since the start of the coverage of the Bloomberg dockets database in 1989 . . . .").

11 *See* Caitlin E. Borgmann, *Abortion Exceptionalism and Undue Burden Preemption*, 71 WASH. & LEE L. REV. 1047 (2014); Caroline Mala Corbin, *Abortion Distortions*, 71 WASH. & LEE L. REV. 1175 (2014). For a critique of abortion exceptionalism, see June Med. Servs. LLC v. Russo, 591 U.S. 299, 359–77 (2020) (Thomas, J., dissenting).

12 *See* James T. O'Reilly, *Losing Deference in the FDA's Second Century: Judicial Review, Politics, and a Diminished Legacy of Expertise*, 93 CORNELL L. REV. 939, 956 (2008) ("[T]he FDA has long enjoyed freedom from judicial interference with drug approval decisions."); Brief of Food and Drug Law Scholars and Professors as Amici Curiae in of Support of Defendants' Opposition to

drugs are also relatively rare on the whole, as are direct challenges to substantive policy choices.[13] As explained by Professor Catherine M. Sharkey, "courts have given strong-form deference to the FDA's scientific judgements regarding pharmaceutical drugs and medical devices."[14] Courts have grappled with the proper scope of deference to all scientific agencies for decades, and Professor Sharkey argues that the FDA historically stood apart in the steady attack on deference to agency actions in administrative law and courts are still likely to acquiesce to the FDA's scientific judgments even with concurrent broader attacks on agency deference.[15] Simply put, there is a longstanding trend of deference to the FDA's expertise in drug determinations.[16] This sort of "FDA exceptionalism"[17] suggests that as long as the Agency follows its own protocols and remains consistent in its views unless changes are empirically justified, courts generally defer to the FDA's scientific

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Plaintiffs' Motion for Preliminary Injunction, *supra* note 9, at 19 ("It would also be unprecedented: We are not aware of any case in which a court has removed a drug from the market over FDA's objection."); *cf.* Oral Argument at 103:15, All. for Hippocratic Med. v. FDA, 78 F.4th 210 (5th Cir. 2023) (No. 23-10362), https://www.ca5.uscourts.gov/OralArgRecordings/23/23-10362_5-17-2023.mp3 (memorializing Fifth Circuit Court Judge James Ho specifically referencing other FDA controversies when questioning the FDA's authority during May 2021 oral arguments, concluding "I don't understand this theme, 'the FDA can do no wrong,' We are allowed to look at the FDA just like we're allowed to look at any agency. That's the role of the courts[,]" referring to unrelated FDA controversies including withdrawal of Makena after litigation, food safety failures, and the contributions of the Agency to the opioid crisis).

13 Liam Bendicksen, Aaron S. Kesselheim & C. Joseph Ross Daval, *FDA and* Chevron *Deference: A Case Review*, 78 FOOD & DRUG L.J. 371, 374 (2023); *see also* Donley & Zettler, *supra* note 9, at 67 ("[N]one of [the cases] involves a court revoking the approval of a drug already on the market by substituting its own judgment about safety and effectiveness in place of FDA's."); Parrillo, *supra* note 10, at 45 ("Challenges to the denial of pre-market approval to a new drug have apparently been rare to nonexistent for about 45 years."); *infra* Appendix I.

14 Catherine M. Sharkey & Daniel J. Kenny, *FDA Leads, States Must Follow*, 102 WASH. U. L. REV. 155, 159 (2024) ("[T]hey are apt to acquiesce in the agency's scientific judgments, even as administrative deference doctrines have come under broad attack, including before the U.S. Supreme Court."); *see also* Noah, *supra* note 9, at 50 ("[J]udges rarely invalidate the latter because of the tremendous deference traditionally shown to this agency . . . ."); Lars Noah, *The Little Agency That Could (Act with Indifference to Constitutional and Statutory Strictures)*, 93 CORNELL L. REV. 901, 902 (2008) ("[T]he FDA has had an enviable record of success in the courts because judges have shown tremendous deference to its expertise in implementing its public health mission.").

15 Sharkey & Kenny, *supra* note 14.

16 *Id.*; *see also* Anjali D. Deshmukh, *Can We Get a Refund? Judicial Remedies for Drugs that Do Not Work*, 91 TENN. L. REV. 621, 670 (2024); Parrillo, *supra* note 10, at 48 ("Drugmaker reluctance to sue [the] FDA has been a matter of insider comment for decades.").

17 Carl Wiersum, *No Longer Business as Usual: FDA Exceptionalism, Commercial Speech, and the First Amendment*, 73 FOOD & DRUG L.J. 486, 487 (2018) ("As a result of these special factors, FDA has tended to receive what this article terms 'FDA exceptionalism'—a tendency to apply available exceptions relaxing the general rules that apply across government more broadly. . . . [T]he Court has historically demonstrated a willingness to endorse FDA's statutory interpretations even pre-*Chevron*.").

determinations for drug approvals.[18] If these trends remain, overturning FDA drug approval decisions should be an isolated occurrence.[19]

That assumption may well be wrong. In contextualizing the two mifepristone cases within the last decade of litigation against the FDA,[20] this Article identifies a cluster of recent court cases that have also overturned longstanding FDA policies by questioning science-based policy choices.[21] While it is possibly an aberration, repeated challenges to FDA science-based policy choices would be concerning.

Debates over the scope of agency deference to science-based policy choices are not new for other scientific agencies. Professor Emily Hammond has insightfully described how scientific agencies, such as the U.S. Environmental Protection Agency (EPA), are vulnerable to criticisms of such "metapolic[ies]."[22] All scientific data has uncertainty,[23] so scientific agencies must regularly fill in gaps in data with policy choices guided by statutes, regulations, and judicial standards.[24] For example, the Federal Food, Drug and Cosmetic Act (FDCA) requires a drug to be safe

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18 Catherine M. Sharkey, *The Opioid Litigation: The FDA Is MIA*, 124 DICK. L. REV. 669 (2020).

19 *Cf.* Jordan Paradise, *Mifepristone Paternalism at the FDA*, 51 J.L. MED. & ETHICS 554, 558 (2023) ("This direct challenge to the drug approval process threatens the entire structure of the pharmaceutical regulatory system and will undoubtedly ultimately play out at the Supreme Court." (footnote omitted) (citing Patricia J. Zettler, Eli Y. Adashi & I. Glenn Cohen, Alliance for Hippocratic Medicine v. FDA—Dobbs*'s Collateral Consequences for Pharmaceutical Regulation*, 388 NEW ENG. J. MED, Feb. 2023, at e29)).

20 *See* Sydney Lupkin, *Here's What Really Happened During the Abortion Drug's Approval 24 Years Ago*, NPR (Mar. 26, 2024, 12:51 PM), https://www.npr.org/sections/health-shots/2023/04/14/1169859888/heres-what-really-happened-during-the-abortion-drugs-approval-24-years-ago [https://perma.cc/XP45-6FPP].

21 *See infra* Appendix I.

22 Emily Hammond, *Super Deference, the Science Obsession, and Judicial Review as Translation of Agency Science*, 109 MICH. L. REV. 733, 744–45 (2011). For an excellent discussion of arguments for and against agency deference, see Christopher J. Walker, *Attacking* Auer *and* Chevron *Deference: A Literature Review*, 16 GEO. J.L. & PUB. POL'Y 103 (2018) and Wendy E. Wagner, *The "Bad Science" Fiction: Reclaiming the Debate over the Role of Science in Public Health and Environmental Regulation*, 66 L. & CONTEMP. PROBS. 63, 64–75 (2003).

23 *See* Baruch Fischhoff & Alex L. Davis, *Communicating Scientific Uncertainty*, 111 PNAS 13664 (2014); Genna Reed et al., *The Disinformation Playbook: How Industry Manipulates the Science-Policy Process—And How to Restore Scientific Integrity*, 42 J. PUB. HEALTH & POL'Y 622, 623 (2021) ("By reframing this procedural scrutiny as 'doubt,' industry can undermine commercially inconvenient science. For industry, this means that debating the science is a shortcut to debating policy, making attacks on science a powerful tactic to shape regulation and insulate against litigation." (endnote omitted)); Wagner, *supra* note 22, *passim.*

24 *See* Holly Fernandez Lynch, Steven Joffe & Matthew S. McCoy, *The Limits of Acceptable Political Influence over the FDA*, 27 NATURE MED. 188, 188–89 (2021) ("The FDA cannot make decisions on the basis of science alone, and political considerations sometimes do have a role to play." (footnote omitted) (citing Peter Van Doren, *When and How We Should "Trust the Science,"* CATO INST. (Sept. 15, 2020), https://www.cato.org/publications/pandemics-policy/when-how-we-should-trust-science [https://perma.cc/YT9F-KWMR])).

and effective prior to FDA approval, and the Agency has regulations that lay out the acceptable levels of risk for a drug to be considered "safe."[25] Deeming a drug safe requires clinical trials to collect data on how the drug impacts patients with the disease. That data allows researchers to determine risks and benefits of potential new drugs.[26] However, all clinical trials require judgment calls: How many patients are necessary? Which exact outcomes should be monitored? How long should approval of a potentially useful drug be delayed while researchers try to determine whether it causes devastating side effects that may take years to develop, like cancer? There is no singular legal or scientifically correct answer to these questions. Akin to questions of discretion,[27] such choices involve normative policy decisions that lack a correct answer in either law or fact; any answer can be criticized as incorrect, incomplete, or inappropriately delayed especially when viewed in isolation.[28]

While there are reasons to think the emerging trend of judicial review of FDA science-based policy questions will be limited, financial pressures to keep drugs on the market colors almost all pharmaceutical litigation.[29] Blockbuster drugs can be exceptionally lucrative,[30] regardless of if they work as intended.[31] Any litigation or regulatory actions that extend government-backed patent-monopolies can be worth billions.[32]

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25 Food and Drugs, 21 C.F.R. § 314.2 (1985) ("The purpose of this part is to establish an efficient and thorough drug review process in order to: (a) Facilitate the approval of drugs shown to be safe and effective; and (b) ensure the disapproval of drugs not shown to be safe and effective.").

26 *Id.* § 314.510.

27 *See, e.g.*, Gwendolyn Savitz, *Reviewing Mixed Questions of Fact and Law in Administrative Adjudications: Why Courts Should Move to "Substantially Established Facts,"* 68 VILL. L. REV. 463, 468–71 (2023).

28 *See* Transcript of Oral Argument at 12–13, Relentless, Inc., v. Dep't of Com., 144 S. Ct. 325 (2023) (mem.) (No. 22-1219). Justice Kagan stated, "But sometimes law runs out. Sometimes there's a gap. Sometimes there's a genuine ambiguity. And I—I don't know. In that case, I would rather have people at HHS telling me whether this new product was a dietary supplement or a drug." *Id.*

29 *See* T. Joseph Mattingly II & Linda Simoni-Wastila, *Patient-Centered Drug Approval: The Role of Patient Advocacy in the Drug Approval Process*, 23 J. MANAGED CARE & SPECIALTY PHARMACY 1078, 1078 (2017) (requiring less data at the time of approval allows pharmaceutical manufacturers to cut initial development costs and collect more revenue over a longer portion of patent terms).

30 *See infra* notes 287–291 and accompanying text.

31 Megan Brooks, *Billions Spent on DMD Meds Despite Scant Proof of Efficacy*, MEDSCAPE (Mar. 19, 2024), https://www.medscape.com/viewarticle/billions-spent-dmd-meds-despite-scant-proof-efficacy-2024a1000536?form=fpf [https://perma.cc/WNQ7-KAAZ] (describing three drugs for Duchenne muscular dystrophy that cost the U.S. healthcare system more than $3 billion despite a lack of confirmatory efficacy data).

32 For an excellent discussion on the cost of pay-for-delay settlements and evergreening patents, see Robin Feldman, *The Price Tag of "Pay-For-Delay,"* 23 COLUM. SCI. & TECH. L. REV. 1, 16–17 (2022) and Robin Feldman, *May Your Drug Price Be Evergreen*, 5 J.L. & BIOSCIENCES 590, 601 (2018).

Even unsuccessful cases that delay pharmaceutical competitors from selling similar products can be lucrative.[33] Regulatory approval of (or failure to approve) a drug also has immense societal and economic impacts—patients can suffer and die while waiting for a potential lifesaving treatment or from side effects of an approved unsafe drug.[34] Litigation that revokes approval of a competitor product or grants a regulatory exclusivity that limits approval of a competitor product can impact how much Americans pay for drugs. Therefore, trends in judicial review of and deference to FDA drug approval choices can impact all Americans financially and medically.

This Article does not argue that judicial review of drug approval choices, in itself, is problematic. While there are reasons to be concerned about more frequent judicial review and declining deference to the FDA, courts have an important role to ensure agency accountability and guarantee the Agency and the public benefit from judicial review in some cases.[35] Rather, this Article contends it is crucial to better understand the role of courts in ensuring drug safety and efficacy and traces outcomes in a decade of challenges to drug approvals in courts.

After discussing recent successful challenges to FDA science-based policy choices,[36] this Article explores why this trend occurs and whether it will continue. Part I examines the norms of judicial review of FDA drug determinations before laying out a case series of the last decade of litigation involving the FDA. A full list of the fifty-eight cases from 2013

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33 *See Apotex Clopidogrel At-Risk Launch Costs US $442 Million*, GABI ONLINE (Feb. 3, 2012), https://www.gabionline.net/generics/news/Apotex-clopidogrel-at-risk-launch-costs-US-442-million [https://perma.cc/Q5Z2-PGJP] (describing a case where a large generic manufacturer launched at risk for three weeks and subsequent settlement was only half of profit made during those three weeks); *see also* Scott Gottlieb, *FDA Working to Lift Barriers to Generic Drug Competition*, FDA VOICES (June 21, 2017), https://www.fda.gov/news-events/fda-voices/fda-working-lift-barriers-generic-drug-competition [https://web.archive.org/web/20241027160602/https://www.fda.gov/news-events/fda-voices/fda-working-lift-barriers-generic-drug-competition] ("We know that sometimes our regulatory rules might be 'gamed' in ways that may delay generic drug approvals beyond the time frame the law intended, in order to reduce competition.").

34 Approved drugs may still be criticized as having required too much data prior to approval and causing unnecessary suffering due to delayed approval. For example, in the 1980s and 1990s, as the death toll from HIV/AIDS mounted without any effective treatments, the FDA denied most AIDS patients access to experimental drugs. Through strategic civil disobedience, AIDS activists including the AIDS Coalition to Unleash Power (ACT UP) launched arguably the most effective campaign against federal restrictions on drug approvals. For a more complete history of the controversy, see Douglas Crimp, *Before Occupy: How AIDS Activists Seized Control of the FDA in 1988*, ATLANTIC (Dec. 6, 2011), https://www.theatlantic.com/health/archive/2011/12/before-occupy-how-aids-activists-seized-control-of-the-fda-in-1988/249302 [https://perma.cc/HK8A-VCHV].

35 *See infra* Part III.

36 As explained below, there is an important distinction between judicial review of informal adjudicatory decisions to approve a drug and FDA decisions on awarding highly lucrative benefits.

to 2023 examined can be found in Appendix I. While conventional wisdom is that courts historically deferred to the FDA, with many courts declaring themselves ill-equipped to second guess the Agency's scientific judgments under arbitrary and capricious review,[37] these cases suggest deference was not universal. Moreover, after 2019, multiple courts overturned longstanding FDA policies by questioning or making assumptions about science-based policy considerations.[38]

Part II examines who brings such cases and why. The data suggests brand companies with few FDA approved products were more likely to sue compared to either highly profitable brand or generic drug manufacturers. Most cases sought competitive advantage by either limiting FDA approval of competitor products (and thus removing competitors from market) or seeking exceptions to expensive regulatory obligations that their competitors must follow. Other cases involved highly lucrative benefits like designations and exclusivities or the obligation to comply with expensive regulatory requirements.

Part III looks to understand why this subtle change in outcomes occurred and offers insights for optimizing judicial review of FDA drug determinations. It suggests that judicial review of scientific policy choices may be connected in part to the FDA's eroding reputation after back-to-back national drug approval controversies. Between the ongoing opioid epidemic, the SARS-Co-V2 (COVID-19) pandemic, and the 2021 controversial approval of the Alzheimer's Disease treatment aducanumab, the FDA has faced numerous concurrent crises since 2019. All three resulted in significant public concern about the sufficiency of data underlying FDA approvals and the potential for improper influence. Administrative scholars have long demonstrated the connection between judicial deference and public trust in agency expertise.[39] FDA scholars traditionally connect the FDA's authority to public confidence in its decisions.[40] This Article connects the two, suggesting that the shift in judicial scrutiny may be related to eroding public trust in the FDA.

Part III also considers these cases in light of broader changes in administrative law. Prior to the 2023 Term, courts deferred to agencies' interpretations of ambiguous statutes as long as they were reasonable under the *Chevron* doctrine.[41] Many scholars have argued that *Chevron*

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37 *See, e.g.*, Teva Pharms. USA, Inc. v. FDA, 514 F. Supp. 3d 66, 98, 100–03, 106–11, 115–17 (D.D.C. 2020).

38 *See* Appendix I.

39 *See infra* Section III.B.

40 *See infra* Section III.A.

41 Chevron U.S.A., Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837, 843–44 (1984) (premising the *Chevron* doctrine upon the proposition that Congress intended agencies to exercise primary

deference has been eroding for over a decade.[42] While the FDA has traditionally been understood to have received strong deference,[43] this cluster of cases may also be explained by shifting judicial norms of administrative deference.

While there are many reasons to think the shift may revert, there are also reasons to be concerned. Scholars believe agency discretion and authority will be more broadly limited[44] as *Loper Bright Enterprises v. Raimondo* now requires judges to determine the "best read" of ambitious statutes.[45] If so, it is more important than ever to restore trust in the FDA and consider the proper role of deference to science-based policy choices related to pharmaceutical litigation.

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interpretive authority over a delegated statutory provision, instructing courts to defer to agency interpretations of ambiguous laws; benefits of deference include flexibility, political participation in the administrative process, and predictability of outcomes, amongst others).

42 *See, e.g.*, Christopher J. Walker, *What Loper Bright Enterprises v. Raimondo Means for the Future of Chevron Deference*, YALE J. ON REGUL. (June 28, 2024), https://www.yalejreg.com/nc/what-loper-bright-enterprises-v-raimondo-means-for-the-future-of-chevron-deference [https://perma.cc/DW5R-XXDF]; Kristin E. Hickman & Aaron L. Nielson, *Narrowing* Chevron*'s Domain*, 70 DUKE L.J. 931, 933–35 (2021) [hereinafter Hickman & Nielson, *Narrowing* Chevron*'s Domain*]; *see also* Kristin E. Hickman & Aaron L. Nielson, *The Future of* Chevron *Deference*, 70 DUKE L.J. 1015, 1016 (2021) ("[T]he Supreme Court has not been very receptive to *Chevron* deference claims in recent years. In fact, the Court has been reluctant to apply the doctrine."); *id.* at 1017–24.

43 *See, e.g.*, Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973) (deferring to the FDA's authority to determine whether a product was or was not a "new drug" and within FDA jurisdiction); United States v. Rutherford, 442 U.S. 544, 544 (1979) (stating that the Court was "reluctant to disturb a longstanding administrative policy that comports with the plain language, history, and prophylactic purpose of the Act" and instead would defer to FDA authority despite moral arguments brought forth by terminally ill patients); Medtronic, Inc. v. Lohr, 518 U.S. 470, 495–96 (1996) (deferring to the FDA's construction of the scope of preemption); United States v. Bacto-Unidisk, 394 U.S. 784, 791–92 (1969) ("It is enough for us that the expert agency charged with the enforcement of remedial legislation has determined that such regulation is desirable for the public health, for we are hardly qualified to second-guess the Secretary's medical judgment.").

44 *See, e.g.*, Adrian Vermeule, *Chevron by Any Other Name*, NEW DIG. (June 28, 2024), https://thenewdigest.substack.com/p/chevron-by-any-other-name [https://perma.cc/B37D-JV34]; Dena Adler & Max Sarinsky, *With or Without Chevron Deference, Agencies Have Extensive Rulemaking Authority*, YALE J. ON REGUL. (May 13, 2024), https://www.yalejreg.com/nc/with-or-without-chevron-deference-agencies-have-extensive-rulemaking-authority [https://perma.cc/D2FH-NM5E]; Robert Iafolla, *Courts Show Little Interest in Skidmore as a Chevron Alternative*, BLOOMBERG L. (July 29, 2024, 5:05 AM), https://news.bloomberglaw.com/daily-labor-report/courts-show-little-interest-in-skidmore-as-a-chevron-alternative [https://web.archive.org/web/20240918185613/https://news.bloomberglaw.com/daily-labor-report/courts-show-little-interest-in-skidmore-as-a-chevron-alternative].

45 603 U.S. 369, 417 (2024) (Gorsuch, J., concurring) ("Today, the Court places a tombstone on *Chevron* no one can miss.").

I. INCREASING CHALLENGES TO FDA SCIENCE-BASED POLICY CHOICES FOR DRUGS BETWEEN 2013 AND 2023

Over the last decade, growing skepticism of the FDA in congressional, executive, and judicial decisions has left the FDA on defense.[46] This Part examines cases from the last ten years of litigation against the FDA to understand judicial skepticism of the Agency.[47] It shows the start of a subtle shift in the outcomes of pharmaceutical companies challenging the FDA between 2019 and 2023 where courts increasingly overturned longstanding FDA policies by questioning the Agency's authority to make scientifically based policy choices.

Section I.A explains agency deference and defines scientifically based policy choices. Section I.B examines recent cases compared to the last ten years of federal litigation against the FDA to illustrate this emerging trend. Section I.C examines the limitations of these conclusions.

A. *Agency Deference and Science-Based Policy Choices*

Recognizing trends in the last decade of litigation against the FDA requires an understanding of the type of actions that the FDA takes and the relevant standards of judicial review. Fundamentally, drug approval decisions require distilling mountains of often conflicting and convoluted clinical trial data based on legal, policy, and scientific choices into a single yes or no question: Is the drug safe and effective?[48] There is never a simple answer.

1. Understanding Agency Deference

Over the last thirty years, the FDA's standards determining safety and efficacy has been legislatively extended to favor regulatory flexibility

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46 Patricia J. Zettler, Eli Y. Adashi & I. Glenn Cohen, *A Divisive Ruling on Devices*—Genus Medical Technologies v. FDA, 385 NEW ENG. J. MED. 2409, 2410 (2021) ("[T]he *Genus* decision comes at the end of a decade of growing challenges to the FDA's authority to regulate."). Examination of trends in deference to FDA decisions on devices, tobacco, cosmetics, and other products are outside the scope of this Article.

47 *See infra* Appendix I.

48 Prior to marketing a new drug, a sponsor must file a New Drug Application (NDA) pursuant to Section 505(b) of the FDCA and must demonstrate that the drug is safe and effective for the proposed indication. *See* 21 U.S.C. § 355(b), (d).

with expedited approvals.[49] The FDA's licensure-like approvals are a powerful regulatory tool; the FDA is able to grant, suspend, or revoke approvals and recall products that are no longer safe, pure, or potent.[50] Drug approvals are a form of informal adjudication. Like other regulatory agencies, the FDA interprets relevant statutes and issues regulations following notice and comment informal rulemaking.[51] The FDA also issues non-binding guidance (including draft guidance) that clarifies the agency's approach to both implementing statutes and addressing timely new issues.[52]

In addition to approvals, the FDA also makes ongoing safety, efficacy, and innovation determinations about drug products.[53] For example, the FDA evaluates changes made to product ingredients after approval.[54] As new information about a drug's safety and efficacy is understood, the FDA ensures that drug labels are updated with adequate warnings.[55] It also sets standards for and investigates facilities to ensure drugs are manufactured safely, which are known as Current Good Manufacturing Practice (CGMP) regulations.[56] Additionally, the FDA awards lucrative benefits with government-backed monopolies; it

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49 Janet Woodcock & Peter Marks, *Delivering Promising New Medicines Without Sacrificing Safety and Efficacy*, FDA (Aug. 27, 2019), https://www.fda.gov/news-events/fda-voices/delivering-promising-new-medicines-without-sacrificing-safety-and-efficacy [https://perma.cc/8JWF-TTA8]; Michelle Meadows, *Promoting Safe & Effective Drugs for 100 Years*, FDA (Apr. 23, 2019), https://www.fda.gov/about-fda/histories-product-regulation/promoting-safe-effective-drugs-100-years [https://perma.cc/XX6X-DCUE].

50 Kelsey Hall, Tyler Stewart, Jongwha Chang & Maisha Kelly Freeman, *Characteristics of FDA Drug Recalls: A 30-Month Analysis*, 73 AM. J. HEALTH-SYS. PHARMACY 235 (2016).

51 5 U.S.C. § 706 (explaining that FDA drug approvals are informal adjudicatory type proceedings akin to licensing or permitting).

52 FDA, FDA LAWS, REGULATIONS, AND GUIDANCE DOCUMENTS, https://www.fda.gov/media/133830/download [https://perma.cc/NNS8-9MZQ].

53 *Modernizing FDA's New Drugs Regulatory Program*, FDA (June 21, 2024), https://www.fda.gov/drugs/regulatory-science-research-and-education/modernizing-fdas-new-drugs-regulatory-program [https://perma.cc/NX88-F6SU] (noting that since 2017, the FDA's Center for Drug Evaluation and Research initiative to modernize the New Drugs Regulatory Program includes "work[ing] to establish a unified post-market safety surveillance framework to monitor the benefits and risks of drugs across their life-cycles, both before and after approval"); *see also* Rachel E. Sachs, W. Nicholson Price II & Patricia J. Zettler, *Rethinking Innovation at FDA*, 104 B.U. L. REV. 513, 542 (2024).

54 21 C.F.R. § 201.10 (2024).

55 *Frequently Asked Questions About Labeling for Prescription Medicines*, FDA (Apr. 1, 2024), https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/frequently-asked-questions-about-labeling-prescription-medicines [https://perma.cc/FT35-CU5R].

56 *Facts About the Current Good Manufacturing Practice (CGMP)*, FDA (Jan. 21, 2025), https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practice-cgmp [https://web.archive.org/web/20250129050622/https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practice-cgmp].

determines which of competing products are entitled to certain congressionally created exclusivities like new chemical entity exclusivity, orphan drug exclusivity, or pediatric exclusivity amongst others.[57] Determining whether a product is entitled to various lucrative, sought-after benefits[58] requires interpreting multiple statutes and applying the law to the relevant circumstances.[59]

Informal adjudications and application of related rules are reviewed by courts under the Administrative Procedure Act (APA).[60] Both the right to judicial review and the legal standards are defined in APA Section 706(2)(A), but appropriate deference to scientific agencies is often debated.[61] Typically, unless the agency ignores a serious aspect of the problem, reviewing courts do not engage in de novo examinations of scientific issues and only consider evidence in the record.[62] Discretionary decisions are reviewed for abuse and questions of law are reviewed de novo.

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57 CTR. FOR BIOLOGICS EVALUATION & RSCH, & CTR, FOR DRUG EVALUATION & RSCH., FDA, U.S. DEP'T OF HEALTH & HUM. SERVS., GUIDANCE FOR INDUSTRY: LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS—IMPLEMENTING THE PLR CONTENT AND FORMAT REQUIREMENTS (2013), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/labeling-human-prescription-drug-and-biological-products-implementing-plr-content-and-format [https://web.archive.org/web/20231221010603/https://www.fda.gov/media/71836/download].

58 Kathleen L. Miller, *Do Investors Value the FDA Orphan Drug Designation?*, ORPHANET J. RARE DISEASES, June 19, 2017, at 1, 4 (observing that, for example, research has demonstrated a company's stock price increases when a product receives orphan drug designation); Michael S. Sinha, Mehdi Najafzadeh, Elizabeth K. Rajasingh, James Love & Aaron S. Kesselheim, *Labeling Changes and Costs for Clinical Trials Performed Under the US Food and Drug Administration Pediatric Exclusivity Extension, 2007 to 2012*, 178 JAMA INTERNAL MED. 1458, 1458–59 (2018) (providing pediatric exclusivities net median return of $176 million, which is "a median ratio of net return to cost of investment of 680%").

59 These include the Federal Food Drug and Cosmetic Act of 2012, Pub. L. No. 112-144, 126 Stat. 993 (codified as amended at 21 U.S.C. §§ 301–392), the 21st Century Cures Act of 2016, Pub. L. No. 114-255, 130 Stat. 1033 (codified as amended in scattered sections of 21 & 42 U.S.C.), the Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, 115 Stat. 1408 (codified as amended in scattered sections of 21 & 42 U.S.C.), and the Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (codified as amended at 21 U.S.C. § 355c), among many others. *See* 21 C.F.R. §§ 314.108, 316.31 (2024).

60 5 U.S.C. §§ 551–559; BEN HARRINGTON & DANIEL J. SHEFFNER, CONG. RSCH. SERV., R46930, INFORMAL ADMINISTRATIVE ADJUDICATION: AN OVERVIEW 24 n.193 (2021) ("[I]n their application to the requirement of factual support the substantial evidence test and the arbitrary or capricious test are one and the same." (quoting Butte County v. Hogen, 613 F.3d 190, 194 (D.C. Cir. 2010)); *see also* Jordan Paradise, *Regulatory Silence at the FDA*, 102 MINN. L. REV. 2383 (2018).

61 For an excellent discussion of this ongoing debate, see Sapna Kumar, *Scientific and Technical Expertise After* Loper Bright, 74 DUKE L.J. (forthcoming 2025), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4939536 [https://perma.cc/J7QD-SLAK].

62 *See* Nat'l Audubon Soc'y v. U.S. Forest Serv., 46 F.3d 1437, 1447 (9th Cir. 1993) (describing exceptions to the record evidence rule).

Over the last forty years, under *Chevron* deference, courts deferred to federal agencies' "reasonable" interpretations of ambiguous statutes, but would overturn agency actions contrary to a clear legislative intent.[63] *Chevron* deference was perceived to favor regulators, and the proper scope of deference to agency decisions has been hotly debated.[64] Some scholars argue that judicial deference doctrines safeguard agency decisions against "judges' policy preferences . . . play[ing] . . . a larger role in review of agency statutory interpretations."[65] Others argue against unaccountable agency discretion, incentives for agency misbehavior,[66] and improper delegation.[67] Many scholars have noted that courts have been less deferential to expert agencies since at least 2016.[68]

In the 2023 Term, the Supreme Court overturned *Chevron* deference in *Loper Bright Enterprises v. Raimondo*.[69] Rejecting that "statutory ambiguities are implicit delegations to agencies,"[70] the Court

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63 Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837 (1984), *overruled by* Loper Bright Enters. V. Raimondo, 603 U.S. 369 (2024); *see also* Linda Jellum, Chevron*'s Demise: A Survey of* Chevron *from Infancy to Senescence*, 59 ADMIN. L. REV. 725, 781–82 (2007).

64 *See, e.g.*, Hickman & Nielson, *Narrowing* Chevron*'s Domain*, *supra* note 42; Jack M. Beermann, *End the Failed* Chevron *Experiment Now: How* Chevron *Has Failed and Why It Can and Should Be Overruled*, 42 CONN. L. REV. 779, 843–50 (2010); Abbe R. Gluck & Richard A. Posner, *Statutory Interpretation on the Bench: A Survey of Forty-Two Judges on the Federal Courts of Appeals*, 131 HARV. L. REV. 1298, 1348 (2018) ("Although every judge we interviewed told us that he or she was bound by *Chevron*—and all but one of the judges did apply that rule in opinions—most of the judges we interviewed do not favor the *Chevron* rule." (footnote omitted)).

65 Brief of Law Professors Kent Barnett and Christopher J. Walker as Amici Curiae in Support of Neither Party at 3, Loper Bright Enters. v. Raimondo, 45 F.4th 359 (D.C. Cir. 2022) (No. 22-451), 2023 WL 4824944; *see also* Christopher J. Walker, *The (Judicially) Conservative Case for Keeping Chevron Deference*, YALE J. ON REGUL. (July 24, 2023), https://www.yalejreg.com/nc/the-judicially-conservative-case-for-keeping-chevron-deference [https://perma.cc/BNP2-5WHP].

66 *See* Orrin G. Hatch, *Congress Must Act to Restore Accountability to the Regulatory Process*, YALE J. ON REGUL. (Sept. 22, 2016), https://www.yalejreg.com/nc/congress-must-act-to-restore-accountability-to-the-regulatory-process-by-senator-orrin-g-hatch [https://perma.cc/NVF5-6HKC] ("[C]ourts thus stand as the only government actor truly capable of restraining overzealous regulators. But deference to agencies undercuts the judiciary's ability to hold administrative officials accountable to the law.").

67 *See* Nicholas Bednar, Chevron *and Candor*, YALE J. ON REGUL. (July 24, 2023), https://www.yalejreg.com/nc/chevron-and-candor-by-nicholas-r-bednar [https://perma.cc/LNA7-3BPW] (noting that the causal claims "are empirically observable, petitioners do not cite any studies, facts, or figures to support their claims" and "[s]tatutes also have become more specific rather than more ambiguous" (citing Sean Farhang, *Legislative Capacity & Administrative Power Under Divided Polarization*, 150 DAEDALUS 49, 54 (2021))).

68 *See* Nathan Richardson, *Deference Is Dead (Long Live* Chevron*)*, 73 RUTGERS L. REV. 441, 445 (2021) ("Agencies before the Supreme Court in recent years appear to receive little or no interpretive deference, whatever *Chevron* says. In my view it is fair to say that deference is dead at the Supreme Court, though it is worth noting that lower courts and agencies do not seem to have followed, at least not yet.").

69 603 U.S. 369, 412 (2024).

70 *Id.* at 399.

held 6-to-3 that the APA requires courts to exercise independent judgment in deciding whether an agency has acted within its statutory authority.[71] Courts could still look to agency expertise as "informative," and prior cases decided under *Chevron* deference are still respected due to stare decisis.[72] While it has been described as a watershed moment in administrative law, distinguished administrative law professors openly debate the impact of this case.[73]

This decision highlighted the importance of determining appropriate deference to the FDA's science-based policy decisions. The dissent raised concerns about court competence, pointing to FDA science-based policy decisions related to drug approvals.[74] The dissenting Justices illustrated that questions such as what qualifies as a protein (and thus what is regulated as a biologic drug as opposed to a small molecule drug) is a technical regulatory question not fully answered by either statute or scientific fact, and it has profound financial and medical implications.

Taken together, the FDA makes a variety of important scientific and regulatory decisions related to multiple aspects of drug approvals, many of which have significant medical and financial implications. These choices are reviewable by courts, although the framework of judicial review and agency deference is actively shifting.

2. Science-Based Policy Choices

Part of the complicated relationship between courts, the FDA, and the pharmaceutical industry is the nature of FDA drug approval decisions. In theory, judicial deference should never be absolute. A fair and rational system would never prevent a court from correcting a true scientific error; we would want judicial review to rectify all scientific errors discovered.[75] While this is a seemingly obvious principle, it can be

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71 *Id.* at 393–94, 398–99, 412–13.

72 *Id.* at 402.

73 *See* Vermeule, *supra* note 44; Dena Adler & Max Sarinsky, *With or Without Chevron Deference, Agencies Have Extensive Rulemaking Authority*, YALE J. ON REGUL. (May 13, 2024), https://www.yalejreg.com/nc/with-or-without-chevron-deference-agencies-have-extensive-rulemaking-authority [https://perma.cc/D2FH-NM5E].

74 *Loper Bright*, 603 U.S. at 452 (Kagan, J., dissenting) ("Consider a few examples from the caselaw. They will help show what a typical *Chevron* question looks like—or really, what a typical *Chevron* question *is*. . . . Under the Public Health Service Act, the [FDA] regulates 'biological product[s],' including 'protein[s].' When does an alpha amino acid polymer qualify as such a 'protein'? Must it have a specific, defined sequence of amino acids?" (alterations in original) (citation omitted) (quoting 42 U.S.C. § 262(i)(1)).

75 Assuming a court correctly identified an error rather than identifying an expert disagreement or policy debate.

difficult to apply consistently as scientific error is a complicated concept for pharmaceuticals products.

Error and uncertainty are not the same thing.[76] Scientifically speaking, there are two types of errors with drug approvals. Unsafe or minimally effective drugs can be approved (Type I errors) and safe, effective drugs can fail to gain approval ever or in a timely manner (Type II errors).[77] The two types of errors are in many ways a policy tradeoff; additional data improves certainty in safety and efficacy but can lead to delays.[78] Therefore, exactly how much data is required before a drug is approved can be a debatable, normative, science-based policy question. Reasonable minds disagree on what is a "better" choice or which policy goal should be prioritized at any one time (early access to patients or confirmation of safety and benefit).[79] A decision despite uncertainty can easily be mischaracterized as error, especially with poor outcomes.[80] Esteemed Professor Daniel Carpenter has argued that the FDA's reputational concerns favor preventing Type I errors at the expense of committing more Type II errors.[81] Therefore, differentiating true error

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76 *See* John Lemons, Kristin Shrader-Frechette & Carl Cranor, *The Precautionary Principle: Scientific Uncertainty and Type I and Type II Errors*, 2 FOUNDS. OF SCI. 207, 209 (1997); *see also* Lisa M. LaVange, *Statistics at FDA: Reflections on the Past Six Years*, 11 STAT. BIOPHARMACEUTICAL RSCH. 1 (2019).

77 *See* Michael D. Intriligator, Professor, Presentation to the UCLA Pharmaceutical Economics and Policy Seminar: Drug Evaluations: Type I vs. Type II Errors (May 1, 1996).

78 Leah Isakov, Andrew W. Lo & Vahid Montazerhodjat, *Is the FDA Too Conservative or Too Aggressive?: A Bayesian Decision Analysis of Clinical Trial Design*, 211 J. ECONOMETRICS 117, 118 (2019) ("This leads to the unavoidable regulatory tradeoff between reducing false positives (incorrectly approving an ineffective therapy) and false negatives (incorrectly rejecting an effective therapy).").

79 *See* Leah Z. Rand et al., *Securing the Trustworthiness of the FDA to Build Public Trust in Vaccines*, 53 HASTINGS CTR. REP., Sept–Oct. 2023, at S60, S60 ("Exhortations to 'follow the science' posit that the role of the FDA is to make independent, authoritative, scientific decisions about vaccines. However, approvals require judgments about acceptable levels of safety, efficacy, long-term data collection, and public health interests, which involve ethical considerations about what matters most and how best to balance benefits, risks, and speed. There is additional pressure from politicians whose interests, particularly during times of national emergency, may be to direct FDA decision-making rather than allow independence.").

80 Statistical analysis of scientific studies is designed to reject or fail to reject the null hypothesis. Therefore, the appropriate conclusion is to say the outcome is "not inconsistent with." *See* Mary Ellen Schneider, *Califf, Past FDA Chiefs Look for Partners to Curb Misinformation*, REGUL. AFFS. PROS. SOC'Y (Jan. 9, 2023), https://www.raps.org/news-and-articles/news-articles/2023/1/califf-past-fda-chiefs-look-for-partners-to-curb-m [https://perma.cc/Y988-4XCT] (explaining that some "criticism of FDA and other public health agencies is having unintended consequences" because, according to FDA Commissioner Robert Califf, "to a lot of unsuspecting people that hear it, it just completely erodes their belief in the institution").

81 DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA (Ira Katznelson, Martin Shefter & Theda Skocpol eds., 2010).

that should be corrected in judicial review from uncertainty, expert disagreements, or policy tradeoffs is complicated.

Every drug-regulating agency in the world must make decisions based on some factual uncertainties.[82] The FDA too must base every one of its decisions on inherently imperfect information.[83] Drug approval decisions involve multiple normative and policy questions, such as how the scientific data is collected, analyzed, and extrapolated.[84] As eloquently explained by Professor Holly Fernandez Lynch,

> [D]ecisions about drug approval—though guided by science, as well as relevant statutes, regulations, and guidance documents—reflect normative judgments about how the agency should exercise its discretion. . . . A key challenge in evaluating normative judgments . . . is . . . reasonable people can disagree, rendering it difficult to proclaim with certainty that a particular decision is right or wrong.[85]

The questions of how much data is enough and trade-offs between certainty and access reflect scientifically based policy choices, all of which can be questioned in litigation. In this regard, FDA approval actions

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82 Tort law plays an important role in addressing harms caused by drugs later shown to be unsafe or ineffective. The interplay of tort law and the FDA regulatory framework is a complicated but impactful issue that has been examined by multiple scholars from multiple perspectives. For insightful discussions, see Catherine M. Sharkey, *Field Preemption: Opening the "Gates of Escape" from Tort Law*, 50 J. LEGAL STUD., June 2021, at S27; Catherine T. Struve, *The FDA and the Tort System: Postmarketing Surveillance, Compensation, and the Role of Litigation*, 5 YALE J. HEALTH POL'Y, L. & ETHICS 587 (2005); Catherine M. Sharkey, *Direct-to-Consumer Genetic Testing: The FDA's Dual Role as Safety and Health Information Regulator*, 68 DEPAUL L. REV. 343 (2019).

83 Clinical trial data is far from perfect, as patients often drop out, refuse to participate, or have undiagnosed conditions. Further, clinical trials are not the same as how the drug performs in the real world (effectiveness). Thus, real-world outcomes are estimated from inherently imperfect clinical trial data. *See generally* Deshmukh, *supra* note 16, at 635 (citing GERALD GARTLEHNER, RICHARD A. HANSEN, DANIEL NISSMAN, KATHLEEN N. NOHR & TIMOTHY S. CAREY, AGENCY FOR HEALTHCARE RSCH. & QUALITY, U.S. DEP'T. OF HEALTH & HUM. SERVS., CRITERIA FOR DISTINGUISHING EFFECTIVENESS FROM EFFICACY TRIALS IN SYSTEMATIC REVIEWS 3 (2006)); Rick A. Vreman et al., *Decision Making Under Uncertainty: Comparing Regulatory and Health Technology Assessment Reviews of Medicines in the United States and Europe*, 108 CLINICAL PHARMACOLOGY & THERAPEUTICS 350, 350–51 (2020) (noting that "[h]aving to accept some uncertainties at approval is inherent to the limited information on benefits and risks available at the time of marketing authorization" and finding "that US and European regulators report uncertainties related to safety for almost all drugs (85–94%)" and "[r]egulators as well as HTA bodies reported uncertainties related to the patient population for 60–95% of drugs").

84 *See* Catherine M. Sharkey, *Cutting in on the* Chevron *Two-Step*, 86 FORDHAM L. REV. 2359, 2395–97 (2018).

85 Emily A. Largent, Andrew Peterson, Jason Karlawish & Holly Fernandez Lynch, *Aspiring to Reasonableness in Accelerated Approval: Anticipating and Avoiding the Next Aducanumab*, 39 DRUGS & AGING 389, 389 (2022) ("Science informs each of these tasks, while relevant statutes, regulations, and guidance documents provide constraints and guideposts. Yet substantial discretion inevitably remains.").

related to pharmaceutical products exemplify "metapolicy" described by Professor Hammond examining the EPA[86] and can be easily criticized as "incorrect."

Thus, it can be difficult to articulate a consistent standard of deference that both corrects error without second guessing uncertainty, policy choices, or requiring hindsight, especially as the FDA has been widely respected for its track record balancing scientific and normative questions of safety, efficacy, access, medical need, quality, and certainty.[87] However the FDA also has made many choices perceived as incorrect, sometimes with deadly consequences.[88] Because it is such a complex question, understanding deference to FDA drug approval decisions is important.

3. Deference and the FDA

Shifts in deference to the FDA are noteworthy as scholars have argued that the FDA perhaps excelled because of its strong historic judicial deference.[89] Professors Elizabeth Fisher and Emily Hammond argued that courts co-evolved with scientific agencies to optimize internal and external review processes.[90] That is, agencies may historically have responded to declining trust and deference by increasing their procedures and transparency, creating agencies-as-experts models including internal and external peer review, such that judicial review ensured agencies provided clear, well-supported explanations for their intertwined

86 Hammond, *supra* note 22, at 743 ("[A]gency science is marshaled to fulfill legal standards in statutes consistent with executive-branch policy.").

87 Fernandez Lynch et al., *supra* note 24, at 189; Lindsey R. Baden, Caren G. Solomon, Michael F. Greene, Ralph B. D'Agostino & David Harrington, *The FDA and the Importance of Trust*, 383 NEW ENG. J. MED., Sept. 2020, at e148(1), e148(1)–(2) ("The FDA has been the envy of the world, setting standards for the studies it requires and then following the resulting science and data in its regulatory decisions. Today more than ever, as science is being manipulated and disregarded, it is critical that the FDA uphold its standards and its objectivity.").

88 *See, e.g.*, Sharkey, *supra* note 18, at 672; Frank M. McClellan, *The Vioxx Litigation: A Critical Look at Trial Tactics, the Tort System, and the Role of Lawyers in Mass Tort Litigation*, 57 DEPAUL L. REV. 509, 514 (2008); Harlan M. Krumholz, Joseph S. Ross, Amos H. Presler & David S. Egilman, *What Have We Learnt from Vioxx?*, 334 BRITISH MED. J. 120 (2007).

89 O'Reilly, *supra* note 12, at 942 ("A historic strength of the FDA has been the deference received from courts during enforcement actions; indeed, the FDA has long nurtured its aura of expertise in order to win the accommodating acceptance of judges. . . . [D]eference, now more than ever, is central to the FDA's effectiveness as an administrative agency.").

90 *See* Elizabeth Fisher, Pasky Pascual & Wendy Wagner, *Rethinking Judicial Review of Expert Agencies*, 93 TEX. L. REV. 1681, 1682–84 (2015); *see also* Hammond, *supra* note 22, at 738, 778–79 (extolling the benefits of the judiciary's insistence on reason-giving as applied to agencies' science-intensive rules).

scientific and policy choices.[91] The FDA, with its stellar reputation and track record, may have been afforded strong deference. This is not to say that the FDA has always enjoyed universal "super-deference" or extreme exceptionalism. Academics have described "searching in vain" for a coherent theory to make sense of judicial review of science more broadly.[92] Judicial deference to technical decisions made by scientific agencies remains inconsistent and may be cyclic.[93] The FDA has also lost many significant cases; Professors Patricia Zettler and Glen Cohen have skillfully argued that the FDA has recently faced a "decade of defense."[94]

Rather, deference has a complex meaning.[95] In addition to deference to an agency's statutory interpretation (questions of law), deference can also roughly be defined "as the willingness of a court to accept an agency's interpretation of a statute or policy over competing interpretations offered by regulated persons or public interest groups."[96] This latter form of deference that the FDA has historically been afforded is difficult to measure and is not limited to agency interpretations of ambiguous statutes.

While the concept of super-deference to technical determinations made by scientific agencies has been repeatedly questioned,[97] courts tasked with reviewing the FDA's decisions under the APA have acknowledged their comparative disadvantages and a willingness to defer in the latter sense. In 1973, the Supreme Court even explained "[t]he determination whether a drug is generally recognized as safe and

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91 *See* Wendy E. Wagner, Essay, *A Place for Agency Expertise: Reconciling Agency Expertise with Presidential Power*, 115 COLUM. L. REV. 2019, 2021–23, 2025 n.20 (2015) ("[U]ncertainties result from inability to test key inputs to scientific models and from gaps in knowledge that make it impossible to know which of several competing models is correct[.]" (citing COMM. ON RISK ASSESSMENT OF HAZARDOUS AIR POLLUTANTS, NAT'L RSCH. COUNCIL, SCIENCE AND JUDGMENT IN RISK ASSESSMENT 86 (1994))).

92 Fisher et al., *supra* note 90, at 1683 ("[I]f this study of the courts' review of a best-case science-intensive regulatory program does not yield useful insights about judicial review, then we may be willing to join the scholarly ranks in concluding that the search for a deeper understanding of the judicial review of science may be futile after all.").

93 *See id.* at 1684 ("[T]he Agency introduced an epistemic framework into the administrative record, . . . [and] the courts now appear to be conducting judicial review with more coherence. The courts, in other words, hold the EPA accountable based on the Agency's own analytical processes, methods, and epistemic frames.").

94 Zettler et al., *supra* note 46; *see, e.g.*, FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120 (2000). For a complete list of litigation against the FDA since 2000, see Bendicksen et al., *supra* note 13, at 386–90.

95 Loper Bright Enters. v. Raimondo, 609 U.S. 369, 469 (2024) (Kagan, J., dissenting) (explaining that some legal questions involve both "pure legal question[s]" of statutory interpretation and "mixed questions" of policy and discretionary decisions, and the two concepts can be difficult to separate).

96 O'Reilly, *supra* note 12, at 941.

97 *See* Hammond, *supra* note 22.

effective . . . necessarily implicates complex chemical and pharmacological considerations. Threshold questions within the peculiar expertise of an administrative agency are appropriately routed to the agency, while the court stays its hand."[98]

For the last forty years, courts have continued to defer to FDA pharmaceutical decisions in the latter form that allows judges to limit their inquiry. As the Third Circuit held in 1995, "[the FDA's] judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from [judges]."[99] In 2015, the First Circuit held that "the FDA has [the] discretion to determine" whether the data presented is "sufficient to establish effectiveness."[100] Even Justice Kagan quipped in 2019,

> [T]ake the more technical "moiety" example [of regulatory ambiguities that requires an exercise of judgment grounded in policy concerns]. Or maybe, don't. If you are a judge, you probably have no idea what FDA's rule means, or whether its policy is implicated when a previously approved moiety is connected to lysine through a non-ester covalent bond.[101]

Altogether, the FDA has historically received strong judicial deference to both its statutory interpretation and its discretionary choices involving policy decisions, especially for review of a drug's safety and efficacy.[102]

The importance of that latter form of deference is not to be underestimated. Scholars have argued strong judicial deference may have been critical to both the FDA's rise to the international "gold standard of

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98 Weinberger v. Bentex Pharms., Inc., 412 U.S. 645, 654 (1973) ("[I]n cases raising issues of fact not within the conventional experience of judges or cases requiring the exercise of administrative discretion, agencies created by Congress for regulating the subject matter should not be passed over. This is so even though the facts after they have been appraised by specialized competence serve as a premise for legal consequences to be judicially defined. Uniformity and consistency in the regulation of business entrusted to a particular agency are secured, and the limited functions of review by the judiciary are more rationally exercised, by preliminary resort for ascertaining and interpreting the circumstances underlying legal issues to agencies that are better equipped than courts by specialization, by insight gained through experience, and by more flexible procedure." (quoting Far E. Conf. v. United States, 342 U.S. 570, 574–75 (1952))).

99 Schering Corp. v. FDA, 51 F.3d 390, 399 (3d Cir. 1995).

100 *In re* Celexa & Lexapro Mktg. & Sales Pracs. Litig., 779 F.3d 34, 36 (1st Cir. 2015) (quoting 21 U.S.C. § 355(d)(7)).

101 Kisor v. Wilkie, 588 U.S. 558, 563 (2019) (citation omitted).

102 *See* Duggan v. Medtronic, Inc., 840 F. Supp. 2d 466, 472 (D. Mass. 2012) ("The FDA, not litigants, is entrusted with the responsibility to police the sufficiency of the evidence to support a PMA approval."); Ctr. for Sci. in the Pub. Int. v. FDA, 74 F. Supp. 3d 295, 305 (D.D.C. 2014).

independent scientific review"[103] in drug evaluations and to the pharmaceutical industry's growth because judicial deference contributes to predictability.[104] Many interdisciplinary academics have demonstrated the pharmaceutical industry benefits from regulatory predictability, as drug development is a time-consuming, costly, and highly unpredictable scientific field. Most drugs take an average of ten to fifteen years[105] to come to market at a median cost of $1.1 billion,[106] although some estimate the cost to be about $2.6 billion.[107] Ninety percent of potential new drugs fail clinical trials despite showing initial promise, and the failure rate is higher when considering preclinical trial products.[108] Moreover, pharmaceutical products cannot be sold (and thus cannot make a profit) until they are approved. As it takes years of advanced planning to set up clinical trials according to current regulatory requirements, litigation challenging governing regulatory requirements has meaningful risks.

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103 Gluck, *supra* note 2, at 2121; *see also* Rachel Roubein, Laurie McGinley & David Ovalle, *Abortion Pill Fight May Have Broader Implications for FDA Drug Approval*, WASH. POST (Mar. 15, 2023, 5:12 PM), https://www.washingtonpost.com/health/2023/03/15/abortion-pill-fda [https://web.archive.org/web/20240617053223/https://www.washingtonpost.com/health/2023/03/15/abortion-pill-fda] ("'The FDA is the gold standard for determining whether a medicine is safe and effective for people to use,' [said] Priscilla VanderVeer, a vice president at Pharmaceutical Research and Manufacturers of America. . . ."); Meadows, *supra* note 49; PHILIP J. HILTS, PROTECTING AMERICA'S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION xiv (2004) ("[The FDA] is the most known, watched, and imitated of regulatory bodies. . . . [I]t has also been described as the most important regulatory agency in the world.").

104 *See* O'Reilly, *supra* note 12, at 942 ("If an agency does not receive consistent deference from the courts, regulated entities will likely deem the agency less potent; in turn, those entities will be less likely to respect agency decisions. As with any administrative agency, deference is a cornerstone of the FDA's effectiveness." (footnote omitted) (citing JAMES T. O'REILLY, ADMINISTRATIVE RULEMAKING § 18:1 (2d ed. 2007))); *see also* Bendicksen et al., *supra* note 13.

105 Peter Corr & David Williams, *The Pathway from Idea to Regulatory Approval: Examples for Drug Development*, *in* CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE 375, 375 (Bernard Lo & Marilyn J. Field eds., 2009); *see also* J.A. DiMasi, L. Feldman, A. Seckler & A. Wilson, *Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs*, 87 CLINICAL PHARMACOLOGY THERAPEUTICS 272 (2010); *see also* Jörg J. Möhrle, *How Long Does It Take to Develop a New Drug?*, 43 LANCET REG'L HEALTH—EUR., Aug. 2024, at 1, 1 (2024) (finding that it takes 7.3 years of development time for anti-infectives in Europe).

106 Oliver J. Wouters, Martin McKee & Jeroen Luyten, *Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009–2018*, 323 JAMA 844, 845 (2020); *see also* DAVID AUSTIN & TAMARA HAYFORD, CONG. BUDGET OFF., RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 2 (2021), https://www.cbo.gov/publication/57126 [https://perma.cc/M39J-HF4A].

107 Joseph A. DiMasi, Henry G. Grabowski & Ronald W. Hansen, *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 20 (2016).

108 Duxin Sun, Wei Gao, Hongxiang Hu & Simon Zhou, *Why 90% of Clinical Drug Development Fails and How to Improve It?*, 12 ACTA PHARMACEUTICA SINICA B 3049, 3050 (2022) (providing that this peer-reviewed study should be considered with some caution as it was conducted in collaboration with a large pharmaceutical company).

Logically, it follows that lawsuits against the FDA's drug approval decisions that challenge predicted outcomes should be generally rare.

Many legal scholars have demonstrated this trend, arguing both strong judicial deference and losing records are deterrents to litigation,[109] with some theorizing that the FDA has largely avoided scrutiny compared to other agencies because its "regulatory interest generally align with the business interest of drug companies."[110] Professor Nick Parrillo has argued that "drugmakers' reluctance to sue likely rests partly on two other factors: the firms' stake in their bilateral relationships to FDA and their need for FDA-fostered credibility with the consuming public."[111] That is, pharmaceutical companies may be more likely to comply with FDA-communicated expectations rather than delay making profits (by delaying approval) or increasing costs (from litigation).[112] Altogether, the history of strong judicial deference benefiting the Agency and industry along with the complicated nature of the pharmaceutical industry that highly values predictability appears to have created a peculiar symbiotic relationship between courts, the FDA, and the industry. Therefore, even the subtle shift in the frequency and outcomes of judicial review of FDA drug approvals choices as suggested in Section I.B is striking as it has the potential to disrupt that dynamic.[113]

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109 *See, e.g.*, Noah, *supra* note 9, at 53 ("[T]he federal district court in Wisconsin found no merit to their objections—not because FDA licensing enjoys immunity, but in light of the deference accorded to the agency's expertise in making such judgments."); Jason J. Czarnezki, *An Empirical Investigation of Judicial Decisionmaking, Statutory Interpretation, and the* Chevron *Doctrine in Environmental Law*, 79 U. COLO. L. REV. 767, 817 (2008); Fisher et al., *supra* note 90, at 1682; O'Reilly, *supra* note 12, at 977 ("Doubt about the jurisprudential basis for claiming deference would disable the FDA's potent regulatory power of deterrence.").

110 Sharkey & Kenny, *supra* note 14, at 171 ("There is likely no appetite among the courts to inject great uncertainty into the drug approval system by reinterpreting [the statutory provision regarding adequate and well controlled investigations], especially given that it includes an explicit reference to the judgments of 'experts . . . .'").

111 Parrillo, *supra* note 10, at 50.

112 *See* Chad Landmon, Alexander Alfano & Michelle Divelbiss, *Open the Floodgates: The Potential Impact on Litigation Against FDA if the Supreme Court Reverses or Curtails* Chevron *Deference*, 74 FOOD & DRUG L.J. 358, 359 (2019) ("[T]he deference afforded by *Chevron* has made it difficult to successfully challenge FDA's application of these guidelines.").

113 *See* Michelle Long, Justin Lo & Kaye Pestaina, *SCOTUS Case Could Weaken the Impact of Regulation on Key Patient and Consumer Protections*, KFF (Apr. 9, 2024), https://www.kff.org/private-insurance/issue-brief/upcoming-scotus-case-could-weaken-impact-regulation-key-patient-consumer-protections [https://perma.cc/76HS-U33K] ("Overturning regulations could provide more incentive for litigants to challenge agency regulations, resulting in more federal litigation crowding court dockets."); *see also* O'Reilly, *supra* note 12, at 940 (arguing that during the Bush Administration, "political direction of the FDA—both overt and covert— . . . diminished the likelihood of future judicial deference to the Agency").

B. *Trends in Judicial Rulings Challenging FDA Pharmaceutical Decisions over the Last Decade*

This Section describes the recent mifepristone litigation and three unrelated cases between 2021 and 2023 that overturned longstanding FDA policies. Each of the four cases described herein can be understood as retellings of the same story: a court overturned different longstanding FDA policies followed by the Supreme Court reversal or Congress considering or passing statutes that restored the FDA's initial approach.[114] While multiple successful challenges to agency actions is in line with the steady attack on deference to administrative agencies described in Section I.A.1,[115] the pattern is atypical for the FDA as described in Section I.A.3.[116] Section I.B illustrates that the shift in questions of FDA authority over longstanding policies governing pharmaceutical drugs predates *Loper Bright* and argues that the cases share a common theme of skepticism of science-based policy questions. This trend is drawn from a larger sample of fifty-eight cases from federal district and appellate courts[117] over the last ten years (January 1, 2013, to December 31, 2023, ninety-four opinions).[118] Courts ruled in favor of the FDA in sixty-five of ninety-four opinions analyzed, against the Agency in twenty-three of ninety-four opinions analyzed, and issued mixed rulings in six opinions.[119]

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114 *See* Parrillo, *supra* note 10, at 49 ("The pharmaceutical lobby's influence in Congress is deep.").

115 *See* Walker, *supra* note 42.

116 *See* Sharkey & Kenny, *supra* note 14; *cf.* O'Reilly, *supra* note 12, at 950 ("[T]he Agency's decisions [were] elevated to a rarified status, achieving a degree of judicial deference that rose to the highest degree possible, short of an express mandate from Congress.").

117 The cases were found using a Lexis+ database search. The Boolean string search used "name ("FDA" OR "Food and Drug Administration") AND pharm!" and limited to federal cases in the relevant timeframe. Cases related to pro se litigants, the False Claims Act, informed consent or research ethics, medical devices, food, animals, the Freedom of Information Act, and Bivens motions, as well as dietary supplements and brief opinions of less than two paragraphs were excluded. Cases related to tobacco, food, or animal products were outside the scope of this analysis. Litigation related to compound and homeopathic drugs were included. Cases related to COVID-19, abortion, and contraception were analyzed separately and not included. After exclusion criteria, ninety-four opinions were identified. Twenty of these were appellate decisions. Related opinions, in addition to appellate decisions, were connected. The final data set consisted of fifty-eight cases (n = 58). Outcomes were classified as favoring the FDA, not favoring the FDA, or neither based on each opinion identified.

118 *Amarin Pharmaceuticals Ireland Limited v. FDA* was excluded from review as outside the scope although it did meet the previously mentioned criteria. 139 F. Supp. 3d 437 (D.D.C. 2015). In this case, the court found that it lacked jurisdiction to review a motion to intervene during an appeal. *Id.*

119 *See* Appendix I.

The four-part case study presented here illustrates that between 2021 and 2023, courts overturned multiple longstanding FDA policies. Specifically, courts overturned longstanding interpretations of the Orphan Drug Act,[120] the Prohibitive Act of the FDCA,[121] and drug/device classification under the FDCA,[122] with remedies that limit the FDA's discretion and flexibility. While only one case directly challenged the FDA's decision to approve a drug, one removed competitor products from the market, and two avoided costly drug safety regulatory compliance requirements.[123]

1. Mifepristone Litigation

The mifepristone dueling opinions stand out as a rare substantive challenge to a drug's approval in an industry that had historically preferred predictability.[124] President Biden warned on April 7, 2023, that "[i]f [the mifepristone] ruling were to stand, then there will be virtually no prescription, approved by the FDA, that would be safe from these kinds of political, ideological attacks."[125] Much has been written about this case and its implications, but this Section argues that the lower courts' opinions align with this recent cluster of cases questioning the FDA's science-based policy decisions related to drug approvals.

The District Court for the Northern District of Texas asked and answered four fundamental drug approval policy questions. First, what types of drugs should qualify for accelerated approval?[126] Second, what outcomes must be tested in clinical trials to demonstrate meaningful clinical benefit?[127] Third, how should data comparing the safety of

120 *See infra* Section I.B.2.

121 *See infra* Section I.B.3.

122 *See infra* Section I.B.4.

123 *See infra* Section I.B.4.

124 *See* sources cited *supra* notes 5–12.

125 Joe Biden, Pres., Statement from President Joe Biden on Decision in Alliance for Hippocratic Medicine v. FDA (Apr. 7, 2023), https://bidenwhitehouse.archives.gov/briefing-room/statements-releases/2023/04/07/statement-from-president-joe-biden-on-decision-in-alliance-for-hippocratic-medicine-v-fda [https://perma.cc/2PD7-U6ME].

126 All. for Hippocratic Med. v. FDA, 668 F. Supp. 3d 507, 543–46 (N.D. Tex. 2023) (noting that mifepristone did not receive accelerated approval and was only subject to additional requirements under Subpart H (21 U.S.C. § 321(h)) which provides for approval with restrictions to assure safe use and post marketing safety reporting).

127 *Id.* at 554; *see also* All. for Hippocratic Med. v. FDA, 78 F.4th 210, 251 (5th Cir. 2023) ("[The FDA] did not refer to any literature that affirmatively supported the notion that mifepristone would remain safe and effective even without the in-person dispensing requirement.").

alternative therapies be collected and weighed?[128] And fourth, are the conditions of approval sufficiently close to the clinical trial conditions?[129] Arguably, these questions do not have a single "right" answer.[130]

The Court of Appeals for the Fifth Circuit and the contradictory opinion from the District Court for the Eastern District of Washington reviewed more limited questions on data quality and quantity.[131] On the merits of the preliminary injunction, the Fifth Circuit concluded that the FDA's decision on mifepristone was not internally consistent with the underlying data.[132] Because of what it characterized as the conflicting data, it held that the FDA failed to consider an important aspect of the problem: whether mifepristone qualifies for Risk Evaluation and Management System (REMS) and Elements to Ensure Safe Use based on the statute.[133] The Fifth Circuit also held that the FDA's explanation for its drug safety analysis did not "consider the cumulative effect" of several

128 *All. for Hippocratic Med.*, 668 F. Supp. 3d at 548 ("On balance, the data reflect little to no benefit over surgical abortion—much less a 'meaningful therapeutic' benefit."); *id.* at 550 (finding that a surgical abortion is far safer and the FDA failed to consider an "important aspect of the problem"); *see also* Rachel Treisman, *How an Abortion Pill Ruling Could Threaten the FDA's Regulatory Authority*, NPR (Apr. 11, 2023, 2:30 PM), https://www.npr.org/2023/04/11/1169194827/abortion-pill-mifepristone-fda-authority-regulation [https://perma.cc/7FVU-SSL4] (quoting Holly Fernandez Lynch, stating that "[w]hat has happened in this case from the Northern District of Texas is that we have a single federal judge who has inserted himself, standing in for the agency to say FDA should have never approved mifepristone because they did not have adequate data to determine that it was safe").

129 *All. for Hippocratic Med.*, 668 F. Supp. 3d at 548–49, 555–56 (concluding both that the Subpart H restrictions and REMS did not match the clinical trial conditions perfectly and that the 2016 reporting requirements were not directly studied).

130 *Development & Approval Process*, FDA (Aug. 8, 2022), https://www.fda.gov/drugs/development-approval-process-drugs [https://perma.cc/AUX4-DTJQ] ("Although many of the FDA's risk-benefit assessments and decisions are straightforward, sometimes the benefits and risks are uncertain and may be difficult to interpret or predict. The agency and the drug maker may reach different conclusions after analyzing the same data, or there may be differences of opinion among members of the FDA's review team.").

131 Washington v. FDA, 668 F. Supp. 3d 1125, 1135 (E.D. Wash.), *opinion clarified*, 669 F. Supp. 3d 1057 (E.D. Wash. 2023) (noting that Washington State had requested a preliminary injunction "affirming FDA's original conclusion that mifepristone is safe and effective," enjoining the FDA from removing the drug from market, and enjoining the 2023 dispersal restrictions and further providing that the 2023 REMS removed the in-person dispensing requirement and added a pharmacy-certification requirement but maintained the Prescriber and Patient Agreement Form requirements); *All. for Hippocratic Med.*, 78 F.4th 210.

132 *All. for Hippocratic Med.*, 78 F.4th 210; *Washington*, 668 F. Supp. 3d at 1141 (noting that the record demonstrated potentially internally inconsistent FDA findings regarding mifepristone's safety profile as the drug is approved for unrelated conditions without considering fetal loss and some concluded the drug is safe and effective through seventy days gestation).

133 *All. for Hippocratic Med.*, 78 F.4th at 243–48.

changes in the 2016 Amendments, although they were considered individually.[134]

In addition to these questions of data quality, the court criticized conclusions drawn from the underlying data in the FDA Adverse Event Reporting System (FAERS) system, noting that "considerable evidence shows that FAERS data is insufficient to draw general conclusions about adverse events."[135] Criticism of the data underlying drug determination decisions and federally run drug safety reporting systems such as FAERS remains atypical for courts.[136] FAERS collects data on post-approval adverse events for all FDA approved drugs and its limitations are well known.[137] Nevertheless, regulators and researchers regularly extrapolate appropriately limited conclusions on drug safety from this "flawed" data for all drugs.[138] Some have argued that the mifepristone FAERS data was more complete than the data for most drugs,[139] and that the FDA has "subject[ed mifepristone] to more scrutiny and regulation than most other prescription drugs."[140] The Eastern District of Washington concluded that the same data suggests the FDA was overly cautious in approval.[141] Many scholars have noted that it is atypical for courts to reevaluate questions of drug approval data sufficiency.[142]

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134 *Id.* at 246 (reviewing the FDA's 2016 revisions to the REMS and 2021 nonenforcement decision restricting mifepristone and determining that the FDA "failed to consider whether it needed to continue to collect data of non-fatal adverse events" for "major" REMS changes).

135 *Id.* at 249. The Fifth Circuit noted that the FAERS system is a widely used, voluntary collection of data on adverse events for all FDA-approved drugs. *Id.* "[M]any adverse events will go unreported," and physicians do not use FAERS consistently, but this problem is not specific to mifepristone. *Id.*

136 While there is much to criticize about FAERS, other courts did not reconsider the sufficiency of data from the standard post-approval drug monitoring systems in the cases examined. *See generally infra* Appendix I; Bendicksen et al., *supra* note 13.

137 *See FDA Adverse Event Reporting System (FAERS) Public Dashboard*, FDA (Dec. 7, 2023), https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard [https://perma.cc/GW2K-DESR]; Juan M. Banda et al., *A Curated and Standardized Adverse Drug Event Resource to Accelerate Drug Safety Research*, 3 SCI. DATA, May 2016, at 1.

138 *See* Banda et al., *supra* note 137, at 1 ("Spontaneous reporting systems (SRS) data which [include FAERS as] the mainstay of traditional drug safety surveillance [and] are used for hypothesis generation and to validate the newer approaches.").

139 *See* Greer Donley, *Medication Abortion Exceptionalism*, 107 CORNELL L. REV. 627 (2022).

140 Zettler & Sarpatwari, *supra* note 6, at 7.

141 Washington v. FDA, 668 F. Supp. 3d 1125, 1135 (E.D. Wash.), *opinion clarified*, 669 F. Supp. 3d 1057 (E.D. Wash. 2023).

142 Donley & Zettler, *supra* note 9, at 66 ("[T]he brief asserts that the amici were not aware of cases involving a court revoking a drug approval for a product already on the market based on a differing opinion about the drug's safety and effectiveness."); *see also* Brief of Food and Drug Law Scholars and Professors as Amici Curiae in of Support of Defendants' Opposition to Plaintiffs' Motion for Preliminary Injunction, *supra* note 9, at 29 & n.22; *cf.* Oral Argument, *supra* note 12, at 1:03:15–1:04:23.

Strikingly, all three courts seem to be asking and answering a science-based policy question: how much data is needed to approve a drug? In addressing this question, all three cases follow the "textbook" approach for political challenges to environmental science metapolicy concerns described by Professors Emily Hammond and Wendy Wagner, where policy-motivated litigants claim an agency used "bad science" to reach a disliked policy outcome.[143] As Professor Hammond explained, litigants typically allege that an agency "ignored important scientific studies, that the agency's own science involved flawed methodologies, that the agency did not do enough science, or that the science somehow dictated a different conclusion—in essence, that if the science had been 'right,' a different outcome would have resulted."[144] However, like other scientific agencies, the FDA has conflicting goals that require tradeoffs,[145] such as ensuring timely access to innovative new drugs and collecting sufficient data to be sure that products on the market are high-quality, safe, and effective.[146] Science-based policy choices are vulnerable to criticism as one can always do "better" by prioritizing a different policy goal and conventions may seem unreasonable when examined in isolation.[147]

Considered alone, substantive challenges to FDA approval of an abortifacient may be isolated, consistent with abortion exceptionalism.[148]

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143 Hammond, *supra* note 22, at 749; Wagner, *supra* note 22, at 109–18.

144 Hammond, *supra* note 22, at 749.

145 *See* Brad Beauvais et al., *Testing Kissick's Iron Triangle—Structural Equation Modeling Analysis of a Practical Theory*, 1753 HEALTHCARE, Dec. 2021, at 1, 1 ("William Kissick's health care 'Iron Triangle' . . . [argues] it is typically challenging—if not impossible—to simultaneously achieve a low-cost, high-quality, open access health care system; [Empirical testing demonstrates] bending the health care cost curve, increasing access to care, and advancing quality of care is as challenging now as it was [in 1994] . . . ."); Genevieve P. Kanter, *The Real Question the FDA Is Asking Its Advisory Committees*, 4 JAMA HEALTH F. July 7, 2023, at 1, 1; Joanne S. Eglovitch, *Califf Says Major Effort Underway to Reform Advisory Committee Meetings*, REGUL. AFFS. PRO. SOC'Y (Feb. 1, 2024), https://www.raps.org/news-and-articles/news-articles/2024/2/califf-says-major-effort-underway-to-reform-adviso [https://perma.cc/9WHK-JLWU]; Dan Troy, Dan Mendelson & David Beier, *FDA Reform: It's Time to Act, but Not as an Independent Agency*, HEALTH AFFS. (Mar. 19, 2019), https://www.healthaffairs.org/content/forefront/fda-reform-s-time-act-but-not-independent-agency [https://perma.cc/X2ZB-B7L2]; Bobby Clark & Jeff Callis, *The Accelerated Approval Pathway for New Drug Therapies: Controversies and Proposed Fixes*, COMMONWEALTH FUND (July 14, 2022), https://www.commonwealthfund.org/publications/explainer/2022/jul/accelerated-approval-pathway-new-drug-therapies-controversies-fixes [https://perma.cc/R39V-U58V].

146 *See* Christopher Buccafusco & Samuel N. Weinstein, *Antisocial Innovation*, 58 GA. L. REV. 573, 586 (2024) ("[I]nnovation governance involves risk-risk tradeoffs. . . . [E]xcessive regulation may deprive society of valuable new inventions, [but] insufficient regulation poses serious, even catastrophic risks to society." (footnote omitted)).

147 *See supra* note Section I.A.2.

148 For an excellent review of medication abortion regulation, see Donley, *supra* note 139.

Mifepristone has been subject to restrictive regulatory choices,[149] scientific and political scrutiny, and intense advocacy actions such as patient demand, boycotts,[150] litigation,[151] and even violence,[152] since it was invented. Juxtaposed against the last decade of FDA litigation, this may also be part of the new trend overturning longstanding FDA policies through questioning science-based policy choices. Unlike the deeply political question that colors the mifepristone case, however, other examples appear to be financially driven as litigants sought either lucrative benefits or to minimize costly restrictions.

2. Thirty Years of Orphan Drug Act Precedents

Two years prior to the mifepristone cases, in *Catalyst Pharmaceuticals, Inc. v. Becerra*, the Court of Appeals for the Eleventh Circuit overturned the FDA's three-decade-long interpretation of the scope of orphan drug exclusivity ("ODE").[153] The FDA's interpretation of the phrase "same disease or condition" to mean same "use or indication" was found to be arbitrary and capricious and contravened the plain language of the Orphan Drug Act.[154] This case stands apart from other

149 *See* Eli Y. Adashi, Rohit S. Rajan, Daniel P. O'Mahony & I. Glenn Cohen, *The Next Two Decades of Mifepristone at FDA: History as Destiny*, 109 CONTRACEPTION 1, 3 (2022); Elizabeth Sepper, *Anti-Abortion Exceptionalism After* Dobbs, 51 J.L., MED. & ETHICS 612, 612 (2023) (treating "abortion differently than other areas and favor[ing] anti-abortion over pro-choice viewpoints . . . "); Donley, *supra* note 139, at 642; Paradise, *supra* note 19, at 556 ("The FDA's approach to medication abortion has garnered that characterization of paternalistic regulation. Post-approval, the FDA has imposed various REMS requirements." (footnote omitted) (citing Donley, *supra* note 139)); *see also* Lupkin, *supra* note 20; JUDITH A. JOHNSON, CONG. RSCH. SERV., RL30866, ABORTION: TERMINATION OF EARLY PREGNANCY WITH RU-486 (MIFEPRISTONE) (2001); R. Alta Charo, *A Political History of RU-486*, *in* BIOMEDICAL POLITICS 43, 76–78 (Kathi E. Hanna ed., 1991); Philip J. Hilts, *Abortion Pills Are Confiscated by U.S. Agents*, N.Y. TIMES, July 2, 1992, at A12 (discussing the FDA ban on the importation of RU-486 for personal use); Benten v. Kessler, 505 U.S. 1084 (1992).

150 *See* Alexander Dorozynski, *Boycott Threat Forces French Company to Abandon RU486*, 314 BRIT. MED. J. 1145, 1150 (1997); Julie Rovner, *US Antiabortionists Boycott Allergy Drug*, 349 LANCET 1079, 1079 (1997) (noting that protesters in the United States threatened to boycott the manufacturer's unrelated blockbuster allergy drug, *Allegra* (fexofenadine hydrochloride), and caused production of RU-486 to briefly cease); *see also* Charo, *supra* note 149, at 54–58.

151 Most recently: *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (2021) (Mem.).

152 *See generally* NAT'L ABORTION FED., 2021 VIOLENCE & DISRUPTION STATISTICS (2021), https://prochoice.org/wp-content/uploads/2021_NAF_VD_Stats_Final.pdf [https://perma.cc/5HZM-6KYG] (documenting murders, violence, vandalism, and other activities aimed at disrupting patients and providers seeing abortive care have increased since 1999).

153 14 F.4th 1299 (11th Cir. 2021).

154 *Id.* at 1306–08, 1313.

ODE challenges in the last forty years[155] for two reasons: first, it overturned longstanding policy and, second, it appears that the court questioned the FDA's science-based policy choices to reach its conclusion.[156]

The 1983 Orphan Drug Act created financial incentives to encourage the development of drugs for rare diseases and conditions.[157] In addition to grants and tax credits, the Orphan Drug Act instructs the FDA to award manufacturers of qualifying drugs seven years of market exclusivity during which the FDA cannot approve another version of the "same drug for the same disease or condition."[158] While the FDA can grant orphan drug *designations* to multiple products in development, only the first approved product is awarded exclusivity.[159] ODE promises a near monopoly with only three narrow statutory exceptions; after granting ODE, the FDA can only approve another drug to treat the "same rare disease or condition" if the drug is in shortage, if the orphan drug sponsor consents, or if the subsequent drug is the "same" and the manufacturer can demonstrate that it is "clinically superior."[160] Before the *Catalyst* case, the FDA promogulated rules declaring a drug is the "same" if it contains the "same active moiety" for the same use or indication.[161]

Following its rule, the FDA granted orphan drug designation to two amifampridine products for the treatment of Lambert-Eaton myasthenic syndrome (LEMS), first in 1990 to Jacobus Pharmaceutical Company

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155 *See* Eagle Pharms., Inc. v. Azar, No. 16-790, 2018 WL 3838265 (D.D.C. June 8, 2018), *aff'd*, 952 F.3d 323 (D.C. Cir. 2020); United Therapeutics Corp. v. U.S. Dep't of Health & Hum. Servs., No. 17-01577, 2020 WL 6498619 (D.D.C. Sept. 2, 2020); Spectrum Pharms., Inc. v. Burwell, 107 F. Supp. 3d 23 (D.D.C. 2015); Depomed, Inc. v. U.S. Dep't of Health & Hum. Servs., 66 F. Supp. 3d 217 (D.D.C. 2014).

156 *See* HANNAH-ALISE ROGERS, CONG. RSCH. SERV., R47653, THE ORPHAN DRUG ACT AND *CATALYST PHARMACEUTICALS, INC., V. BECERRA* 11 (2023); *Catalyst Pharms., Inc.*, 14 F.4th 1299.

157 Orphan Drug Act of 1983, Pub. L. No. 97-414, 96 Stat. 2049 (codified as amended at 21 U.S.C. §§ 360aa–360ee). Products that prevent, diagnose, or treat rare diseases or conditions can receive Orphan Drug Designation (ODD). *See id.* Rare disease impacts fewer than 200,000 people in the United States or "affects more than 200,000 persons in the United States" but for which the company is not reasonably expected to recover costs as defined. 21 U.S.C. § 360bb(a)(2). ODD benefits are particularly lucrative and include tax credits, exemption from user fees, and up to seven years of market exclusivity after approval. *See* Kao-Ping Chua, Lauren Kimmel & Rena M. Conti, *Spending for Orphan Indications Among Top-Selling Orphan Drugs Approved to Treat Common Diseases*, 40 HEALTH AFFS. 453, 453 (2021) ("Paradoxically, however, many partial orphan drugs have blockbuster sales.").

158 21 U.S.C. § 360cc(a)(2).

159 *See id.*

160 *Id.* §§ 360cc(a)–(b), (c)(1)–(3); *see also id.* § 360cc(c)(2) (defining "clinically superior" to "mean[] that the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care"); *see also Catalyst Pharms., Inc.*, 14 F.4th at 1303–04.

161 21 C.F.R. § 316.3(b)(14)(i) (2013).

(Jacobus) and then in 2009 to Catalyst Pharmaceuticals, Inc. (Catalyst).[162] Both proposed products had the same active ingredient (amifampridine),[163] but Catalyst received FDA approval first in November 2018.[164] Its amifampridine drug (Firdapse®) was awarded a seven-year exclusivity period under the Orphan Drug Act for the treatment of LEMS in adults.[165]

The price of amifampridine increased drastically after Firdapse® was approved; Jacobus had previously provided the medication to patients for free while their competitor product was in development under an expanded access program.[166] Three months after Firdapse's® approval, U.S. senators raised concerns about the cost of amifampridine and urged the FDA to ensure that more affordable versions were available.[167] In May 2019, the FDA concluded that the treatment of LEMS in children was a separate indication and thus would not be blocked by Firdapse's® ODE for treatment in adults.[168] The FDA approved Jacobus's amifampridine product (Ruzurgi®) in 2019 for children, splitting the approved

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162 *Catalyst Pharms., Inc.*, 14 F.4th at 1304–05.

163 *Id.* at 1304.

164 *Id.*

165 *Id.*; *see also* Sara W. Koblitz, *Catalyst Pharmaceuticals, Inc. v. Becerra*, FOOD & DRUG L. INST., https://www.fdli.org/2022/06/catalyst-pharmaceuticals-inc-v-becerra [https://perma.cc/D96N-8G8B]; *Catalyst Pharms., Inc.*, 14 F.4th at 1304 ("[T]he FDA approved Firdapse for the treatment of LEMS 'in adults' on November 28, 2018. Consistent with the Orphan Drug Act, the FDA granted Catalyst exclusivity through November 28, 2025." (citing 21 U.S.C. § 360cc(a))).

166 *See* Eric Sagonowsky, *First, a Pricing Scandal for Catalyst's Firdapse. Next, Off-Label Competition?*, FIERCE PHARMA (May 7, 2019, 12:02 PM), https://www.fiercepharma.com/pharma/first-a-pricing-scandal-for-catalyst-s-firdapse-next-off-label-competition [https://perma.cc/8CST-YFBG] ("For decades, Jacobus Pharmaceuticals gave away the unapproved drug amifampridine to patients with a rare neuromuscular disorder called LEMS. Then, Catalyst Pharma licensed certain rights to the drug, scored an FDA nod, and priced the med at $375,000 a year. An outcry ensued. But now, the FDA may have given patients a workaround."); *see also* Press Release, Bernie Sanders, U.S. Sen. for Vt., Sanders Investigates a $375,000 Price Spike on Old Drug (Feb. 4, 2019), https://www.sanders.senate.gov/press-releases/sanders-investigates-a-375000-price-spike-on-old-drug-2 [https://perma.cc/232W-BTWG].

167 Press Release, *supra* note 166; *see also* Wayne Drash, *$375,000 Price Leads Disabled Mom to Ration Meds*, CNN HEALTH (Feb. 21, 2019, 9:28 AM), https://www.cnn.com/2019/02/20/health/firdapse-expensive-drug-mom-bernie-sanders-eprise/index.html [https://perma.cc/AD8C-VRJK] ("The patient . . . [had] been getting the drug from Jacobus for free since 2004 and . . . [now] would have to pay $3,800 a month in co-pay. . . . [She] decided she's not going to take the medicine—even if it means a rapid decline in her health. . . . [She stated] 'I'm going to do without. I'm not going to be a party of enriching the pockets of this predatory pharmaceutical.'").

168 Clarification of Orphan-Drug Exclusivity Following Catalyst Pharms., Inc. v. Becerra; Notification, 88 Fed. Reg. 4086, 4086 (Jan. 24, 2023) ("In approving Jacobus's drug, FDA followed its longstanding rule, codified in its regulations, that the orphan-drug exclusivity for Catalyst's drug protected only the approved use or indication within the designated disease." (citing 21 C.F.R. §§ 316(b)(12), 316.31(a)–(b) (2022))).

indication between adults and pediatrics.[169] Notably, Jacobus did not conduct specific pediatric clinical trials but had safety data from the free drugs provided under the expanded access program.[170]

Both the magistrate judge and district judge for the District Court for the Southern District of Florida afforded the FDA *Chevron* deference after holding that the Orphan Drug Act language was ambiguous and the Agency's interpretation was reasonable.[171] The Eleventh Circuit reviewed the challenge de novo.[172] The parties agreed that the two competitor drugs were the "same" under the Orphan Drug Act and that LEMS was a single disease, but disagreed about whether approval was for the entire "disease or condition" or only the disease or condition in adults (as per the clinical trials and approved label).[173] The Eleventh Circuit held that the scope of ODE applies to the rare "disease or condition,"[174] not the approved use or indication standard that the FDA had used since 1992 and had previously been upheld by the Fourth Circuit.[175] In finding that the FDA's longstanding approach to ODE policy was arbitrary and capricious in violation of the APA, the court made the ODE determination broader than the data-backed indication approved on the label.[176]

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169 Press Release, FDA, FDA Approves First Treatment for Children with Lambert-Eaton Myasthenic Syndrome, a Rare Autoimmune Disorder (May 6, 2019), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-children-lambert-eaton-myasthenic-syndrome-rare-autoimmune-disorder [https://perma.cc/6DFR-VV9S].

170 *Catalyst Pharms., Inc.*, 14 F.4th at 1304–05.

171 *Id.* at 1305–06; Catalyst Pharms., Inc. v. Azar, No. 19-cv-22425, 2020 WL 5514187 (S.D. Fla. July 30, 2020), *R. & R. adopted sub nom.* Catalyst Pharms., Inc. v. FDA, No. 19-cv-22425, 2020 WL 5792595 (S.D. Fla. Sept. 29, 2020), *rev'd and remanded sub nom. Catalyst Pharms., Inc.*, 14 F.4th 1299 (11th Cir. 2021).

172 *Catalyst Pharms., Inc.*, 14 F.4th at 1306.

173 *Id.* at 1305–06.

174 *Id.* at 1302. The Eleventh Circuit distinguished interpretations of ODE as ambiguous in both *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002) and *Spectrum Pharmaceuticals, Inc. v. Burwell*, 824 F.3d 1062 (D.C. Cir. 2016), describing the former as "deal[ing] with the scope of market exclusivit[ies] in the context of off-label use." *Catalyst Pharms., Inc.*, 14 F.4th at 1310–11.

175 *Schwetz*, 288 F.3d at 145 ("Congress made clear its intention that § 360cc(a) was to be disease-specific, not drug-specific. In other words, the statute as written protects uses, not drugs for any and all uses.").

176 *Catalyst Pharms., Inc.*, 14 F.4th 1299; *see* Koblitz, *supra* note 165 (noting that the Eleventh Circuit's interpretation could limit ODD grants, disincentive innovation for patients unable to benefit from the first drug and lead to additional litigation); *cf.* Yifan Wang, Catalyst Pharms., Inc. v. Becerra*: When the Food and Drug Administration Repeatedly Ignores the Plain Language of the Orphan Drug Act (ODA)*, 36 J.L. & HEALTH 139, 158 (2023) ("The FDA does not have the institutional competence to address complex issues such as orphan drug pricing and affordability.").

The case was unusual for overturning thirty years of codified precedent.[177] Scholars have noted that the holding expanded the value of ODE and upended industry reliance.[178] Second, the court reversed an FDA drug approval after challenged by a competitor though not through a substantive challenge to the FDA's determination of a drug's safety and efficacy.[179]

Third, while the court may have been concerned about improper political influences,[180] the remedy did more than reverse the specific case. It limited the FDA's authority beyond the fact of the case at hand. To conclude that ODE applies to the entire disease rather than the approved indication, the Eleventh Circuit assumes that drugs approved for an indication treats the entire disease in all cases.[181] However, even when patients have the same "disease or condition,"[182] some subpopulations can require different treatments. For example, cystic fibrosis is a single disease that can arise due to different thousands of genetic mutations, so therapies targeting one gene mutation do not work for subpopulations with a different gene mutation.[183] What is labeled as a separate disease or

177 *See* Clarification of Orphan-Drug Exclusivity Following Catalyst Pharms., Inc. v. Becerra; Notification, 88 Fed. Reg. 4086 (Jan. 24, 2023).

178 Koblitz, *supra* note 165; *see also* Kathleen L. Miller & Michael Lanthier, *Orphan Drug Label Expansions: Analysis of Subsequent Rare and Common Indication Approvals*, 43 HEALTH AFFS. 18, 24 (2024); Chua et al., *supra* note 157.

179 *Catalyst Pharms., Inc.*, 14 F.4th at 1312–13.

180 *See id.*; Koblitz, *supra* note 165 (contending that the opinion "serve[s] to discourage FDA from deliberately undermining existing exclusivity by artificially subsetting a patient population in response to congressional pressure, as Catalyst alleged the agency did here").

181 Koblitz, *supra* note 165 (explaining that FDA intent was to "permit multiple orphan-drug exclusive approvals for multiple subsets of the same underlying orphan disease or condition," because "such exclusivity would block approval of the same drug even if the exclusivity-protected orphan drug does not treat a given subpopulation." However, the Eleventh Circuit concluded generally that "'same drug or condition' in the exclusivity provision can be read only in one way: the 'same disease or condition' for purposes of awarding exclusivity" (first quoting 76 Fed. Red. 64868, 64871 (Oct. 19, 2011); third quoting *Catalyst*, 14 F.4th at 1308)); *see also* OFF. OF ORPHAN PRODS. DEV., FDA, U.S. DEP'T OF HEALTH & HUM. SERVS., CLARIFICATION OF ORPHAN DESIGNATION OF DRUGS AND BIOLOGICS FOR PEDIATRIC SUBPOPULATIONS OF COMMON DISEASES: GUIDANCE FOR INDUSTRY (2018), https://www.fda.gov/media/109496/download [https://web.archive.org/web/20241207234315/https://www.fda.gov/media/109496/download].

182 21 C.F.R. § 316.20(a) (2013).

183 As the various genetic mutations present with similar symptoms, they were historically considered the same condition. The genetic differences were later identified. Currently, there is a gene therapy for one mutation only. *See* Lucy Allen et al., *Future Therapies for Cystic Fibrosis*, 14 NATURE COMMC'NS, Feb. 2023, at 1, 1, 3 ("[D]espite being a single gene disorder, there are multiple cystic fibrosis-causing genetic variants; mutation-specific drugs are not suitable for all genetic variants and also do not correct all the multisystem clinical manifestations of the disease. For many, there will remain a need for improved treatments, . . . [and t]here are more than 350 recogni[z]ed CF-causing mutations in the *CFTR* gene, from a total of >2000 identified variants. *CFTR* mutations

condition can be a mere accident of history, as doctors historically grouped together constellations of observable symptoms as a single disease for hundreds of years before modern testing.[184] Deciding when diseases require different treatment for subpopulations of the same disease (including developing children at a given age or variations in a disease's presentation) requires judgment calls based on complex data and evolving medical developments;[185] it is a science-based policy decision impacting lucrative incentives.[186] With this case, both the FDA's authority to identify and approve treatments for subpopulations of orphan diseases and the statutory system to incentivize development of treatments for subpopulations of orphan diseases was limited.

The limits to FDA authority on subpopulations differs from a 2015 case, where the District Court for the District of Maryland held that ODE for a pediatric indication does not prevent approval of a competitor's generic product that carved out the pediatric indication, citing "the complexity of the statutory regime under which the FDA operates, the FDA's expertise [and] the careful craft of the scheme it devised to reconcile the various statutory provisions."[187] It also diverges from statements from both the FDA and Congress in amended statutes that addressed situations where exclusivity in pediatric products blocked

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have historically been grouped into six classes, . . . [but i]n practice, this distinction is not clear-cut . . . ." (citation omitted) (citing *Welcome to the CFTR2 Website*, CLIN. & FUNCTIONAL TRANS. OF CFTR (Sept. 25, 2024), https://cftr2.org [https://perma.cc/3GR6-M3SV])).

184 *See* Lizzie Crouch, *The Twists and Turns of Naming Diseases*, BBC (Nov. 29, 2015), https://www.bbc.com/news/health-34913764 [https://perma.cc/7PPL-DZVM]; *see also* Leah Samuel, *Why Do We Call It That? Backstories of Seven Disease Names*, STAT (Oct. 24, 2017), https://www.statnews.com/2017/10/24/etymology-disease-names [https://perma.cc/Q86Y-5F7N]. *See generally* Syed Yousaf Kazmi, *The Etymology of Microbial Nomenclature and the Diseases These Cause in a Historical Perspective*, SAUDI J. BIOLOGICAL SCIS., Nov. 2022, at 1.

185 *See, e.g.*, Yi-Da Chiu, Franz Koenig, Martin Posch & Thomas Jaki, *Design and Estimation in Clinical Trials with Subpopulation Selection*, 37 STATS. MED. 4335, 4335 (2018) ("Different subpopulations defined by those baseline factors can lead to differences in the benefit or safety profile of a therapeutic intervention. Ignoring heterogeneity between subpopulations can substantially impact on medical practice."); *see also* Evelyn P. Whitlock et al., *An Approach to Addressing Subpopulation Considerations in Systematic Reviews: The Experience of Reviewers Supporting the U.S. Preventive Services Task Force*, 6 SYSTEMATIC REVS., Mar. 2017, at 1–2.

186 *See* 21 U.S.C. § 355a(b)(1)(A) (2006); Landmon et al., *supra* note 112, at 371 ("[A]nother way that drug developers can seek to maintain control of the market and maximize the return on research and development expenses[] [is] [b]y conducting pediatric studies[] . . . [which] can earn [drugs] additional exclusivity to extend other marketing exclusivity and the term of certain patents.").

187 Otsuka Pharm. Co. v. Burwell, No. 15-852, 2015 WL 3442013, at *7 (D. Md. May 27, 2015); *id.* at *11 ("Representative John Dingell, the ranking minority member of the relevant House committee, expressly noted that the misuse of pediatric information to garner three-year exclusivity for a certain indication and wholly block generic competition for all approved indications is 'a fundamental abuse of the system and were the FDA . . . to accept the claim, consumers would be harmed.'" (quoting 147 CONG. REC. H8105)).

entry of competitor products.[188] Others recognize that children may need different treatments than adults for the same disease as children are not small adults.[189]

The case is similar to two prior ODE challenges that resulted in congressional intervention. In 2014 and 2020, litigants sued over whether a company could receive multiple ODEs on the same ingredient or whether the FDA could require a company to demonstrate "clinical superiority"[190] to obtain ODE.[191] In the first opinion, written by now Supreme Court Justice Ketanji Brown Jackson, the D.C. Circuit held that the language of the Orphan Drug Act prior to the 2017 amendments was not ambiguous and that the secretary must award ODE if a company had an orphan designation and FDA approval.[192] Commenters raised concerns that judicial review of ODE determinations could negatively impact children's health, drug costs, and investment incentives for rare

188 21 U.S.C. § 355a(b). Pediatric exclusivities blocking adult approvals is the opposite scenario of this case, where an adult exclusivity blocked a pediatric approval.

189 Steven E. Krug & Yae Sul "Hazel" Jeong, *Children Are Not Little Adults*, CDC (June 12, 2023), https://www.cdc.gov/childrenindisasters/features/children-are-not-little-adults.html [https://perma.cc/C4X7-GDU3]; WORLD HEALTH ORG., CHILDREN ARE NOT LITTLE ADULTS: TRAINING FOR HEALTH CARE PROVIDERS (2d ed. 2019), https://iris.who.int/bitstream/handle/10665/331237/WHO-CED-PHE-EPE-19.12.07-eng.pdf [https://perma.cc/Y6EA-SFE2]; Jonathan Gills & Patricia Loughlan, *Not Just Small Adults: The Metaphors of Paediatrics*, 92 ARCHIVES DISEASE CHILDHOOD 946 (2007).

190 Clinical superiority is the third exception to allow subsequent orphan drug approvals for the same condition and decisions are often litigated. *See* Policy on Orphan-Drug Exclusivity; Clarification, 79 Fed. Reg. 76888 (Dec. 23, 2014) (limiting the judicial opinion construing "clinical[] superior[ity]" to the product at issue in that case (Gralise®, gabapentin) only in 2014); Depomed, Inc. v. U.S. Dep't of Health & Hum. Servs., 66 F. Supp. 3d 217, 225 (D.D.C. 2014); *see also* Rachael E. Hunt, *Industry—3, FDA—0: Will the Agency Finally Throw in the Towel?*, FDA L. BLOG: HYYMAN, PHELPS & MCNAMARA P.C. (Apr. 3, 2020), https://www.thefdalawblog.com/2020/04/industry-3-fda-0-will-the-agency-finally-throw-in-the-towel [https://perma.cc/58ZU-VNN4]; Kurt R. Karst, *Orphan Drugs: The Current Firestorm, a Real Evergreening Issue and a Possible Solution*, HYMAN, PHELPS & MCNAMARA P.C. (Mar. 12, 2017), https://www.thefdalawblog.com/2017/03/orphan-drugs-the-current-firestorm-a-real-evergreening-issue-and-a-possible-solution [https://perma.cc/A8DH-JEMZ]; Phebe Hong, Ameet Sarpatwari & Aaron S. Kesselheim, *Orphan Drug Designation and Exclusivity for "Same Drugs,"* 47 J.L., MED. & ETHICS 347, 348 (2019) ("The court decision thereby created an exclusivity 'loophole' that allowed new orphan-designated formulations of old drugs to automatically be entitled to exclusivity once approved for marketing, with no required showing of clinical superiority.").

191 *See* Depomed, Inc. v. U.S. Dep't of Health & Hum. Servs., 66 F. Supp. 3d 217 (D.D.C. 2014); Eagle Pharms., Inc. v. Azar, No. 16-790, 2018 WL 3838265, at *1–4 (D.D.C. June 8, 2018); Eagle Pharms., Inc. v. Azar, 952 F.3d 323, 325–26, 328–29 (D.C. Cir. 2020).

192 Depomed, Inc. v. U.S. Dep't of Health & Hum. Servs., 66 F. Supp. 3d 217, 230 (D.D.C. 2014) (declining to grant *Chevron* deference due to unambiguous statutory language "employ[ing] the familiar and readily diagrammable formula, 'if x and y, then z'"—if designation and approval, then exclusivity").

disease therapies.[193] Congress changed the law to reflect the FDA's initial policy in 2017 after the 2014 decision, but the 2020 second litigation started before the legislative reversal went into effect.[194] Legislative intervention can be interpreted as validating the FDA's original approach.[195]

In both the 2014 and 2020 ODE challenges, as well as *Catalyst*, the FDA chose nonacquiescence.[196] That is, the Agency complied with the holding for the single product but refused to change internal proceedings to be consistent with the adverse ruling. In September 2024, the U.S. House of Representatives passed the RARE Act to clarify the FDA's longstanding interpretations of the Orphan Drug Act's scope, limiting ODE to the same approved use or indication instead of the same disease or condition.[197]

Collectively, these cases illustrate that courts routinely scrutinized FDA regulatory actions.[198] The *Catalyst* case specifically limited agency

193 Koblitz, *supra* note 163; Clarification of Orphan-Drug Exclusivity Following Catalyst Pharms., Inc. v. Becerra; Notification, 88 Fed. Reg. 4068 (Jan. 24, 2023).

194 CONG. RSCH. SERV., *supra* note 175, at 6.

195 Retaining Access and Restoring Exclusivity (RARE) Act, H.R. 7383, 118th Cong. (2024) (demonstrating that revised legislation is under consideration after *Catalyst* to restore the prior regulatory approach); *see also* Luke Halpern, *Overturning Chevron Deference Could Lead to Confusion, Chaos Across Pharmaceutical Industry*, PHARMACY TIMES (Aug. 21, 2024), https://www.pharmacytimes.com/view/overturning-chevron-deference-could-lead-to-confusion-chaos-across-pharmaceutical-industry [https://perma.cc/PXZ8-ZB9J] ("The FDA has a unique relationship with Congress which will serve it well in creating rules and regulations without ambiguities." (quoting Interview by Pharmacy Times with Ron Lanton III, Partner, Lanton Law PLLC (July 31, 2024)).

196 ROGERS, *supra* note 156, at 11–12; *see also* Policy on Orphan-Drug Exclusivity; Clarification, 79 Fed. Reg. 76888 (Dec. 23, 2014); Clarification of Orphan-Drug Exclusivity Following Catalyst Pharms., Inc. v. Becerra; Notification, 88 Fed. Reg. 4086, 4087 (Jan. 24, 2023) ("FDA intends to continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved."). In both prior cases, the FDA complied with the decision for the single drug but made a statement in the Federal Register that it will continue to require the sponsor of a designated drug that is the "same" as a previously approved drug to demonstrate "clinical superiority" before awarding ODE. ROGERS, *supra* note 156, at 11. In *Catalyst*, the FDA once again chose nonacquiescence but also explicitly challenged the court's holding that the relevant statutory provision is unambiguous. *See id.* at 11–13 (citing Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299, 1301, 1306 (11th Cir. 2021)).

197 Press Release, Doris Matsui, U.S. Rep. of Cal, House Passes Matsui's RARE Act: Legislation Included as Part of Rare Disease Package (Sept. 23, 2024), https://matsui.house.gov/media/press-releases/house-passes-matsuis-rare-act [https://perma.cc/G8M8-H5PZ]; Retaining Access and Restoring Exclusivity (RARE) Act, H.R. 7383, 118th Cong. (2024).

198 Karissa Waddick, *Why FDA's Approach to Orphan Drug Exclusivity Is Ripe for More Legal Challenges*, PHARMAVOICE (Feb. 23, 2023), https://www.pharmavoice.com/news/Catalyst-FDA-orphan-drug-exclusivity-legal-challenge/643308 [https://perma.cc/VNU4-ZDN3].

reliance.[199] Some have argued this financially lucrative litigation may herald additional challenges to the FDA's ODE determinations.[200] While the concerns underlying *Catalyst* may involve improper political interference, the case can also be interpreted as limiting the FDA's ability to address science-based policy questions of how to define subpopulations.[201] Instead, the court extended exclusivity to all diseases or conditions granted ODE rather than the specific indication on the label for which the FDA has determined the risks outweigh the benefits based on available data. The science-based policy question is subtle, and some may consider this a case of pure statutory construction, especially in the setting of overt political interference.[202] Even if disputed, this case remains another example of judicial reviews overturning longstanding FDA drug approval policies since 2020.

3. FDA Authority over Unapproved Drug Ingredients

A third example of judicial review overturning longstanding FDA science-based policy choices is the 2023 United States Court of Appeals for the Third Circuit criminal case related to active ingredients sources, *United States v. Vepuri*.[203] Pharmaceutical company KVK Tech manufactured hydroxyzine, a generic prescription drug for anxiety.[204] The company applied for and was awarded three Abbreviated New Drug Applications (ANDAs) in 2006 to market different strengths of hydroxyzine.[205] In those approved applications, KVK Tech told the FDA that it would make pills using an active pharmaceutical ingredient

199 *See, e.g.*, Sigma-Tau Pharms., Inc. v. Schwetz, 288 F.3d 141 (4th Cir. 2002); Depomed, Inc. v. U.S. Dep't of Health & Hum. Servs., 66 F. Supp. 3d 217 (D.D.C. 2014); *see also* James A. Boiani, *FDA Issues Orphan Drug Exclusivity Policy That Could Be a Catalyst for Future Litigation*, EPSTEIN BECKER GREEN (Jan. 31, 2023), https://www.healthlawadvisor.com/fda-issues-orphan-drug-exclusivity-policy-that-could-be-a-catalyst-for-future-litigation [https://perma.cc/MQ5Z-QTWG] ("*Catalyst* therefore remains a basis upon which persons aggrieved by FDA's policy can challenge its application, either prospectively (through threat of litigation during discussions with FDA, or pursuit of a declaratory judgment) or following FDA actions such as approval or orphan drug designation. Regardless, developers will need to account for this uncertainty in their product development strategies.").

200 Waddick, *supra* note 198("[A]ttorneys have suggested it's not a matter of if future litigation against FDA's orphan exclusivity interpretation will pop up—but when and where.").

201 *See supra* notes 178–183.

202 *See* Koblitz, *supra* note 165.

203 74 F.4th 141 (3d Cir. 2023).

204 *Id.* at 143.

205 *Id.* at 143–44.

("API") from a facility in Belgium in 2006.[206] They updated the application in 2008 to include another API facility in Italy.[207]

Despite these two approved API sources, KVK Tech made the drug with API from a facility in Mexico starting in at least in 2011, without informing the FDA or obtaining prior approval of the API site.[208] Preapproval of API sources allows the FDA to determine the purity of a drug ingredient and conduct surveillance inspections to ensure ingredients are made safely in compliance with CGMP regulations.[209] Drugs are made by combining different ingredients and a drug composition would be contaminated if their individual ingredients are contaminated.

In the criminal case, the Department of Justice (DOJ) alleged that the company leadership filed paperwork with the FDA stating that they were changing the API two weeks after KVK Tech directors made multiple false statements to FDA investigators.[210] The DOJ also alleged that about 368,000 bottles were distributed to customers before the FDA discovered the unauthorized substitution in 2013 and blocked the next shipment of the API from Mexico.[211] The company and its leaders were

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206 *Id.*

207 *Id.* at 144.

208 *Id.*

209 CTR FOR BIOLOGICS EVALUATION & RSCH. & CTR. FOR DRUG EVALUATION & RSCH., FDA, U.S. DEP'T OF HEALTH & HUM. SERVS., Q7A GOOD MANUFACTURING PRACTICE GUIDANCE FOR ACTIVE PHARMACEUTICAL INGREDIENTS: GUIDANCE FOR INDUSTRY 5 (2001) ("The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related activities should be defined and documented.").

210 *Vepuri*, 74 F.4th at 144.

211 *Id.*; *see also* Press Release, U.S. Atty's Off., E.D. Pa., Bucks County Drug Manufacturer and Two Executives Charged with Conspiracy to Defraud the FDA (June 11, 2021), https://www.justice.gov/usao-edpa/pr/bucks-county-drug-manufacturer-and-two-executives-charged-conspiracy-defraud-fda [https://perma.cc/TVC3-6PBW] ("The cGMP violations were so severe that the FDA issued an import alert for all DRL Mexico API from July 2011 through July 2012. Nonetheless, from 2011 through 2013, KVK-TECH is charged with having knowingly distributed more than 383,000 bottles of the unapproved Hydroxyzine without the FDA's knowledge or approval."); Warning Letter No. 608236 from Diana Amador-Toro, Prog. Div. Dir./Dist. Dir., FDA, to Anthony Tabasso, Pres. & CEO of KVK Tech, Inc., Regarding Violations of CGMP Regulations for Finished Pharmaceuticals (Oct. 8, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/kvk-tech-inc-608236-10082020 [https://perma.cc/RH5A-4UTY]; Warning Letter No. 592387 from Diana Amador-Toro, Prog. Div. Dir./Dist. Dir., FDA, to Anthony P. Tobasso, Pres. & CEO of KVK Tech, Inc., Summarizing Significant Violations of CGMP Regulations for Finished Pharmaceuticals (Feb. 11, 2020), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/kvk-tech-inc-592387-02112020 [https://perma.cc/LR2R-LJCF] (detailing that the FDA investigated the facility in Mexico and found multiple serious CGMP violations which caused the FDA to place an important alert requiring detention of all API products shipped to the United States between 2010 and 2012).

indicted on June 10, 2021, for two charges including "introducing or delivering for introduction 'unapproved new drugs' in violation of 21 U.S.C. §§ 331(d) and 355(a)."[212] The District Court for the Eastern District of Pennsylvania dismissed the portion of the indictment related to violations of §§ 331(d) and 355(a), and the Third Circuit agreed based on its interpretation of the statutory term "new drug."[213]

Specifically, the DOJ had argued that a compound manufactured with an unapproved API means the final product is a "new drug" that required approval prior to sales, but the district court and Third Circuit disagreed.[214] Both held that the API from Mexico had the "same" chemical composition as the API from the approved places, and therefore matched the ANDA application, regardless of inspection and compliance with manufacturing requirements.[215]

Engaging in a textualist analysis, the Third Circuit reasoned that the substituted API drugs were not different "[b]ecause the Hydroxyzine at issue has the same composition and labeling as the Hydroxyzine for which an approval of an ANDA is effective."[216] Instead, the court held that the government could not rely "upon the premise that the two drugs are different" since the labels matched.[217] The Third Circuit's strict textualist analysis also did not consider whether the FDA's approach was entitled to deference or how the case would impact industry reliance on the prior

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212 *Vepuri*, 74 F.4th at 145; *see also* Press Release, *supra* note 211 (quoting then Acting U.S. Attorney Damian Williams explaining that "[w]hen companies attempt to game the system to avoid these regulations and increase their profits, the ramifications are potentially catastrophic"); 21 U.S.C. § 355(a) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) [concerning NDAs] or (j) [concerning ANDAs] is effective with respect to such drug.").

213 *Vepuri*, No. 21-132, 2022 WL 541772, at *3, *7 (E.D. Pa. Feb. 23, 2022), *aff'd and remanded*, 74 F.4th 141, 143 (3d Cir. 2023).

214 *Vepuri*, 74 F.4th at 146, 149; Press Release, *supra* note 211 ("The Indictment highlights [that] . . . DRL Mexico was not an FDA-approved source. To the contrary, as alleged, the defendants knew that DRL Mexico's API was considered adulterated by the FDA due to significant violations of good manufacturing practices (cGMP) at DRL Mexico's manufacturing plant.").

215 *Vepuri*, 2022 WL 541772; *Vepuri*, 74 F.4th at 150; *see also* Michael Tanenbaum, *Bucks County Drug Manufacturer, Execs Charged with Conspiracy to Defraud FDA*, PHILLY VOICE (June 11, 2021), https://www.phillyvoice.com/bucks-county-kvk-tech-fda-fraud-vepuri-panchal-anxiety-drugs-newtown [https://perma.cc/3ARN-XBMA] ("The Mexican lab's violations were so severe that the FDA issued an import alert for its products from 2011 through 2013.").

216 *Vepuri*, 74 F.4th at 150 (footnote omitted).

217 *Id.* at 150; *see also id.* at 146 ("But the relevant statutory provisions do not prohibit the introduction of 'unapproved' new drugs. They instead prohibit the introduction of any 'new drug, unless an approval of an [NDA or ANDA] is effective with respect to such drug.' We have held that the provision 'requires only that a new drug approval be *in effect* before a new drug is marketed . . . .'" (alteration in original) (citations omitted) (first quoting 21 U.S.C. § 355(a); then quoting United States v. Kaybel, Inc., 430 F.2d 1346, 1347 (3d Cir. 1970))).

approach, suggesting instead that a legislative solution was needed to return to the prior status quo.[218]

Underlying this approach is the presumption that the API product was actually what it claimed to be; put another way, the textual analysis requires that the uninspected substance was without contamination.[219] That presumption, however, may not be true. The Third Circuit and district court did not consider that the API was from a facility with known manufacturing issues,[220] or the high prevalence of substandard and falsified APIs around the world.[221] The World Health Organization estimated that 10.5% of medicines worldwide were substandard or falsified in 2017.[222] The FDA issued multiple warning letters to the unauthorized API facility when later inspected as well as to KVK Tech over multiple serious manufacturing issues.[223] Ultimately, how many

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218 *See Vepuri*, 74 F.4th at 149 n.7 ("[T]o the extent that our decision has identified a gap in the FDA's ability to regulate the drugs that are introduced into interstate commerce, Congress has the tools necessary to fill it.").

219 Logically, if the API was contaminated, the composition referenced in 21 U.S.C. § 355(b)(1)(A) could not be the same.

220 *See generally Vepuri*, 74 F.4th 145. The purity of the alleged misbranded product was unknown, and the issue was not raised by either party. Logically, if the previously identified issues with manufacturing impacted this API, the purity of that API would be compromised, making the final drug product not identical to the label.

221 *See* Sachiko Ozawa, Hui-Han Chen, Yi-Fang (Ashley) Lee, Colleen R. Higgins & Tatenda T. Yemeke, *Characterizing Medicine Quality by Active Pharmaceutical Ingredient Levels: A Systematic Review and Meta-Analysis Across Low- and Middle-Income Countries*, 106 AM. J. TROPICAL MED. & HYGIENE 1778, 1787 (2022) ("Our findings of 12.4% overall prevalence of substandard and falsified medicines are consistent with previous analyses and WHO reports. Our analysis goes further by finding that nearly one in seven poor-quality medicine samples were likely to be falsified based on reported API amounts of < 50%, whereas the remaining six in seven samples were likely to be substandard. Separating out substandard from falsified medicines is essential to better inform tailored interventions to ensure medicine quality throughout the supply chain." (footnotes omitted)).

222 WORLD HEALTH ORG., A STUDY ON THE PUBLIC HEALTH AND SOCIOECONOMIC IMPACT OF SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS 7 (2017), https://iris.who.int/bitstream/handle/10665/331690/9789241513432-eng.pdf [https://perma.cc/HED7-TGLS]; *see also* Press Release, World Health Org., Seventieth World Health Assembly Update (May 29, 2017), https://www.who.int/news/item/29-05-2017-seventieth-world-health-assembly-update-29-may-2017 [https://perma.cc/29P9-PN6D] (defining "substandard" medicines officially as "authorized . . . [medical products that] fail to meet either . . . [their] quality standards or specifications . . . or . . . both" due to poor manufacturing, shipping or storage conditions, or when the drug is sold beyond the expiration date, and defining falsified medicines as "medical products [that] deliberately or fraudulently misrepresent their identity, composition or source").

223 Specifically, an opioid pill was on the packaging line for a beta-blocker drug in 2023; the company failed to meet testing standards for weight loss medication in 2020; foreign particles were found in an ADHD drug batch; and the cleaning protocols were not followed in 2020. While having incorrect pills in a prescription bottle is always dangerous, this combination is particularly problematic as the two pills appear nearly identical. Beta-blockers slow the heart rate, which could

inspections are needed to ensure ingredients are actually pure and safe as claimed is a science-based policy question. Global regulatory agencies and manufacturers have different approaches to ensuring drug quality, but this judicial opinion erodes FDA discretion to enforce its decisions through investigations and criminal sanctions by limiting consequences for evading FDA manufacturing inspections.[224]

In addition to enforcement through litigation, there is a question of deterrence. There is a longstanding debate amongst scholars if future transgressions by regulated entities can be deterred without strict criminal liability.[225] Prior cases applied strict criminal liability for deviations from FDA-approved applications, including two Supreme Court cases from 1943 and 1975, and 2006 and 2007 opinions in other circuits.[226] Commentators have declared that *United States v. Vepuri* "has the potential to undermine the legal framework for FDA drug approvals" by shielding copycat products without prior approval from enforcement actions.[227] That is, implying investigations into an API supplier are not necessary to demonstrate "sameness" for criminal charges undermines ongoing data collection from inspections to ensure drugs are safe.

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become deadly if consumed with opioids. Zoey Becker, *Drugmaker KVK Tech Pulls Batch of Beta Blockers After Finding Opioid Tablet on Packaging Line*, FIERCE PHARMA (Oct. 5, 2023, 1:59 PM), https://www.fiercepharma.com/manufacturing/kvk-tech-pulls-batch-beta-blockers-after-finding-opioid-tablet-packaging-line [https://web.archive.org/web/20240825183852/https://www.fiercepharma.com/web/20240825183852/https://www.fiercepharma.com/manufacturing/kvk-tech-pulls-batch-beta-blockers-after-finding-opioid-tablet-packaging-line].

224 Donald Ashley, Kalah Auchincloss & Elizabeth Oestreich, *Implications of Recent Third Circuit Court of Appeals Decision for FDA Drug Approval Framework*, 78 FOOD & DRUG L.J. 257, 262 (2023) (declaring that it was "troubling, relying on the Third Circuit decision, [that] companies could entirely forego submitting an application to FDA, claim that they are manufacturing drugs with chemical compositions and labeling identical to approved NDA and ANDA drug products, and argue that they were *not* introducing unapproved new drugs into interstate commerce in violation of 21 U.S.C. § 355(a)").

225 *See* Patrick O'Leary, *Credible Deterrence: FDA and the Park Doctrine in the 21st Century*, 68 FOOD & DRUG L.J. 137, 145–46 (2013) ("FDA has at times made a case for the importance of using criminal law, emphasizing that the threat of prosecution can be a uniquely effective deterrent."); *see also* Patrick O'Leary, *Recalibrating Enforcement in the Biomedical Industry: Deterrence and the Primacy of Protecting the Public Health*, *in* FDA IN THE TWENTY-FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 162 (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015).

226 United States v. Dotterweich, 320 U.S. 277, 280–82 (1943); United States v. Park, 421 U.S. 658, 670–71 (1975); United States v. Genendo Pharm., N.V., 485 F.3d 958, 962 (7th Cir. 2007) (holding that deviations from FDA-approved application, including site of packaging, labeling and expiration date, required a new drug application prior to interstate transport); *In re* Canadian Imp. Antitrust Litig., 470 F.3d 785, 788–89 (8th Cir. 2006) (siding with the FDA, which "repeatedly has expressed the view that virtually all importation of drugs into the United States by individual consumers violates the FFDCA").

227 Ashley et al., *supra* note 224, at 257.

Altogether, the Court overturned the FDA's decades-long policy choice favoring inspection and certainty of drug safety despite the benefits of deterrence from strict liability, longstanding precedent, and industry reliance. Unlike in the mifepristone litigation, the Court did not directly consider the science-based policy question of how much testing or inspection should be required and what level of contamination should be considered de minimis.

4. Revised Remedies

Along with reconsiderations of science-based policy questions directly or by assumption, remedies have shifted towards limiting the FDA's regulatory flexibility.[228] There is much debate in administrative law if courts should invalidate entire rules or sever offending provisions when agencies exceed legal authority.[229] The D.C. District Court and D.C. Circuit answered a similar question differently in 1997 and 2021.[230] The issue in both cases was how to classify contrast agents[231] that meet the statutory definitions of both "drug" and "device." There is overlap in the definitions under the FDCA and the FDA has issued final guidance in 2017 to address the issue, focusing on how the product would be expected to achieve its primary intended purpose.[232] The guidance acknowledges

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228 *See infra* notes 237–263.

229 *See* Charles W. Tyler & E. Donald Elliott, *Administrative Severability Clauses*, 124 YALE L.J. 2286, 2298 (2015); Nicholas Bagley, *Remedial Restraint in Administrative Law*, 117 COLUM. L. REV. 253, 256 (2017).

230 Bracco Diagnostics, Inc. v. Shalala, 963 F. Supp. 20, 31 (D.D.C. 1997); Genus Med. Techs. LLC v. FDA, 994 F.3d 631, 632–33 (D.C. Cir. 2021).

231 Contrast agents are a class of substances used to improve visualization of various bodily structures when a provider is obtaining a medical imaging study, such as an X-ray, CT, ultrasound, or MRI. *See generally* AM. COLL. OF RADIOLOGY COMM. ON DRUGS & CONTRAST MEDIA, AM. COLL. RADIOLOGY, ACR MANUAL ON CONTRAST MEDIA (2024), https://edge.sitecorecloud.io/americancoldf5f-acrorgf92a-productioncb02-3650/media/ACR/Files/Clinical/Contrast-Manual/ACR-Manual-on-Contrast-Media.pdf [https://perma.cc/BFM4-CU86].

232 Both drugs and devices are "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease . . . ." 21 U.S.C. § 321(h)(1)(B). The FDCA defines "drug[s]" to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man . . . ." § 321(g)(1)(B). If the article is a "drug" within the general definition of the FDCA, the FDA can subject it to premarket clearance regulations, while device regulations are subject to less stringent requirements. § 321(g)(1), (h)(1). The Center for Drug Evaluation and Research (CDER) has primary jurisdiction over drugs, while the Center for Devices and Radiological Health (CDRH) has primary jurisdiction over medical devices. *See* 21 C.F.R. § 3.5 (2023); FDA, Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (Oct. 31, 1991), https://www.fda.gov/combination-products/jurisdictional-information/intercenter-agreement-between-center-drug-

determining the primary intended purpose of a product requires the FDA to "use its best scientific judgment."[233]

What qualifies as a drug or device has been litigated multiple times for multiple decades.[234] Deciding if a product is a drug or device is a threshold question with profound financial and public health implications[235] as drugs are subject to more complex, costly testing and approval standards.[236] Contrast agents, in particular, pose unique classification challenges as they are ingested to facilitate visualization of other conditions and assist in diagnoses rather than to treat conditions.[237] Patients typically drink or inject the contrast agent and, theoretically, the

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evaluation-and-research-and-center-devices-and [https://perma.cc/T4QR-2YNB]; OFF. OF THE COMM'R, OFF. OF SPECIAL MED. PRODS, & OFF. OF COMBINATION PRODS., FDA, U.S. DEP'T OF HEALTH & HUMAN SERVS., CLASSIFICATION OF PRODUCT AS DRUGS AND DEVICES & ADDITIONAL PRODUCT CLASSIFICATION ISSUES: GUIDANCE FOR INDUSTRY AND FDA STAFF: FINAL GUIDANCE 6 (2017), https://www.fda.gov/media/80384/download [https://web.archive.org/web/20240929012748/https://www.fda.gov/media/80384/download]. Device regulation has its own requirements for marketing authorization depending on the risk they pose to the public. *Overview of Device Regulation*, FDA (Jan. 31, 2024), https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/overview-device-regulation [https://perma.cc/8QUR-PBKM]. Products are classified in one of three classes based on the risk of illness or injury posed, with different requirements for authorization. To introduce a new Class III device into the market, the manufacturer must provide the FDA with "reasonable assurance" that the device is both safe and effective. 21 U.S.C. § 360e(d)(2)(A)–(B); Juan Espinoza, Payal Shah, Gautam Nagendra, Yaniv Ben-Cohen & Frances Richmond, *Pediatric Medical Device Development and Regulation: Current State, Barriers, and Opportunities*, 149 PEDIATRICS, May 2022, at 1, 8. The FDCA does not apply to articles that fall under either definition.

233 OFF. OF THE COMM'R, OFF. OF SPECIAL MED. PRODS, & OFF. OF COMBINATION PRODS, *supra* note 232, at 6.

234 *See, e.g.*, United States v. Bacto-Unidisk, 394 U.S. 784, 799 (1969) ("Despite the obvious areas of overlap in definition, we are not entirely without guidance in determining the propriety of the Secretary's decision below, given the overall goals of the Act and its legislative history.").

235 Zettler et al., *supra* note 46, at 2409 (finding that it would have cost $60,000 to regulate the product as a device but nearly $500,000 to secure approval for the product as a drug); *see also infra* Appendix I (illustrating that there has been significant litigation over the classification of products including cosmetics, supplements, and food additives); *Is It a Cosmetic, a Drug, or Both? (Or Is It Soap?)*, FDA (Sept. 11, 2024), https://www.fda.gov/cosmetics/cosmetics-laws-regulations/it-cosmetic-drug-or-both-or-it-soap [https://perma.cc/T5HG-7GUA]; Theodora McCormick, *Food and Supplement Class Action Suits That Rely on Alleged Regulatory Violations*, UPDATE MAG.: FOOD & DRUG L. INST., Summer 2021, at 12–13.

236 AMANDA K. SARATA, CONG. RSCH. SERV., R47374, FDA REGULATION OF MEDICAL DEVICES 1, 3 (2023); *see also* Aylin Sertkaya, Rebecca DeVries, Amber Jessup & Trinidad Beleche, *Estimated Cost of Developing a Therapeutic Complex Medical Device in the US*, 5 JAMA NETWORK OPEN, Sept. 2022, at 8; MEDICARE PAYMENT ADVISORY COMM'N, *An Overview of the Medical Device Industry*, *in* JUNE 2017 REPORT TO THE CONGRESS: MEDICARE AND THE HEALTH CARE DELIVERY SYSTEM 207–08 (2017), https://www.medpac.gov/wp-content/uploads/import_data/scrape_files/docs/default-source/reports/jun17_ch7.pdf [https://perma.cc/PQX7-Z8HV].

237 *See generally* Reabal Najjar, *Clinical Applications, Safety Profiles, and Future Developments of Contrast Agents in Modern Radiology: A Comprehensive Review*, 2 IRADIOLOGY 430 (2024); SARATA, *supra* note 234.

substance does not cause any systemic effects as it is not absorbed into the body if it works as intended.[238] Contrast agents were generally regulated as drugs since the first iodine-based contrast agents were approved in the early 1950s and uniformly regulated as drugs after the 1997 *Bracco Diagnostics, Inc. v. Shalala* litigation.[239] *Bracco* addressed contrast products that were regulated using different standards and the D.C. Circuit held the APA required that

> the FDA either must provide a rational basis for treating . . . [one] agent as a device while simultaneously regulating essentially identical agents as drugs, or it must treat all four of these similar products in the same way. A failure to do one of these two things is arbitrary and capricious agency action . . . .[240]

The *Bracco* court enjoined the FDA from acting on approval of any of the other products "[u]ntil uniform rules that will govern all are established."[241] Because of this case and other court decisions in the late 1960s that upheld the FDA's authority to regulate some medical devices as drugs due to the overlapping definitions,[242] the FDA adopted a uniform regulatory system for contrast agents as drugs.[243]

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238 *See generally* Najjar, *supra* note 237.

239 963 F. Supp. 20, 28 (D.D.C. 1997); James A. Boiani, *Deconstructing* Genus Medical Technologies, LLC v. FDA*: A Misunderstood Court Decision*, EPSTEIN, BECKER & GREEN (Apr. 1, 2022), https://www.ebglaw.com/insights/publications/deconstructing-genus-medical-technologies-llc-v-fda-a-misunderstood-court-decision-continues-to-sow-confusion-and-may-prompt-congressional-action [https://perma.cc/3AAP-VYFT]; Nassim Parvizi & Kent Woods, *Regulation of Medicines and Medical Devices: Contrasts and Similarities*, 14 CLINICAL MED. 6 (2014).

240 *Bracco Diagnostics*, 963 F. Supp. at 28.

241 *Id.* at 31.

242 *See* SARATA, *supra* note 236, at 34.

243 Genus Medical Technologies LLC Versus Food and Drug Administration; Request for Information and Comments, 86 Fed. Reg. 43553, 43553–54 (Aug. 9, 2021) ("Although FDA has generally regulated products that meet the *device* definition under the device authorities of the [FDCA], we have regulated as drugs certain types of products that meet the *drug* definition and may also meet the *device* definition. FDA's classification of all contrast imaging agents, including barium sulfate contrast agents, as drugs allowed us to regulate them consistently under the same authority in the Center for Drug Evaluation and Research (CDER) and was intended to be consistent with a previous court decision, *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997)."). *See generally* CTR. FOR BIOLOGICS EVALUATION & RSCH. & CTR. FOR DRUG EVALUATION & RSCH., FDA, GUIDANCE FOR INDUSTRY DEVELOPING MEDICAL IMAGING DRUG AND BIOLOGICAL PRODUCTS PART 2: CLINICAL INDICATIONS (2004), https://www.fda.gov/media/71226/download [https://perma.cc/7U5Z-XFQN]; CTR. FOR BIOLOGICS EVALUATION & RSCH. & CTR. FOR DRUG EVALUATION & RSCH., GUIDANCE FOR INDUSTRY: NEW CONTRAST IMAGING INDICATION CONSIDERATIONS FOR DEVICES AND APPROVED DRUG AND BIOLOGICAL PRODUCTS (2009), https://www.fda.gov/media/77679/download [https://perma.cc/6GEA-DXF5].

The D.C. District Court again considered the proper classification of Diphoterine® Skin Wash ("DSW") as a drug or device in 2014.[244] DSW is a combination product manufactured by Prevor that minimizes the impact of chemical burns by neutralizing acids and bases.[245] Litigation over the classification of DSW as a drug or device took over five years, but the court ultimately found the relevant statute to be unambiguous and did not grant *Chevron* deference to the FDA's initial determination that the product was a drug.[246] Prevor "ask[ed] the [c]ourt (1) to reject FDA's expert findings, and (2) to make a classification directly contrary to those findings" and the court held "[t]hat second step [was] not one this [c]ourt [was] willing to take."[247] While the court remanded the issue to the Agency, it refused to order the FDA to regulate DSW as a device.[248]

Yet seven years later, the D.C. District Court and D.C. Circuit were both willing to take that step despite a twenty-five-year precedent of the FDA regulating all contrast agents as drugs.[249] The manufacturer of a barium sulfate contrast agent tried unsuccessfully to convince the FDA to regulate its product differently.[250] Genus Medical Technologies responded to an FDA warning letter about distributing the product as an authorized drug by challenging the classification.[251] Both courts disagreed with the FDA's longstanding interpretations,[252] holding the FDCA language was unambiguous and foreclosing the FDA's interpretation such that *Chevron* deference was inappropriate.[253] In limiting the FDA from regulating a product as a drug when it also qualified as a device,[254] the appellate judges specifically criticized the FDA's assertion that they could classify any device as a drug.[255]

The aftermath of *Genus* was swift. The FDA responded with a policy shift that some approved products were expected to be "transition[ed]

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244 Prevor v. FDA, 67 F. Supp. 3d 125 (D.D.C. 2014).

245 *Id.* at 128–29.

246 *Id.* at 128, 136.

247 *Id.* at 140.

248 *Id.* at 139 ("Prevor argues against a second remand and asks the Court to order FDA to regulate DSW as a device. Such relief is not warranted.").

249 Genus Medical Technologies LLC Versus Food and Drug Administration; Request for Information and Comments, 86 Fed. Reg. at 43554.

250 Genus Med. Techs., LLC v. FDA, 427 F. Supp. 3d 74, 87 (D.D.C. 2019), *aff'd*, 994 F.3d 631 (D.C. Cir. 2021).

251 *Id.* at 79.

252 *Id.* at 87; *Genus Med. Techs.*, 994 F.3d at 644.

253 *Genus Med. Techs.*, 994 F.3d at 632, 643.

254 *See generally* Yifan Wang, *Regulating Contrast Agents as Drugs: What's Next for FDA?*, UPDATE MAG., Summer 2023, at 32.

255 *Genus Med. Techs.*, 427 F. Supp. 3d at 83–84.

from drug status to device status" as a result of the *Genus* decision.[256] Scholars worried that inconsistent regulations would cause confusion, a wave of litigation from financially impacted parties, and poor patient outcomes.[257] With pressure from regulated entities, Congress passed legislation in December 2022 restoring the FDA's longstanding approach.[258]

The opinion not only overturned longstanding precedent and limited FDA authority, but it also made assumptions on science-based policy questions. As drugs and devices are regulated differently, the classification necessarily implicates how much testing is required to be reasonably sure a product is safe before public use. How much data is enough to make sure a product is safe involves science-based policy judgement and reasonable minds can disagree. In *Genus*, the court limited the FDA's authority to make this determination.[259]

In addition, the evolution of remedies from the same court over twenty-five years is noteworthy. All three cases overturned the Agency's interpretation of the drug and device definitions in the FDCA, but the first calls on the Agency to explain its classification,[260] the second remands the action back to the Agency for further evaluation,[261] and the third narrows the Agency's discretion to classify products.[262] It is particularly striking as the D.C. Circuit had previously "developed a practice of remanding an agency action without vacating it when the defects in the agency's rule are modest and invalidation would be disruptive."[263] Moreover, the holding sits in contrast to statements made by Justice Amy Coney Barrett during oral argument for the *Loper Bright*

256 Genus Medical Technologies LLC Versus Food and Drug Administration; Request for Information and Comments, 86 Fed. Reg. 43553, 43553 (Aug. 9, 2021).

257 *See* Zettler et al., *supra* note 46, at 2410; Douglas B. Farquhar & Sara W. Koblitz, *Proposed Legislation Would Reverse Genus Decisions*, HYMAN, PHELPS & MCNAMARA P.C. (Mar. 30, 2022), https://www.thefdalawblog.com/2022/03/proposed-legislation-would-reverse-genus-decisions [https://perma.cc/845B-J4G5]; Wang, *supra* note 254; Celine Castronuovo, *Drug or Device? Manufacturers See Burden in FDA Reclassifying*, BLOOMBERG L. (Jan. 11, 2022, 5:30 AM), https://news.bloomberglaw.com/health-law-and-business/drug-or-device-manufacturers-see-burden-in-fda-reclassifying [https://perma.cc/6ET3-DF4V] ("Patients could face disruptions in medical treatment if the FDA moves ahead with plans to regulate some products as devices instead of drugs, according to manufacturers who decry the shift as onerous and time-consuming.").

258 Consolidated Appropriations Act, Pub. L. No. 117-328, § 3621, 136 Stat. 4459, 5877 (2022).

259 *See* SARATA, *supra* note 236, at 34.

260 Bracco Diagnostics v. Shalala, 963 F. Supp. 20, 31 (D.D.C. 1997).

261 Prevor v. FDA, 67 F. Supp. 3d 125, 131 (D.D.C. 2014).

262 Genus Med. Techs., LLC v. FDA, 994 F.3d 631, 632–33 (D.C. Cir. 2021).

263 Bagley, *supra* note 229, at 256.

case.[264] Justice Barrett suggested the product category differences between a drug or a supplement would be a matter of statutory interpretation, but "which category any one thing fell in might be a question of policy for the [FDA]."[265] In *Genus*, though, the court weighed in on that policy question.[266]

Justice Barrett's comment speaks to the subtle shift occurring in the cases described here and further described in Appendix I. These judicial opinions appear to be readdressing science-based policy decisions rather than applying the historic broad form deference to FDA decisions discussed in Section I.A.3.[267] Therefore, courts are forced to grapple with the inherent difficulty in separating policy choices filling in gaps in the law from interpretations of the law itself and scientific uncertainty described in Section I.A.2. While differing in their substance and approach, three trends are clear: since 2019, courts have narrowed FDA authority, overturned decades long precedents despite *Chevron* deference in some cases,[268] and directly, indirectly, or implicitly questioned normative science-based policy choices.[269] The outcomes in these cases since 2019 are atypical compared to the rest of the decade and, taken together, may signal either an unusual time-limited cluster of cases or, more concerningly, an early emerging trend.

C. *Limitations of the Evaluation*

Conclusions of an emerging trend must be evaluated with caution and considered in light of data set limitations, including the relatively small number of cases overall and after 2019. A small sample size limits the ability to detect trends and may overstate the impact of a limited set

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264 Transcript of Oral Argument at 31, Relentless, Inc. v. Dep't of Com., 144 S. Ct. 325 (2024) (No. 22-1219) ("But whether the particular cholesterol-reducing drug fell . . . in one category or the other, I mean, you know . . . presumably, that depends on how does this function? What is the mechanism by which it decreases cholesterol?").

265 *Id.*

266 *See Genus Med. Techs.*, 994 F.3d 631; Wang, *supra* note 254.

267 *See infra* Appendix I.

268 The series of cases presented may raise questions on the predicted impact of *Loper Bright* on FDA regulation. Long et al., *supra* note 113 ("If *Chevron* deference is eliminated, Congress and the courts, rather than subject matter experts, would be left to outline the intricacies of laws for which they may not have expertise, perhaps reducing the role of facts and science in policymaking."); Sue Sutter, *Deference No More: More Suits Against US FDA Coming After High Court Tosses Chevron Doctrine?*, CITELINE: PINK SHEET (June 28, 2024), https://pink.citeline.com/PS154916/Deference-No-More-More-Suits-Against-US-FDA-Coming-After-High-Court-Tosses-Chevron-Doctrine [https://perma.cc/9P8C-3WVB] ("[T]he absence of *Chevron* deference also could lead to court-by-court differences in rulings on similar lawsuits against the agency.").

269 *See supra* Sections I.B.1–4.

of cases.[270] With a small sample and weak statistical correlation, further observations are warranted. Further, the win/loss determination could be misleading if understood alone as each case has different theories and circumstances that may not be captured and it only reflects the last case in related litigation. Outcomes are skewed by litigation choices, as the DOJ decides litigation strategy including when to appeal, settle, or litigate.[271] The absence of cases may reflect significant litigation strategy or settlements.

The case list can also be skewed by who brings cases in the first place. Not only are cases limited by administrative law principles of standing and final agency actions (which discourage challenges to unapproved products and direct challenges to a competitor product outside awarding exclusivities), the high cost of litigation can be limiting.[272] High cost of entry may limit access to courtrooms to well-funded actors who can afford the economic, political, and social costs.[273] Finally, the shift may reflect growing skepticism of agencies in general.[274] Understanding who brings a case and the impact of deference is further analyzed in Sections II.A and III.A respectively.

Further, the data set may be incomplete. Cases where no opinion was issued or listed in the databases used are not represented in Appendix I but can nevertheless be influential. Second, while the search was repeated and contained with internal checks, as in line with other published data, not all cases are listed in the search engines used and the Boolean search used may not have captured all the cases where the U.S. Department of Health and Human Services (HHS) or the FDA was a litigant.

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270 Ying Cao, Ronald C. Chen & Aaron J. Katz, *Why Is a Small Sample Size Not Enough?*, 29 ONCOLOGIST 761, 762 (2024) ("With small sample sizes (([e.g.], 10 patients in each treatment group), there can be random variation in the results; thus, multiple studies of small sample sizes might provide different/opposite findings.").

271 *See, e.g.*, C. Joseph Ross Daval, *Litigating Authority for the FDA*, 100 WASH. U. L. REV. 175 (2022).

272 *See generally* Bruce S. Manheim Jr., *A Primer: Recent Developments and Strategies in Petitions and Lawsuits Challenging FDA Approval of Generic Drug Products Under the Administrative Procedure Act*, *in* FOOD AND DRUG LITIGATION STRATEGIES: LEADING LAWYERS ON BUILDING STRONG DEFENSES AND ADAPTING TO EVOLVING FDA REGULATIONS 145 (2013).

273 *See also id.* at 11.

274 *See* Section I.A.1; *see also* Consumers' Rsch. v. Consumer Prod. Safety Comm'n, 91 F.4th 342, 345 (5th Cir. 2024) (addressing presidential powers in an unrelated case: "The Supreme Court in recent years has taken a keen interest in administrative law—the law that governs the government—reexamining foundational notions of federal regulatory power.").

Of note, the overall litigation records sit in stark contrast to the seven cases (thirteen opinions) related to pregnancy drugs[275] and two related to COVID-19.[276] In the pregnancy-related litigation, courts sided with the Agency only twice,[277] although some related cases were reversed on standing.[278] These outcomes in judicial review of mifepristone compared to other FDA litigations suggest a different pattern, consistent with Professor Greer Donley's insightful analysis of mifepristone exceptionalism.[279]

Although conclusions should rightfully be limited, the data shows that independent of abortion and COVID-19 cases, multiple longstanding FDA policies have been overturned between 2019 and 2023.[280] Part II seeks to further define the trend and Part III seeks to understand why these outcomes may be occurring, drawing a through line between public discourse on science-based policy choices related to multiple concurrent drug controversies and the outcomes of the judicial opinions previously described in Part I.

II. UNDERSTANDING THE LEGAL LANSCAPE OF CHALLENGES TO FDA DRUG APPROVALS

The ongoing shift in successful litigation challenges to FDA drug approval decisions and deference to the FDA described in Part I can impact patient's access to safe and effective drugs if they become more frequent after *Loper Bright*.[281] Therefore, this trend is worth further consideration to understand the optimal role of judicial review in FDA

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275 Geneva Coll. v. Sebelius, 941 F. Supp. 2d 672 (W.D. Pa. 2013); Tummino v. Hamburg, 936 F. Supp. 2d 198 (E.D.N.Y. 2013); Gomperts v. Azar, No. 19-cv-345, 2020 U.S. Dist. LEXIS 124310 (D. Idaho July 13, 2020); FDA v. Am. Coll. of Obstetricians & Gynecologists, 141 S. Ct. 578 (2021) (mem.), Washington v. FDA, 668 F. Supp. 3d 1125, 1133 (E.D. Wash. 2023); All. for Hippocratic Med. v. FDA, 78 F.4th 210 (5th Cir. 2023); Whole Woman's Health All. v. FDA, No. 23-cv-19, 2023 WL 5401885 (W.D. Va. Aug. 21, 2023).; Am. Coll. of Obstetricians & Gynecologists v. FDA, No. 20-1320, 2020 U.S. Dist. LEXIS 247670 (D. Md. Aug. 19, 2020).

276 Apter v. U.S. Dept' of Health & Hum. Servs., 644 F. Supp. 3d 361 (S.D. Tex. 2022); Child.'s Health Def. v. FDA, No. 21-6203, 2022 WL 2704554 (6th Cir. July 12, 2022); *see also* Jonathan Berman & Colleen Heisey, *FDA's Recent Litigation Records Are Strong, but Imperfect*, LAW360 (Dec. 14, 2023), https://www.jonesday.com/en/insights/2023/12/fdas-recent-litigation-records-are-strong-but-imperfect-law360 [https://perma.cc/V5WL-JZ3U] ("[T]he FDA's advantages can sometimes be overcome, particularly where the limelight shines brightest. The FDA was thus markedly less successful in cases involving mifepristone or treatments for COVID-19.").

277 *Whole Woman's Health All.*, 2023 WL 5401885; *Gomperts*, 2020 U.S. Dist. LEXIS 124310.

278 *See, e.g.*, *All. for Hippocratic Med.*, 78 F.4th at 246, 253; *Washington*, 668 F. Supp. 3d at 1133.

279 *See generally* Donley, *supra* note 139.

280 *See infra* Appendix I.

281 *See supra* Part I; *infra* notes 431–432.

drug regulation. Part II first examines characteristics of the litigants who sued the FDA and then characterizes trends in the sought after outcomes.

A. *Who Sues the FDA?*

Table 1 shows the twenty most profitable pharmaceutical companies in the world brought only eight lawsuits against the FDA between 2013 and 2023, half of which were brought by two generic manufacturers.[282] None of these suits were successful. The FDA won or had a neutral decision in all eight of these cases, the last of which was in 2020.[283] Table 2 shows the same trend in litigation initiated by the ten most profitable generic pharmaceutical companies.[284] In addition to the four cases brought by the two highly profitable generic drug companies, only one other top ten profitable generic drug manufacturer sued the FDA in the last ten years.[285] Courts sided with the FDA in that case as well.[286] These nine cases reflect approximately 15.5% of the fifty-eight cases identified in this study. The case study suggests both highly profitable brand and generic pharmaceutical companies rarely sued the FDA between 2013 and 2023.[287]

There are multiple ways to explain this trend. While the lack of success in litigation and the scarcity of challenges may be connected, the rate of litigation against the FDA particularly amongst profitable companies may be explained by broader dynamics in the pharmaceutical industry.[288] The pharmaceutical industry as a whole has staggering value,

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282 The most profitable pharmaceutical companies are listed annually by Fierce Pharma. *See infra* note 302. Twenty-two companies were listed in the list of the most profitable pharmaceutical companies between 2021 and 2023, demonstrating stability within the list. *Id.* Table 1 lists the year and ranking by profit. Intervenors in lawsuits brought by other entities were excluded. *Infra* Table 1; *infra* Table 2.

283 Astrazeneca Pharms. LP v. Burwell, 197 F. Supp. 3d 53 (D.D.C. 2016); AstraZeneca Pharms. LP v. FDA, 713 F.3d 1134 (D.C. Cir. 2013); Boehringer Ingelheim Pharma GmbH & Co. KG v. FDA, 195 F. Supp. 3d 366 (D.D.C. 2016); Takeda Pharm. U.S.A., Inc. v. Burwell, 691 F. App'x 634 (D.C. Cir. 2016) (per curiam) (mem.); Teva Pharm. Indus. v. Sebelius, No. 14-0786, 2014 U.S. Dist. LEXIS 188256 (D.D.C. May 14, 2014); Teva Pharms. USA, Inc. v. FDA, 514 F. Supp. 3d 66 (D.D.C. 2020); Teva Pharms. USA, Inc. v. Azar, 369 F. Supp. 3d 183 (D.D.C. 2019); Mylan Pharms., Inc. v. FDA, 594 F. App'x 791 (4th Cir. 2014).

284 *See infra* Table 2; Sandoz Inc. v. Becerra, 57 F.4th 272 (D.C. Cir. 2023).

285 *Becerra*, 57 F.4th at 272; *see infra* Table 2.

286 *Becerra*, 57 F.4th at 272.

287 *See infra* Tables 1–2; *infra* Appendix I; Parrillo, *supra* note 10, at 46 ("My search of the period for 2013-2024 turns up no serious challenge to a denial of a new drug approval, no matter the size of the company.").

288 Parrillo, *supra* note 10, at 45 ("The disincentives to challenging [the] FDA's views are formidable; sponsors almost invariably engage the agency on its own terms." (quoting Richard A.

projected to grow to $2.4 trillion by 2029.[289] Mathematicians have demonstrated that large pharmaceutical companies have been more profitable than large companies in other industries.[290] Glaringly, some manufacturers of individual blockbuster drugs are even worth more than the gross domestic product (GDP) of their home nations.[291] FDA approval serves as a gatekeeper that determines whether and when drugs can be sold to make any profit and manufacturers have a financial incentive to maximize profits through time on the market especially with limited competitors.[292] Smaller brand manufacturers with few profitable products are more likely to experience impactful financial losses when one product faces competition, such that "bet the company" litigation against the FDA may be worthwhile, especially as litigation itself may delay generic competition.

This is the absence of the "repeat player effect," which has been frequently cited and analyzed in numerous legal contexts.[293] That effect suggests that repeat players are more likely to help make, comply with,

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Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1781 (1996)).

289 *Analyzing the $1.4 Trillion Global Pharmaceutical Industry 2022*, BUS. WIRE (Nov. 30, 2022, 6:29 AM), https://www.businesswire.com/news/home/20221130005610/en/Analyzing-the-1.4-Trillion-Global-Pharmaceutical-Industry-2022-ResearchAndMarkets.com [https://perma.cc/9FVS-YRXR].

290 Fred D. Ledley, Sarah Shonka McCoy, Gregory Vaughan & Ekaterina Galkina Cleary, *Profitability of Large Pharmaceutical Companies Compared With Other Large Public Companies*, 323 JAMA 834, 835, 838 (2020).

291 Berkeley Lovelace, Jr., *How Viagra Revolutionized the Erectile Dysfunction Market*, CNBC (May 15, 2019, 6:52 AM), https://www.cnbc.com/2019/05/10/how-viagra-revolutionized-the-erectile-dysfunction-market.html [https://perma.cc/9RU6-65M8]; Sanne Wass, Naomi Kresge & Bloomberg, *Novo Nordisk's Market Value of $570 Billion Is Now Bigger Than the Entire Danish Economy—Creating a 'Nokia Risk' for Denmark*, FORTUNE (May 1, 2024, 5:40 AM), https://fortune.com/europe/2024/05/01/novo-nordisk-market-value-570-billion-bigger-than-danish-denmark-economy [https://perma.cc/GG2F-XK33].

292 Taylor Giorno, *Top 5 Largest US Pharma Firms' Net Earnings Topped $81.9 Billion Last Year: Watchdog*, HILL (July 24, 2023, 3:10 PM), https://thehill.com/policy/healthcare/4116604-five-largest-us-pharma-firms-net-earnings-topped-81-9-billion-last-year-watchdog [https://perma.cc/83E7-8EZX] (finding the five largest pharmaceutical companies earned $81.9 billion in 2022).

293 Parrillo, *supra* note 10, at 50–51 ("As to relationships with FDA, most new drugs are made by firms that are repeat players with the agency, continually at its mercy to obtain approvals for new products, or for new uses of old products . . . [such that] the former general counsel of a large drug manufacturer [believes] that large 'repeat player' companies would almost never challenge an FDA adjudicatory decision, especially a scientific one . . . ." (quoting Interview by Nicholas A. Parrillo with Anonymous Interviewee #1, Former General Counsel of a Large Drug Manufacturer (Aug. 23, 2024)).

and seek predicable regulatory requirements.[294] Applied here, large drug companies with multiple products may be more likely to comply with regulations than challenge regulations in any individual case.[295] As pithily explained by Professor Craig Konnoth, "[p]unishment is expensive; persuasion is cheap."[296]

The cases described in Part I follow this prediction; as of August 1, 2024, Eagle Pharmaceuticals had four FDA-approved products listed on its website,[297] Catalyst Pharmaceuticals had three FDA-approved products listed on its website,[298] and Genus Medical Technologies had four FDA-approved products on its website in addition to flavorings.[299] Pfizer, in contrast, had over 315 FDA-approved products listed on its website.[300] The predicted outcomes are generally aligned with the trends in demographics of litigants against the FDA in the last ten years and predictions that companies with only a few FDA-approved products may

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294 *See* Andrew D. Bradt & D. Theodore Rave, *It's Good to Have the "Haves" on Your Side: A Defense of Repeat Players in Multidistrict Litigation*, 108 GEO. L.J. 73, 74 (2019) ("Repeat players benefit from enormous structural advantages in litigation over 'one-shotters.' In addition to their experience and ability to spread costs across many cases, repeat players can 'play for rules.' In other words, repeat players have the incentive and ability to try to shape the rules of the litigation game in their favor at a systemic level." (footnotes omitted) (citing Marc Galanter, *Why the "Haves" Come Out Ahead: Speculations on the Limits of Legal Change*, 9 L. & SOC'Y REV. 95, 97–103 (1974))).

295 Highly respected scholars have demonstrated this principle in related pharmaceutical patent litigation, although not for FDA litigation. Michael A. Carrier, Mark A. Lemley & Shawn Miller, *Playing Both Sides? Branded Sales, Generic Drugs, and Antitrust Policy*, 71 HASTINGS L.J. 307, 307–10 (2020) (suggesting generic drug challengers may not always fight as hard as possible to win the patent case before them, especially for challenges that affect not just the patent in the instant case but might change legal doctrines that may ultimately hurt other parts of the business); *see also* Manheim, *supra* note 272, at 1 ("[B]rand-name manufacturers of drug products are understandably often loath to file a lawsuit against FDA—an agency that maintains jurisdiction over that company's existing products and that must act to approve a brand-name manufacturer's applications to market new drug products. Litigation against FDA is also frequently complex and difficult."); Parrillo, *supra* note 10, at 48 (quoting a top pharmaceutical executive who said "that's not the way you play the game. You just cooperate, and love 'em, and eventually it will work out.").

296 Craig J. Konnoth, *Drugs' Other Side-Effects*, 105 IOWA L. REV. 171, 226 (2019) (modification in original) (citing IAN AYRES & JOHN BRAITHWAITE, RESPONSIVE REGULATION: TRANSCENDING THE DEREGULATION DEBATE 19 (1992)).

297 *Our Products*, EAGLE PHARMS., https://www.eagleus.com/products [https://perma.cc/YJ4X-FC55].

298 *Current Approved Products*, CATALYST PHARMS., https://catalystpharma.com/products [https://perma.cc/3NN7-NVMV].

299 GENUS MED. TECHS., https://genusmedical.com [https://perma.cc/5W2L-HUVP]; *see also Barium Sulfate and Related Products*, GENUS MED. TECHS., https://genusmedical.com/barium-sulfate/#bariumsmoothie [https://perma.cc/4AFS-DSD6].

300 *Products*, PFIZER, https://www.pfizer.com/products [https://web.archive.org/web/20241127041050/https://www.pfizer.com/products].

be more willing to test, and potentially undermine, FDA regulatory power to protect fragile monopolies.[301]

Table 1[302]

Top Pharmaceutical Companies by Revenue	Year and Rank	Number of Cases Against the FDA	Year of Case and Outcomes of Cases (Favor company; Favor FDA; Neither)
Johnson and Johnson	2023: 1 2022: 2 2021: 1	0	-
Roche	2023: 2 2022: 3 2021: 3	0	-
Merck	2023: 3 2022: 4	0	-
Pfizer	2023: 4 2022: 1 2021: 2	0	-
AbbVie	2023: 5 2022: 5 2021: 4	0	-
Sanofi*	2023: 6 2022: 8 2021: 9	0	-
AstraZeneca	2023: 7 2022: 9 2021: 10	2	0: 2013, 2016: 0
Novartis	2023: 8 2022: 6 2021: 5	0	-
Bristol Myers Squibb	2023: 9 2022: 7 2021: 7	0	-

301 *See* Konnoth, *supra* note 296.

302 Kevin Dunleavy, *The Top 20 Pharma Companies by 2023 Revenue*, FIERCE PHARMA (Apr. 15, 2024, 3:00 AM), https://www.fiercepharma.com/pharma/top-20-pharma-companies-2023-revenue [https://perma.cc/5KYX-Q8CU]; Kevin Dunleavy, *The Top 20 Pharma Companies by 2022 Revenue*, FIERCE PHARMA (Apr. 18, 2023, 3:00 AM), https://www.fiercepharma.com/pharma/top-20-pharma-companies-2022-revenue [https://perma.cc/Y6GK-D4H4]; Kevin Dunleavy, *The Top 20 Pharma Companies by 2021 Revenue*, FIERCE PHARMA (Apr. 12, 2022, 3:00 AM), https://www.fiercepharma.com/special-reports/top-20-pharma-companies-2021-revenue [https://perma.cc/6EQU-AFQ9]. The asterisk denotes generic drug companies.

GlaxoSmithKline	2023: 10 2022: 10 2021: 8	0	-
Eli Lilly	2023: 11 2022: 12 2021: 12	0	-
Novo Nordisk	2023: 12 2022: 17 2021: 17	0	-
Amgen	2023: 13 2022: 15 2021: 15	0	-
Boehringer Ingelheim	2023: 14 2022: 16 2021: 16	1	0: 2016: 0
Takeda	2023: 15 2022: 11 2021: 11	1	0: 2016: 0
Gilead	2023: 16 2022: 13 2021: 14	0	-
Bayer	2023: 17 2022: 14 2021: 13	0	-
Merck KGaA	2023: 18 2022: 19	0	-
Teva*	2023: 19	3	0: 2014, 2019, 2020: 0
Viatris* (formerly Mylan and UpJohn)	2023: 20 2021: 20	1	0: 2014: 0
Moderna	2022: 18 2021: 19	0	-
BioNTech	2022: 20 2021: 18	0	-

Table 2[303]

Top Generic Pharmaceutical Companies by Revenue in 2021	Rank	Number of Cases against the FDA	Year of Case and Outcomes of Cases Pharmaceutical Win: Loss: Neutral
Teva	1	3	0: 2014, 2019, 2020: 0
Viatris (formerly Mylan and UpJohn)	3	1	0: 2014: 0
Novartis' Sandoz	2	1	0: 2023**: 0
Sun Pharma	4	0	-
Fresenius Kabi	5	0	-
Aurobindo	6	0	-
Cipla	7	0	-
Aspen Pharmacare	8	0	-
Dr. Reddy's Laboratories	9	0	-
Hikma	10	0	-

B. *Why Sue the FDA?*

In addition to who sues, it is helpful to understand litigation goals and remedies sought. Broadly speaking, the litigants sought reconsideration of FDA decisions as it relates to their drug rather than challenging the regulatory scheme.[304] The cases were subdivided into three overlapping categories: challenges to a competitor product, challenges to awards of regulatory exclusivities, and challenges to the classification of a product as a drug, device, or biologic. Twenty-five cases (43.1%) involved approval of a competitor product.[305] For example, in *Catalyst*, the brand company asked the court to revoke FDA approval of its rival competitor after losing more than 40% of its economic value to

303 Kevin Dunleavy, Zoey Becker, Fraiser Kansteiner, Angus Liu & Eric Sagonowsky, *The Top 10 Generic Drug Makers by 2021 Revenue*, FIERCE PHARMA (July 18, 2022, 3:00 AM), https://www.fiercepharma.com/pharma/top-10-generic-drugmakers-2021-revenue [https://perma.cc/6MWX-CARX]. The date reflects the appellate opinion, but the lower court opinion is also cited *infra* Appendix I. The first two rows are duplicative of the last two rows of Table 1.

304 *See infra* Appendix I. Cases can involve multiple categories.

305 *See infra* Appendix I.

the other company.[306] Twenty-seven of fifty-eight cases examined (46.6%) related to how the FDA awarded designations or exclusivities, such as orphan, pediatric, etc.[307] As explained in Section I.B, these exclusivities can be lucrative and controversial.[308] Of the fifty-eight cases examined,[309] five (8.6%) relate to the classification of a product as a drug or something else (e.g., device, biologic, supplement, or cosmetic). Classification of a product as a drug, device, or biologic can allow a litigant to avoid expenses that apply to competitors like clinical trial requirements or earlier generic competition.[310] These findings demonstrate that in the litigation against the FDA between 2013 and 2023 identified in this data set, many pharmaceutical companies sought some form of financial advantage including lucrative benefits, avoidance of compliance with costly regulations, or limiting competition.

The number of cases challenging competitor products or exclusivities raises concerns, as the staggering financial value of drugs protected by government-backed limited monopolies (patents and FDA-granted exclusivities)[311] already inspires efforts to delay competition and generic competition entry.[312] As well explained by Professor Jordan

306 Sagonowsky, *supra* note 166.

307 *See infra* Appendix I.

308 For an excellent analysis of the FDA's role in regulating innovation, see Sachs et al., *supra* note 53. *See also* Bo Wang, Jun Liu & Aaron S. Kesselheim, *Variations in Time of Market Exclusivity Among Top-Selling Prescription Drugs in the United States*, 175 JAMA INTERNAL MED. 635 (2015); JOHN R. THOMAS, CONG. RSCH. SERV., R44951, REGULATORY EXCLUSIVITY REFORM IN THE 115TH CONGRESS (2017) (describing how the FDA is "require[d] . . . to enforce 16 different regulatory exclusivities"); Ameet Sarpatwari, Reed F. Beall, Abdurrahman Abdurrob, Mengdong He & Aaron S. Kesselheim, *Evaluating the Impact of the Orphan Drug Act's Seven-Year Market Exclusivity Period*, 37 HEALTH AFFS. 732 (2018).

309 Related cases were counted as a single entry for this calculation. *See infra* Appendix I.

310 Similarly, avoiding complying with CGMP is a competitive advantage. *See supra* Sections I.B.3–4.

311 *See* sources cited *supra* notes 59, 292.

312 *See* Michael A. Carrier, *Five Actions to Stop Citizen Petition Abuse*, 118 COLUM. L. REV. 82, 85 (2018) ("Not only do petitions threaten the public but they also harm the FDA, which has lamented the deluge of petitions that has forced it to expend resources 'at the expense of completing the other work of the Agency.'" (quoting FDA, REPORT TO CONGRESS: EIGHTH ANNUAL REPORT ON DELAYS IN APPROVALS OF APPLICATIONS RELATED TO CITIZEN PETITIONS AND PETITIONS FOR STAY OF AGENCY ACTION FOR FISCAL YEAR 2015 8 (2016), https://www.fda.gov/media/99871/download [https://perma.cc/5UN7-T9NL]); Press Release, Fed. Trade Comm'n, FTC Challenges More than 100 Patents as Improperly Listed in the FDA's Orange Book (Nov. 7, 2023), https://www.ftc.gov/news-events/news/press-releases/2023/11/ftc-challenges-more-100-patents-improperly-listed-fdas-orange-book [https://perma.cc/YG3Q-Q9H4].

Paradise, "[t]he pharmaceutical industry is well known for its arsenal of anticompetitive tactics."[313]

Historically, pharmaceutical companies profited from sowing doubts about the safety or efficacy of their competitors.[314] A landmark empirical study of 505(q) citizen petitions by Professor Michael A. Carrier and Carl Minniti found that 92% were filed by brand-name firms attacking proposed generic drugs,[315] 39% were filled within six months of patent or FDA exclusivity expiration potentially to delay generic approvals,[316] and the FDA granted only 8%.[317] Another excellent study by Professor Robin Feldman found just "four dubious citizen petitions" cost society $1.9 billion by delaying generic competition.[318] She illustrated that delaying generic competition by even a short period through FDA challenges or litigation can translate to significant profits for companies.[319] When a court allowed a single generic competitor on market even for a few weeks, it cost the brand company multiple millions of dollars and over 60% of the market share despite winning the case.[320] Senators have even proposed immunizing FDA review of citizen petitions

313 Paradise, *supra* note 60, at 2398; *see also* C. Scott Hemphill & Mark A. Lemley, *Earning Exclusivity: Generic Drug Incentives and the Hatch-Waxman Act*, 77 ANTITRUST L.J. 947, 949 (2011) ("Many of these 'lifecycle management' strategies have been challenged as violations of antitrust law. The results have been mixed.").

314 *See* Elisabeth Mahase, *Drug Company Vifor Is Investigated for Allegedly Spreading Misinformation About Competitor*, 377 BRITISH MED. J. 1536 (2022) (discussing the European Commission investigation into whether a Swiss drug company restricted "competition by illegally disparaging its closest and potentially only . . . competitor for an intravenous iron treatment"); *see also* Michael A. Carrier, *How Biosimilar Disparagement Violates Antitrust Law*, BLOOMBERG L. (Nov. 16, 2020, 4:00 AM), https://news.bloomberglaw.com/health-law-and-business/how-biosimilar-disparagement-violates-antitrust-law [https://perma.cc/P5CE-MC48] ("Rutgers Law professor Michael A. Carrier says biologic manufacturers are violating antitrust law . . . by issuing disparaging statements with foreboding safety warnings.").

315 Michael A. Carrier & Carl Minniti, *Citizens Petitions: Long, Late-Filled, and At-Last Denied*, 66 AM. U. L. REV. 305, 332 tbl. 3 (2016).

316 *Id.* at 339 & tbl. 7.

317 *Id.* at 333 & tbl. 4. Carrier and Minniti also found that the FDA denied 92% of petitions between 2011 and 2015, with denial rates as high as 72% in 2011, 96% in 2012, and even 100% in 2015. *Id.* at 333. They compared this data with a prior study that found that the FDA denied 81% of generic-related petitions between 2001 and 2010. *Id.* at 308 (citing Michael A. Carrier & Daryl Wander, *Citizen Petitions: An Empirical Study*, 34 CARDOZO L. REV. 249 (2012)).

318 Robin Feldman, *The Burden on Society from Eleventh-Hour "Citizen Petitions" Filed to Slow Generic Drugs*, 79 MD. L. REV. ONLINE 1, 3 (2020).

319 *Id.* at 2 & n.7 (illustrating how a 2014 treatment for hepatitis C that earned $7.9 billion in sales in the United States would have made almost $2 billion more with even three months of sales).

320 *See Apotex Clopidogrel At-Risk Launch Costs US $442 Million*, *supra* note 33 (discussing a settlement after a large generic manufacturer launched at risk for three weeks was half of profit made during those three weeks); Leonard Zehr, *Sherman's Bluff Won a Jackpot for Apotex*, GLOBE & MAIL (Aug. 23, 2006), https://www.theglobeandmail.com/report-on-business/shermans-bluff-won-a-jackpot-for-apotex/article1102148 [https://perma.cc/P345-GC6W].

from judicial review due to concerns over "intent to delay" abuse.[321] Protectionist actions taken by pharmaceutical manufacturers have received increasing scrutiny by the Federal Trade Commission (FTC).[322]

There is reason to think "intent to delay" through litigation may already be occurring. While any case seeking financial advantage may or may not be anticompetitive, the 2022 through 2024 litigation strategy by Vanda Pharmaceuticals Inc. (Vanda) exemplifies the potential problems.[323] Vanda filed over ten lawsuits and petitions in less than two

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321 Ensuring Timely Access to Generics Act of 2023, S. 1067, 118th Cong., 1st Sess. (2023) was proposed as an amendment to the Food and Drug Administration Safety and Landmark Advancements Act of 2022, S. 4348, 117th Cong., 2d Sess. (2022). *See* Kurt R. Karst & Michael D. Shumsky, *New Legislation Would Cut Off Access to the Courts and Immunize FDA Actions from Timely Judicial Review*, HYMAN, PHELPS & MCNAMARA P.C. (May 1, 2023), https://www.thefdalawblog.com/2023/05/new-legislation-would-cut-off-access-to-the-courts-and-immunize-fda-actions-from-timely-judicial-review [https://perma.cc/U9Q3-WSS9].

322 *See* PATRICIA M. DANZON, COMPETITION AND ANTITRUST ISSUES IN THE PHARMACEUTICAL INDUSTRY (2014), https://faculty.wharton.upenn.edu/wp-content/uploads/2017/06/Competition-and-Antitrust-Issues-in-the-Pharmaceutical-IndustryFinal7.2.14.pdf [https://perma.cc/2E68-L3HY]; *see also* Karissa Waddick, *Antitrust Watchdogs Have Pharma in Their Sights, and the Landscape Is Getting Thornier*, PHARMAVOICE (Feb. 2, 2023), https://www.pharmavoice.com/news/Pharma-antitrust-mergers-FTC-DOJ-enforcement/641775 [https://perma.cc/BXU7-ZN9L] ("The Biden administration is cracking the whip against anticompetitive corporate practices—and the pharma industry seems to be its ideal prey."); FTC, REPORT ON PHARMACEUTICAL PRODUCT HOPPING (2022), https://www.ftc.gov/reports/federal-trade-commission-report-pharmaceutical-product-hopping [https://perma.cc/2X2C-EP3A]; Michael A. Carrier & Steve D. Shadowen, *Product Hopping: A New Framework*, 92 NOTRE DAME L. REV. 167 (2016); Feldman, *supra* note 32, at 596; Garth W. Strohbehn, Alec J. Kacew, Daniel A. Goldstein, Robin C. Feldman & Mark J. Ratain, *Combination Therapy Patents: A New Front in Evergreening*, 39 NATURE BIOTECH. 1504 (2021); Arthur Allen, *A More Aggressive FTC Is Starting to Target a Drug Mergers and Industry Middlemen*, FIERCE HEALTHCARE (May 22, 2023, 4:10 PM), https://www.fiercehealthcare.com/regulatory/more-aggressive-ftc-starting-target-drug-mergers-and-industry-middlemen [https://perma.cc/5FNC-4DPP]; U.S. DEP'T OF JUST. & FTC, MERGER GUIDELINES (2023), https://www.ftc.gov/system/files/ftc_gov/pdf/2023_merger_guidelines_final_12.18.2023.pdf [https://perma.cc/4NS7-Z2K3]; Olga Gurgula, *Strategic Patenting by Pharmaceutical Companies—Should Competition Law Intervene?*, 51 INT'L REV. INTELL. PROP. & COMPETITION L. 1062 (2020).

323 Halpern, *supra* note 195 ("[Ron] Lanton questioned the logic of the pharmaceutical industry 'biting off the hand that feeds them,' by creating chaos in challenging FDA decisions, since the industry still relies on the FDA's thorough clinical trial process for drugs to gain approvals. . . . [The FDA's reputation as the] 'gold standard' . . . may deter would-be legal challenges." (quoting Interview by Pharmacy Times with Ron Lanton III, *supra* note 195)); Brenda Sandburg, *Vanda Launches Barrage of Suits Against FDA Seeking to Retain Hetlioz Market*, CITELINE: PINK SHEET (Nov. 2, 2023), https://pink.citeline.com/PS149095/Vanda-Launches-Barrage-Of-Suits-Against-FDA-Seeking-To-Retain-Hetlioz-Market [https://perma.cc/VQ4N-5DV7]; Kurt R. Karst, *Vanda-lay Litigation Industries, Inc.: Taking Stock of Vanda Pharmaceuticals, Inc.'s Big Bets on Petitioning and Litigation Against FDA and the Federal Government*, HYMAN, PHELPS & MCNAMARA P.C. (Oct. 2, 2024), https://www.thefdalawblog.com/2024/10/vanda-lay-litigation-industries-inc-taking-stock-of-vanda-pharmaceuticals-inc-s-big-bets-on-petitioning-and-litigation-against-fda-and-the-federal-government [https://perma.cc/Z6R7-LPQV] (explaining that the *Vanda* complaint was, "by [their] count[,] the 31st Vanda litigation against FDA or another government entity in the last five years, including appeals").

years to try to delay entry of generic competition on a single drug, often challenging FDA science-based policy choices not previously challenged by other companies.[324] Vanda was founded in 2003 and has three FDA-approved products as of August 1, 2024.[325] A journalist reported that the company had been facing declining revenue since 2021, as their products faced generic competition.[326] After Vanda lost their 2018 Hatch-Waxman case alleging patent infringement in 2022,[327] they filed a second patent infringement case alleging violations of other patents in 2022 almost immediately after generic companies received FDA approval.[328]

Vanda then alleged the generic company had engaged in false advertisements in violation of the Lanham Act[329] and filed two nearly identical citizen petitions asking the FDA to revoke approval of the generic competition for failing to include their trademarked Braille label.[330] In addition to filing multiple Freedom of Information Act (FOIA)

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324 *See infra* notes 327–336; Appendix I. Not all of these cases meet inclusivity criteria for this case study.

325 *See About*, VANDA PHARMS. INC., https://www.vandapharma.com/about [https://perma.cc/BWY5-SRJD]; *Products*, VANDA PHARMS., https://www.vandapharma.com/products-and-pipeline [https://perma.cc/2APL-Q7VP]. Tasimelteon was approved on January 31, 2014, a second product (iloperidone) was approved originally on May 7, 2009, and for a second indication on April 2, 2024. The third product was approved on March 19, 2021, and the rights to ponesimoid were acquired by Vanda in December 2023. *Drug Approval Package*, FDA (Mar. 7, 2014), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205677Orig1s000TOC.cfm [https://perma.cc/FA5R-YWAK]; Judith Stewart, *Fanapt FDA Approval History*, DRUGS.COM (Apr. 4, 2024), https://www.drugs.com/history/fanapt.html [https://perma.cc/5PY9-SFQR]; Letter from Eric Bastings, Deputy Dir., Off. of Neuroscience, Ctr. for Drug Eval. & Rsch., to Monique Franc, Assoc. Assoc. Dir., Janssen Pharms., Inc. (Mar. 18, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/213498Orig1s000ltr.pdf [https://perma.cc/JD74-58NV]; Press Release, Vanda Pharms. Inc., Vanda Pharmaceuticals Acquires U.S. and Canadian Rights to Ponvory® (Ponesimod), a Selective S1P1R Modulator Approved for Patients with Relapsing Multiple Sclerosis (Dec. 7, 2023, 7:00 AM), https://www.prnewswire.com/news-releases/vanda-pharmaceuticals-acquires-us-and-canadian-rights-to-ponvory-ponesimod-a-selective-s1p1r-modulator-approved-for-patients-with-relapsing-multiple-sclerosis-302008402.html [https://perma.cc/3HZD-5NPK].

326 Kevin Dunleavy, *Vanda Secures FDA Approval for Fanapt to Treat Bipolar I, 15 Years After Schizophrenia Nod* (Apr. 3, 2024, 11:04 AM), https://www.fiercepharma.com/pharma/vanda-secures-fda-approval-fanapt-treat-bipolar-i-15-years-after-schizophrenia-nod [https://perma.cc/FL4R-DZG4].

327 Vanda Pharms., Inc. v. Teva Pharms. USA, Inc., No. 18-651, 2022 WL 17593282, at *26–28 (D. Del. Dec. 13, 2022).

328 Vanda Pharms. Inc. v. Teva Pharms. USA, Inc., No. 22-7528, 2023 WL 1883357, at *1–2 (D.N.J. Feb. 10, 2023).

329 Vanda Pharms., Inc. v. Teva Pharms., Inc., No. 23-511, 2023 WL 8890322, at *1–2 (D.N.J. Dec. 26, 2023).

330 Mark A. Tobolowsky, *FDA Denies Vanda's Citizen Petitions Regarding the Need for Braille Labeling for Tasimelteon Generics*, HYMAN, PHELPS & MCNAMARA PC (Aug. 18, 2023), https://www.thefdalawblog.com/2023/08/fda-denies-vandas-citizen-petitions-regarding-the-need-for-braille-labeling-for-tasimelteon-generics [https://perma.cc/AZF9-GANG].

requests,[331] Vanda sued the FDA alleging substantive error in approving the generic company product as bioequivalent,[332] filed another lawsuit challenging the clinical hold that the FDA placed on an investigational new drug application for an unapproved unrelated product,[333] and filed a third for the FDA's failure to provide an opportunity for a hearing after denying an application three years prior.[334] Vanda also challenged generic approval of a competitor product under the appointments clause in 2024.[335] Later in 2024, Vanda filed a fourth suit alleging that the FDA disclosed trade secrets to competitors seeking generic drug approval, including the rate the pill dissolves and impurities.[336] This also challenges longstanding practices as the FDA typically requires generic drugs to match these features.

Ten legal actions in less than two years from one company over a single drug is atypical. If this tactic successfully limits generic competition, other manufacturers may follow suit to seek financial advantages through courts. As explained by Professor Carrier, "[t]he regulatory regime and economics of the pharmaceutical industry explain why it is uniquely susceptible to behavior delaying competitors' entry."[337] Judges too have recognized that challenging an FDA determination "may

331 Vanda Pharms., Inc. v. FDA, No. 22-cv-938, 2023 WL 2645714, at *1 (D.D.C. Mar. 27, 2023); *see also* Brigid DeCoursey Bondoc & Keunbong Do, *Vanda Pharmaceuticals, Inc. v. Food and Drug Administration*, FOOD & DRUG L. INST. (2023), https://www.fdli.org/2023/06/vanda-pharmaceuticals-inc-v-food-and-drug-administration [https://perma.cc/R9GS-DD2H].

332 Adam Lidgett, *Vanda Challenges FDA's Clearance of Generic Sleep Drug*, LAW360 (Sept. 26, 2023, 3:53 PM), https://www.law360.com/articles/1725508/vanda-challenges-fda-s-clearance-of-generic-sleep-drug [https://perma.cc/4SJR-H42D].

333 Vanda Pharm., Inc. v. FDA, 436 F. Supp. 3d 256, 262 (D.D.C. 2020).

334 Zoey Becker, *After FDA Rejection, Vanda Sues Agency over Regulatory Rebuffs on Jet Lag Med*, FIERCE PHARMA (Sept. 15, 2022, 11:35 AM), https://www.fiercepharma.com/pharma/vanda-pharmaceuticals-comes-after-fda-lawsuit-lack-hearing-jet-lag-disorder-drug [https://perma.cc/48BN-4UTV].

335 Vanda Pharms. Inc. v. FDA, No. 23-cv-2812, 2024 WL 4133623, at *1 (D.D.C. Sept. 10, 2024) ("None too pleased with having yet another competitor in the market, Vanda . . . echoed its grievance in this lawsuit while challenging the FDA's bioequivalence determination as arbitrary and capricious, in violation of the [APA]. Vanda further claims that the approval of MSN's generic drug violated the Appointments Clause of the Constitution because the FDA employees who approved the application were not 'Officers of the United States.'" (citation omitted) (citing 5 U.S.C. §§ 551–559)).

336 Vanda Pharms., Inc. v. United States, 169 Fed. Cl. 196, 203–04 (2024); *see also* DOROTHY C. KAFKA & CHRISTINA L. SHIFTON, CONG. RSCH. SERV., LSB11143, *VANDA PHARMACEUTICALS, INC. V. UNITED STATES*: FIFTH AMENDMENT TAKINGS CLAIMS FOR ALLEGED DISCLOSURES OF TRADE SECRETS AND CONFIDENTIAL INFORMATION 1–2 (2024).

337 Carrier & Minniti, *supra* note 315, at 310.

reflect a legal tactic more than a genuine controversy posed by a member of a regulated industry."[338]

In light of this dynamic, there is a risk that successful challenges to the FDA's science-based policy decisions in courtrooms would incentivize further challenges and even litigation abuse. Litigation abuse could overburden federal courts, increase the costs of all drugs, and leave the FDA less able to ensure drugs in the United States are safe and effective.

III. TRUST, TRANSPARENCY, AND JUDICIAL DEFERENCE

This Part considers four explanations for the subtle shift in litigation outcomes identified in Part I, arguing that the decline in deference may be connected to loss of trust in the FDA amidst three national crises related to drugs and declining public trust in the FDA. Declining trust in the FDA has been well documented for decades,[339] but the COVID-19, opioid, and aducanumab controversies further challenged public trust between 2019 and 2023, and coincide with the cluster of successful challenges in unrelated pharmaceutical cases.[340] If perception of improper influences and changes to public trust in the FDA's evidence-based decisions is contributing to the shifting judicial outcomes described in Part I, improving transparency and trust may be the solution. Part III also contextualizes the cluster of cases within broader changes to agency deference, calling for further conversations and observations.

A. *FDA Approval Drug Crises in 2019 to 2023*

The FDA has faced multiple concurrent controversies between 2019 and 2023; Section A explains how the opioid crisis, aducanumab approval, and COVID-19 national emergency all negatively impacted public trust in the FDA. Foremost, the FDA faced increasing public criticism for its role in approving prescription opioid drugs and allowing

338 Cooper Lab'ys, Inc. v. Comm'r, FDA, 501 F.2d 772, 787 (D.C. Cir. 1974) (Leventhal, J., dissenting).

339 *See* Lewis A. Grossman, *FDA and the Rise of the Empowered Patient*, *in* FDA IN THE TWENTY-FIRST CENTURY, *supra* note 225, at 59, 60 ("One critical trend has been the citizenry's declining trust in the leaders of major institutions, including those that formerly exercised exclusive control over the drug supply."); Robert J. Blendon & John M. Benson, *Trust in Medicine, the Health System & Public Health*, 151 DAEDALUS 67 (2022).

340 *See infra* Section III.A.

marketing for chronic pain treatment.[341] The impact of the opioid epidemic on U.S. patients and communities cannot be understated; Judge Polster described it as a "man-made plague."[342] The FDA approved the addictive product with limited data, allowed opioid manufacturers to promote treatment of chronic pain with increasing doses of an addictive medication, and maintained concerning close ties to the regulated entities.[343] Allowing marketing claims that oxycodone had a less addictive potential and worked for a longer duration based on poorly conducted studies fueled overuse and addiction.[344]

Twenty-six years after initial approval of oxycodone,[345] a 2017 President's Commission on combatting drug addiction and the opioid crisis identified the FDA's inadequate oversight as part of the epidemic's cause.[346] The FDA's credibility was and continues to be damaged "amid

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341 *See Amanpour & Company: "Dopesick:" Purdue Pharma, FDA to Blame for Opioid Crisis* (PBS television broadcast Nov. 9, 2021).

342 Jef Feeley, *Opioid-Industry Claims Proceed as Judge Cites 'Man-Made Plague,'* BLOOMBERG L. (Dec. 20, 2018, 9:24 AM), https://www.bloomberg.com/news/articles/2018-12-20/opioid-industry-claims-proceed-as-judge-cites-man-made-plague [https://web.archive.org/web/20240826071724/https://www.bloomberg.com/news/articles/2018-12-20/opioid-industry-claims-proceed-as-judge-cites-man-made-plague].

343 The FDA's role in the opioid epidemic was widely criticized. *See* Sharkey, *supra* note 18, at 675–76; *see also* Patricia J. Zettler, Margaret Foster Riley & Aaron S. Kesselheim, *Implementing a Public Health Perspective in FDA Drug Regulation*, 73 FOOD & DRUG L.J. 221, 228 (2018); U.S. GOV'T ACCOUNTABILITY OFF., GAO-04-110, PRESCRIPTION DRUGS: OXYCONTIN ABUSE AND DIVERSION AND EFFORTS TO ADDRESS THE PROBLEM (2003); Sujata S. Jayawant & Rajesh Balkrishnan, *The Controversy Surrounding OxyContin Abuse: Issues and Solutions*, 1 THERAPEUTICS & CLINICAL RISK MGMT. 77, 79 (2005) ("News about OxyContin abuse first surfaced in rural areas of Maine during the late 1990s and then spread down the east coast to include West Virginia, Kentucky, Southern Ohio."); Jeffrey Eric Rollman et al., *Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products*, 321 JAMA 676 (2019); Abby Goodnough & Margot Sanger-Katz, *As Tens of Thousands Died, F.D.A. Failed to Police Opioids*, N.Y. TIMES (Dec. 31, 2019), https://www.nytimes.com/2019/12/30/health/FDA-opioids.html [https://web.archive.org/web/20240329161222/https://www.nytimes.com/2019/12/30/health/FDA-opioids.html].

344 *See* Art Van Zee, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy*, 99 AM. J. PUB. HEALTH 221 (2009); *see also* Pamela T.M. Leung, Erin M. Macdonald, Matthew B. Stanbrook, Irfan A. Dhalla & David N. Juurlink, *A 1980 Letter on the Risk of Opioid Addiction*, 376 NEW ENG. J. MED. 2194 (2017).

345 Purdue Pharma filed for bankruptcy to address its debts related to multiple lawsuits alleging that OxyContin contributed to the opioid epidemic, although some of the companies' owners, members of the Sackler Family, have not filed for personal bankruptcy. The Biden administration and eight states challenged the settlement. The proposed bankruptcy settlement was blocked by the U.S. Supreme Court in June 2024. Harrington v. Purdue Pharma L.P., 603 U.S. 204 (2024).

346 *Timeline of Selected FDA Activities and Significant Events Addressing Substance Use and Overdose Prevention*, FDA (Jan. 13, 2025), https://www.fda.gov/drugs/food-and-drug-administration-overdose-prevention-framework/timeline-selected-fda-activities-and-significant-events-addressing-substance-use-and-overdose [https://web.archive.org/web/20250127213037/

accusations that at times it behaved less as a regulator overseeing the pharmaceutical industry than a business partner of drug manufacturers."[347] Public criticism of the Agency's role in the opioid epidemic has been ongoing for decades,[348] but it accelerated after litigation against Purdue Pharma revealed additional details about intentional deceptive marketing practices that the FDA failed to regulate.[349]

In addition to the opioid epidemic, the FDA faced widespread criticism over the accuracy of its determination and decision to approve aducanumab under the Accelerated Approval Program in 2021.[350] While less prominent, aducanumab's approval spurred public discussions on which drugs should qualify for accelerated approval and what is necessary to demonstrate meaningful clinical benefit.[351] Aducanumab was approved under the Accelerated Approval Program for Alzheimer's

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https://www.fda.gov/drugs/food-and-drug-administration-overdose-prevention-framework/timeline-selected-fda-activities-and-significant-events-addressing-substance-use-and-overdose].

347 Chris McGreal, *FDA's Opioids Adviser Accuses Agency of Having 'Direct' Link to Crisis*, GUARDIAN (Jan. 24, 2019, 6:00 AM), https://www.theguardian.com/us-news/2019/jan/24/fda-opioids-big-pharma-prescriptions [https://perma.cc/26DB-J5ZW]; *see also* H. Holden Thorp, *Shared Blame for the Opioid Crisis*, 373 SCI. 6 (2021); *cf.* Richard D. deShazo, McKenzie Johnson, Ike Eriator & Kathryn Rodenmeyer, *Backstories on the US Opioid Epidemic. Good Intentions Gone Bad, an Industry Gone Rogue, and Watch Dogs Gone to Sleep*, 131 AM. J. MED. 595, 598 (2018); Ronald Hirsch, *The Opioid Epidemic: It's Time to Place Blame Where It Belongs*, 114 J. MO. STATE MED. ASS'N 82 (2017).

348 *See* Andrew Kolodny, *How FDA Failures Contributed to the Opioid Crisis*, 22 AMA J. ETHICS 743 (2020). For an excellent discussion on the role of institutions and the opioid crisis, see Daniel J. Hemel & Lisa Larrimore Ouellette, *Innovation Institutions and the Opioid Crisis*, 7 J.L. & BIOSCIENCES, Jan.–June 2020, at 1.

349 *See* PATRICK RADDEN KEEFE, EMPIRE OF PAIN: THE SECRET HISTORY OF THE SACKLER DYNASTY 612, 680–81 (2021); *see also* Hemel & Ouellette, *supra* note 348; Sharkey, *supra* note 18, at 670–74; Shraddha Chakradhar & Casey Ross, *The History of OxyContin, Told Through Unsealed Purdue Documents*, STAT (Dec. 3, 2019), https://www.statnews.com/2019/12/03/oxycontin-history-told-through-purdue-pharma-documents [https://perma.cc/6BE7-MQV8].

350 *See* Pam Belluck, Sheila Kaplan & Rebecca Robbins, *How an Unproven Alzheimer's Drug Got Approved*, N.Y. TIMES (Oct. 20, 2021), https://www.nytimes.com/2021/07/19/health/alzheimers-drug-aduhelm-fda.html [https://web.archive.org/web/20240822021304/https://www.nytimes.com/2021/07/19/health/alzheimers-drug-aduhelm-fda.html]; Joseph Walker, *FDA Approves First New Alzheimer's Drug in Nearly Two Decades*, WALL ST. J. (June 7, 2021, 4;40 PM), https://www.wsj.com/articles/first-alzheimers-drug-to-slow-disease-is-approved-by-fda-11623078912 [https://web.archive.org/web/20220820042618/https://www.wsj.com/articles/first-alzheimers-drug-to-slow-disease-is-approved-by-fda-11623078912].

351 *See* Jacqueline Howard, *In Controversial Decision, FDA Approves First New Alzheimer's Disease Drug in Nearly 20 Years*, CNN (June 7, 2021, 6:54 PM), https://www.cnn.com/2021/06/07/health/alzheimers-drug-aducanumab-fda-approved-wellness/index.html [https://perma.cc/4Q4B-4B63] (quoting Dr. Patrizia Cavazzoni, then director of the FDA's Center for Drug Evaluation and Research, who stated, "There has been considerable public debate on whether Aduhelm should be approved. As is often the case when it comes to interpreting scientific data, the expert community has offered differing perspectives.").

disease in 2021 using a disputed surrogate marker.[352] Congress created the Accelerated Approval Program during the HIV/AIDS crisis to allow certain drugs predicted to be "lifesaving" to reach market more quickly by using surrogate endpoints.[353] This often-utilized[354] approach trades speed for certainty and is not without risk; drugs approved under the Accelerated Approval Program are more likely to have unidentified safety risks[355] and to lack clinical benefits on subsequent testing.[356]

The approval of aducanumab was particularly unusual, as the FDA reinterpreted data despite concerns from both internal experts and a

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352 Accelerated approval is an FDA program designed to facilitate earlier access to certain lifesaving drugs. *See* 21 C.F.R. § 601.40 (2024). Vincent Planche & Nicolas Villain, *U.S. Food and Drug Administration Approval of Aducanumab—Is Amyloid Load a Valid Surrogate End Point for Alzheimer Disease Clinical Trials?*, 78 JAMA NEUROLOGY 1307, 1307 (2021) ("The FDA considered reduction of amyloid load, as measured with amyloid positron emission tomography (PET), to be a valid surrogate end point of clinical benefit in [Alzheimer's disease]. This position is unprecedented and raises numerous controversies."). For a discussion on accelerated approval, see Rachel Sachs, *Understanding Medicare's Aduhelm Coverage Decision*, HEALTH AFFS. (Jan. 12, 2022), https://www.healthaffairs.org/content/forefront/understanding-medicare-s-aduhelm-coverage-decision [https://perma.cc/KAS6-GVW7].

353 Not all drugs approved through this program are lifesaving or effective. *See* Thomas J. Hwang, Quoc-Dien Trinh, Ariadna Tibau & Kerstin N. Vokinger, *Reforms to Accelerated Approval of New Medicines: Long Overdue*, 400 LANCET 357, 357–58 (2022); *see also* Sachs, *supra* note 352; CTR. FOR BIOLOGICS EVALUATION & RSCH. & CTR, FOR DRUG EVALUATION & RSCH, FDA, U.S. DEP'T OF HEALTH & HUM. SERVS., GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS 3 (1998), https://www.fda.gov/media/71655/download [https://perma.cc/Z67J-XYP2]; CTR. FOR BIOLOGICS EVALUATION & RSCH., CTR, FOR DRUG EVALUATION & RSCH & ONCOLOGY CTR. OF EXCELLENCE, FDA, U.S. DEP'T OF HEALTH & HUM. SERVS., DEMONSTRATING SUBSTANTIAL EVIDENCE OF EFFECTIVENESS WITH ONE ADEQUATE AND WELL-CONTROLLED CLINICAL INVESTIGATION AND CONFIRMATORY EVIDENCE: GUIDANCE FOR INDUSTRY 1–2 (2023), https://www.fda.gov/media/172166/download [https://perma.cc/A6CF-NXP5]; 21 U.S.C. § 355(d).

354 *See* OFF. OF INSPECTOR GEN., U.S. DEP'T HEALTH & HUM. SERV., NO. OEI-01-21-000401, DELAYS IN CONFIRMATORY TRIALS FOR DRUG APPLICATIONS GRANTED FDA'S ACCELERATED APPROVAL RAISE CONCERNS 1 (2022) ("Since the accelerated approval pathway began in 1992, drug applications granted accelerated approval by FDA's Center for Drug Evaluation and Research (CDER) have steadily increased—with 278 approved between 1992 and December 31, 2021.").

355 *See* Cassie Frank et al., *Era of Faster FDA Drug Approval Has Also Seen Increased Black-Box Warnings and Market Withdrawals*, 33 HEALTH AFFS. 1453 (2014).

356 *See, e.g.*, Matthew Perrone, *Speedier Drug Approvals Hit Slowdown as FDA Faces Scrutiny*, ASSOCIATED PRESS (Dec. 7, 2022, 12:01 AM), https://apnews.com/article/health-cancer-business-congress-drug-approvals-e029b9f3f72b4282ad39d2d00902edfe [https://perma.cc/C9DB-RLEV] ("Academics have long complained that the [Accelerated Approval Program] has resulted in a glut of expensive, unproven medications, particularly for cancer."); Leonard Sacks et al., *Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000–2012*, 311 JAMA 378, 382–83 (2014). *See generally* ANNA KALTENBOECK, AMANDA MEHLMAN & STEVEN D. PEARSON, INST. FOR CLINICAL & ECON. REV., STRENGTHENING THE ACCELERATED APPROVAL PATHWAY: AN ANALYSIS OF POTENTIAL POLICY REFORMS AND THEIR IMPACT ON UNCERTAINTY, ACCESS, INNOVATION, AND COSTS (2021).

near-unanimous external advisory committee.[357] The response was swift: three advisory committee members resigned to protest the approval decision and its process, the FDA revised the instructions on the types of patients who should receive the drug,[358] Medicare and insurance companies[359] limited payments,[360] and the acting commissioner of the FDA asked the Office of Inspector General to investigate whether her employees worked too closely with employees of Biogen resulting in an eighteen-month congressional investigation citing numerous interactions where the FDA "failed to follow its own . . . protocol."[361] The

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357 Other concerns include questionable clinical benefit observed, reliance on reanalysis of failed studies, and the amount of time given for post-approval confirmatory trials. *See* Dylan Scott, *The New Alzheimer's Drug That Could Break Medicare*, VOX (June 10, 2021, 9:00 AM), https://www.vox.com/policy-and-politics/22524608/new-alzheimers-drug-cost-fda-approval-biogen [https://perma.cc/KU9P-KLHB]; *see also* Rouen Brockmann, Joanna Nixon, Bryan L. Love & Ismaeel Yunusa, *Impacts of FDA Approval and Medicare Restriction on Antiamyloid Therapies for Alzheimer's Disease: Patient Outcomes, Healthcare Costs, and Drug Development*, 20 LANCET REG'L HEALTH, Apr. 2023 at 1, 1–4; Rajesh R. Tampi, Brent P. Forester & Marc Agronin, Editorial, *Aducanumab: Evidence from Clinical Trial Data and Controversies*, DRUGS CONTEXT, Oct. 2021, at 1; Kathy Y. Liu & Robert Howard, *Can We Learn Lessons from the FDA's Approval of Aducanumab?*, 17 NATURE REVS. NEUROLOGY 715, 715, 717 (2021).

358 The drug was initially approved for every patient with Alzheimer's disease despite the data only showing benefit for those in an early stage. The indication was narrowed shortly afterwards. *See* Reshma Ramachandran & Joseph S. Ross, *FDA Indication Extrapolations—Allowing Flexibility While Providing Greater Clarity*, 5 JAMA, Apr. 19, 2022, at 1.

359 *See* Joshua P. Cohen, *Aduhelm's Paltry $1 Million in Q4 Sales Indicates CMS's Coverage with Evidence Development May Be Biogen's Only Chance at Salvaging Something from the Product*, FORBES (Feb. 7, 2022, 10:09 AM), https://www.forbes.com/sites/joshuacohen/2022/02/04/aduhelms-paltry-1-million-in-q4-sales-indicates-cmss-coverage-with-evidence-development-may-be-biogens-only-chance-at-salvaging-something-from-the-product [https://perma.cc/8CVZ-K77B] (reporting that Aduhelm was not being prescribed "[a]t major university hospital systems like the University of Michigan, UCLA, UCSF, Vanderbilt, Wake Forest, University of Rochester, Northwestern, and Johns Hopkins").

360 *See* Sachs, *supra* note 353; Press Release, Ctrs. for Medicare & Medicaid Servs., CMS Finalizes Medicare Coverage Policy for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (Apr. 7, 2022), https://www.cms.gov/newsroom/press-releases/cms-finalizes-medicare-coverage-policy-monoclonal-antibodies-directed-against-amyloid-treatment [https://perma.cc/Q6R8-4SDS]; *see also* C. Joseph Ross Daval & Aaron S. Kesselheim, *Authority of Medicare to Limit Coverage of FDA-Approved Products: Legal and Policy Considerations*, 183 JAMA INTERNAL MED. 999, 999 (2023).

361 Judith L. Heidebrink & Henry L. Paulson, *Lessons Learned from Approval of Aducanumab for Alzheimer's Disease*, 75 ANN. REVS. MED. 99 (2024) (quoting STAFFS OF THE COMM. ON OVERSIGHT & REFORM & COMM. ON ENERGY & COM., U.S. H.R., THE HIGH PRICE OF ADUHELM'S APPROVAL: AN INVESTIGATION INTO FDA'S ATYPICAL REVIEW AND BIOGEN'S AGGRESSIVE LAUNCH PLANS 17 (2022), https://cdn.vox-cdn.com/uploads/chorus_asset/file/24339017/Final_Aduhelm_Report_12.29.22.pdf [https://perma.cc/UX8E-2RUK]); *see also* Jason Karlawish, *Aducanumab and the Business of Alzheimer Disease—Some Choice*, 78 JAMA NEUROLOGY 1303, 1303 (2021); David J. Benjamin & Mark P. Lythgoe, *Modernising the US FDA's Accelerated Approval Pathway*, 24 LANCET ONCOLOGY 203 (2023); Holly Fernandez Lynch et al., *Extending the US Food and Drug Administration's Postmarket Authorities*, 4 JAMA HEALTH F., June 9, 2023, at 1, 7.

U.S. Senate and House also held hearings to investigate the FDA's decision and concerns of improper industry influence and passed new laws.[362] Newspapers nationwide published articles questioning the data supporting drug approval as well as the cost and improper industry influence.[363] This was a public debate over how much data is needed and what drugs should qualify for accelerated approval. The price tag

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362 Section 3210 "Modernizing Accelerated Approval" of the 2022 Food and Drug Omnibus Reform Act sought to strengthen FDA authority in drug withdrawals and confirmatory trial requirements. *See* Consolidated Appropriations Act of 2023, Pub. L. No. 117-328, Div. FF Title III, § 3210 (2022).

363 *See, e.g.*, Jacqueline Howard, *New Alzheimer's Drug Aducanumab: Cost, Side Effects, Timeline, and Other Questions Answered*, CNN: HEALTH (June 10, 2021, 8:06 AM), https://www.cnn.com/2021/06/09/health/aducanumab-questions-answered-wellness/index.html [https://perma.cc/XTU2-SNXG]; Julie Steenhuysen & Deena Beasley, *U.S. Approval of Biogen Alzheimer's Drug Sends Shares Soaring, Hailed as 'Big Day' for Patients*, REUTERS (June 7, 2021, 10:18 PM), https://www.reuters.com/business/healthcare-pharmaceuticals/us-fda-set-rule-controversial-biogen-alzheimers-drug-2021-06-07 [https://perma.cc/9PWD-DSZT]; Pam Belluck & Rebecca Robbins, *F.D.A. Approves Alzheimer's Drug Despite Fierce Debate Over Whether It Works*, N.Y. TIMES (July 20, 2021), https://www.nytimes.com/2021/06/07/health/aduhelm-fda-alzheimers-drug.html [https://web.archive.org/web/20250120122953/https://www.nytimes.com/2021/06/07/health/aduhelm-fda-alzheimers-drug.html]; Michael Hiltzik, *The FDA's Hasty Approval of an Unproven Alzheimer's Drug Is Bad News for Everyone*, L.A. TIMES (June 10, 2021, 5:08 PM), https://www.latimes.com/business/story/2021-06-10/fda-alzheimers-drug-aduhelm [https://perma.cc/8G8L-HJNU]; Matthew Perrone, *FDA Approves Much-Debated Alzheimer's Drug Panned by Experts*, ASSOCIATED PRESS (June 7, 2021, 6:02 PM), https://apnews.com/article/science-government-and-politics-business-health-2147d824af9cfde629041d83d9ca7a8d [https://perma.cc/4542-4EGA]; *FDA Approval of Biogen's Alzheimer's Drug Leaves Some 'Disappointed,'* FOX NEWS (June 8, 2021, 7:10 AM), https://www.foxnews.com/health/fda-approval-biogens-alzheimers-drug [https://perma.cc/YY4M-RHAA]; Scott, *supra* note 357; *How Everyone on Medicare Could End Up Paying for the Pricey New Alzheimer's Drug*, CBS NEWS (July 10, 2021, 12:30 PM), https://www.cbsnews.com/baltimore/news/how-everyone-on-medicare-could-end-up-paying-for-the-pricey-new-alzheimers-drug [https://perma.cc/VK9Z-R468]; Robert King, *Medicare Part B Premiums to Decline Slightly in 2023 Due to Low Aduhelm Use*, FIERCE HEALTHCARE (Sept. 27, 2022, 11:51 AM), https://www.fiercehealthcare.com/payers/medicare-part-b-premiums-decline-slight-2023-due-low-aduhelm-use [https://perma.cc/26D9-V9H3] ("The monthly Medicare Part B premium is expected to decline slightly in 2023 due to lower-than-expected use of the pricey Alzheimer's disease drug Aduhelm."); Tami Luhby, *Aduhelm, Priced at $56,000 a Year, Is a Key Factor Driving Up Medicare Premiums*, CNN (Nov. 16, 2021, 11:52 AM), https://www.cnn.com/2021/11/16/politics/aduhelm-alzheimer-medicare-increase [https://perma.cc/7QT6-SJMB].

($56,000 per patient for one year)[364] contributed to the national uproar.[365] The Center for Medicare and Medicaid Services (CMS) issued a rare "Coverage with Evidence Determination" that conditioned coverage on the manufacturer conducting further research on safety and efficacy.[366] That meant Medicare would only pay for the drug for participants in approved clinical trials.[367] Other payers and hospitals refused to add aducanumab to their formularies.[368] While disagreements between experts over data quantity and quality are ubiquitous in FDA drug approvals, congressional investigations, new statutes, CMS coverage refusals, and front-page media debates are exceptional.[369] Altogether, the

364 *ICER Issues Statement on the FDA's Approval of Aducanumab for Alzheimer's Disease*, INST. FOR CLINICAL & ECON. REV. (June 7, 2021), https://myemail.constantcontact.com/ICER-Issues-Statement-on-the-FDA-s-Approval-of-Aducanumab-for-Alzheimer-s-Disease.html?soid=1115682120931&aid=2vOhd8l4Mrw [https://perma.cc/UG9W-R3YL]; *see also* Juliette Cubanski & Tricia Neuman, *FDA's Approval of Biogen's New Alzheimer's Drug Has Huge Cost Implications for Medicare and Beneficiaries*, KFF (June 10, 2021), https://www.kff.org/medicare/issue-brief/fdas-approval-of-biogens-new-alzheimers-drug-has-huge-cost-implications-for-medicare-and-beneficiaries [https://perma.cc/UXB2-SKJV]; Benjy Sarlin, *How a Single New Alzheimer's Drug Could Blow Up the Federal Budget*, NBC NEWS (June 20, 2021, 7:02 AM), https://www.nbcnews.com/politics/politics-news/how-single-new-alzheimer-s-drug-could-blow-federal-budget-n1271074 [https://perma.cc/RDH2-BP7G] (reporting that Medicare would owe $57 billion a year for the single drug, which is "$20 billion more than Medicare Part B spent on all drugs combined in 2019" if one-sixth of eligible patients took the drug).

365 *See* Francis Crosson, Kenneth Covinsky & Rita F. Redberg, *Medicare and the Shocking US Food and Drug Administration Approval of Aducanumab*, 181 JAMA INTERNAL MED. 1278 (2021).

366 Press Release, *supra* note 360; *see also* Daval & Kesselheim, *supra* note 360, at 999 ("For a limited number of major coverage decisions, CMS issues . . . a statement of policy that supersedes local decision making and determines whether Medicare reimburses for a given product or service nationwide."); Joshua P. Cohen, *Does Medicare Draft Decision to Restrict Coverage of Aduhelm Hold Lessons for Future Launches of Drugs with No Proven Clinical Benefit?*, FORBES (Feb. 3, 2022, 10:27 AM), https://www.forbes.com/sites/joshuacohen/2022/02/01/does-medicare-draft-decision-to-restrict-coverage-of-aduhelm-hold-lessons-for-future-launches-of-drugs-with-no-proven-clinical-benefit [https://perma.cc/Z4LN-VZZQ].

367 *See* Sachs, *supra* note 352.

368 *See* Cohen, *supra* note 359.

369 Other drugs approved since 2021 faced the same difficult questions of how to weigh uncertain benefits against the dearth of effective treatments for a devastating disease and did not garner months of front-page headlines. For example, treatments for amyotrophic lateral sclerosis (ALS) and fibrodysplasia ossificans progressiva in 2022 and 2023. *See* Fernandez Lynch et al., *supra* note 361, at 1–2; Filipe B. Rodriguez & Joaquim J. Ferreira, *The Risks of Converting Post-Hoc Findings into Primary Outcomes in Subsequent Trials*, ANNALS TRANS. MED., Dec. 31, 2019, at 1–2; Andrew Joseph & Damian Garde, *In the Case of a Devastating Disease, the FDA Weighs an Experimental Drug's Muddled Data and a Desperate Need*, STAT (Aug. 14, 2023), https://www.statnews.com/2023/08/14/fop-fibrodysplasia-ossificans-progressiva-fda-decision [https://perma.cc/P6QU-TB4D]; *see also* Jonathan J. Darrow, Ameet Sarpatwari, Jerry Avorn & Aaron S. Kesselheim, *Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs*, 372 NEW ENG. J. MED. 279, 283–84 (2015); Largent et al., *supra* note 85, at 390 ("[M]any of the problems with FDA's aducanumab decision . . . are not unique. [But] aducanumab has

2021 aducanumab controversy and accusations of industry bias negatively impacted the FDA's reputation.[370] Questioning the FDA's science-based policy choices may shift public perceptions and itself further erode confidence in the FDA.[371]

Third, the aducanumab decision occurred concurrently with another hopefully once-in-a-century health crisis: the COVID-19 pandemic. Interdisciplinary real-time and post-emergency research has demonstrated a decline in public trust in the FDA during and after the COVID-19 pandemic.[372] A December 2020 survey by the Kaiser Family Foundation found that 55% of those surveyed did not trust the FDA to ensure safety and effectiveness of new COVID-19 vaccines, 53% were worried the vaccine was too new, and 51% were concerned about the role of politics in the development problem.[373] Questions of drug approval standards, such as how much data is sufficient to justify approval of COVID-19 therapies and who should decide, were debated across both newspaper headlines and kitchen tables.[374] This includes for example

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magnified attention to growing concerns about how FDA should balance evidence and access . . . .").

370 *See* Perrone, *supra* note 356.

371 *See* Schneider, *supra* note 80 (reporting that Califf said: "[T]hey're critiquing it to make it better. But to a lot of unsuspecting people that hear it, it just completely erodes their belief in the institution.").

372 *See* Tara Law, *More Than Half of Americans Worry That White House Pressure Will Lead to a Rushed Coronavirus Vaccine*, TIME (Sept. 11, 2020, 11:57 AM), https://time.com/5887777/rushed-vaccine-democrats-republicans [https://perma.cc/8Z3V-QACU] ("[H]alf of U.S. adults polled by Kaiser said the FDA and CDC are not paying enough attention to science when considering coronavirus treatments and recommendations, while 39% and 42% said the FDA and CDC, respectively, are paying too much attention to politics. Again, there's a significant gap between Democrats and Republicans, with the former much more worried about the politicization of the federal health agencies."); *see also* Robert Blendon & Mary Findling, *Nearly Half of Americans Don't Trust CDC and FDA—That's a Problem*, HILL (May 15, 2021, 8:30 AM), https://thehill.com/opinion/healthcare/553600-nearly-half-of-americans-dont-trust-cdc-and-fda-thats-a-problem [https://web.archive.org/web/20230929220824/https://thehill.com/opinion/healthcare/553600-nearly-half-of-americans-dont-trust-cdc-and-fda-thats-a-problem]; Williams B. Feldman et al., *Trust in the Food and Drug Administration: A National Survey Study*, 116 CLINICAL PHARMACOLOGY & THERAPEUTICS 408 (2024); Sarah D. Kowitt, Allison M. Schmidt, Anika Hannan & Adam O. Goldstein, *Awareness and Trust of the FDA and CDC: Results from a National Sample of US Adults and Adolescents*, PLOS ONE, May 16, 2017, 1, 10; Rand et al., *supra* note 79, at S60 ("The pandemic highlighted the need to scrutinize public trust in the FDA vaccine-approval process and the relationship of the FDA and its decisions to politics.").

373 Liz Hamel, Ashley Kirzinger, Cailey Muñana & Mollyann Brodie, *KFF COVID-19 Vaccine Monitor: December 2020*, KFF (Dec. 15, 2020), https://www.kff.org/coronavirus-covid-19/report/kff-covid-19-vaccine-monitor-december-2020 [https://perma.cc/9XJH-5WS3].

374 *See* Feldman et al., *supra* note 372, at 408 ("[T]he trustworthiness of public health agencies can be easily undermined. The FDA faced criticism, particularly during the early part of the COVID-19 pandemic. . . . ").

convalescent plasma, remdesivir,[375] hydroxychloroquine,[376] ivermectin,[377] and nirmatrelvir.[378] Surveyed citizens at the time raised questions regarding the reliability, quality, and quantity of data supporting COVID-19 treatments and declining confidence in the FDA.[379] It is exceptional that the public had strong views on vaccine and drug safety data[380] as most patients do not have opinions on new drugs. In 2016, drug companies spent almost $6 billion on direct-to-consumer advertisements to try to inform patients about new treatment options, among other goals.[381]

Scholars found that mistrust in the FDA was due to multiple factors including perceived political interference and "premature [FDA] statements of efficacy or safety that [were] later contradicted by emerging evidence."[382] For example, in May 2020, Operation Warp Speed created

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375 Jon Cohen & Kai Kupferschmidt, *The 'Very, Very Bad Look' of Remdesivir, the First FDA-Approved COVID-19 Drug*, SCI. (Oct. 28, 2020), https://www.science.org/content/article/very-very-bad-look-remdesivir-first-fda-approved-covid-19-drug [https://perma.cc/3SAZ-4PUZ] ("[O]n 22 October, the [FDA] approved remdesivir for use against [COVID-19] in the United States—the first drug to receive that status. . . . [This] decision[] baffled scientists who have closely watched the [disappointing] clinical trials . . . .").

376 Roy Perlis et al., *Misinformation, Trust, and Use of Ivermectin and Hydroxychloroquine for COVID-19*, JAMA HEALTH F., Sept. 29, 2023, at 1, 1 (finding in a study of 13,438 individuals with prior COVID-19 infections that "[a]pproximately 1 in 20 people . . . reported using a non-evidence-based treatment, and these individuals were more likely to exhibit specific deleterious beliefs and attitudes not captured by political affiliation").

377 Darius Tahir, *Few Firm Beliefs and Low Trust: Americans Not Sure What's True in Age of Health Misinformation*, KFF HEALTH NEWS (Aug. 22, 2023), https://kffhealthnews.org/news/article/few-firm-beliefs-low-trust-health-misinformation-kff-poll [https://perma.cc/W7QR-P9N4] (finding that only 20% of survey responders "had 'a great deal' of trust in the" FDA and "[a]round 3 in 10 Americans still believe ivermectin is an effective treatment for [COVID]. . . . [and] few place significant trust in any form of news media or official institution to accurately convey information about health topics").

378 Dan-Yu Lin et al., *Nirmatrelvir or Molnupiravir Use and Severe Outcomes from Omicron Infections*, 6 JAMA, Sept. 21, 2023, at 1.

379 Rand et al., *supra* note 79, at S61–S62.

380 Sarah Elbeshbishi & Ledyard King, *Exclusive: Two-Thirds of Americans Say They Won't Get COVID-19 Vaccine When it's First Available, USA TODAY/Suffolk Poll Shows*, USA TODAY (Sept. 7, 2020, 12:57 PM), https://www.usatoday.com/story/news/politics/2020/09/04/covid-19-two-thirds-us-wont-take-vaccine-right-away-poll-shows/5696982002 [https://perma.cc/WN2Y-3R67] (reporting that, in a survey of 1,000 people, "[t]wo-thirds of U.S. voters say they won't try to get a coronavirus vaccine as soon as it becomes available, and one in four say they don't want to ever get it . . . [as] the number of COVID-19 cases surpassed 6 million").

381 Lisa M. Schwartz & Steven Woloshin, *Medical Marketing in the United States, 1997–2016*, 321 JAMA 80, 80 (2019); Natasha Parekh & William H. Shrank, *Dangers and Opportunities of Direct-to-Consumer Advertising*, 33 J. GEN. INTERNAL MED. 586, 586 (2018).

382 Aris Angelis & Jonathan Darrow, *Safeguarding Evidence-Based Decision Making in the FDA for COVID-19 Vaccines*, 39 VACCINE 2328, 2328 (2021); *see* Jordan Paradise & Becky Bavlsik, *Pandemic, Politics, Public Health, and the FDA*, 8 BELMONT L. REV. 301, 328 (2021); Allison M. Whelan, *Executive Capture of Agency Decisionmaking*, 75 VAND. L. REV. 1787, 1833 (2022).

partnerships between multiple agencies and private industries to fast-track vaccine development and distribution.[383] To some, these industry partnerships in combination with statements from the executive branch appeared to pressure the FDA to approve a vaccine before it was ready.[384] Some members of the public were concerned that politically motivated actions would compromise the FDA's "time-tested, science- and evidence-based processes, including risk-benefit assessment by independent advisory committees of nongovernment scientists, physicians, and other experts."[385] By September of 2020, 62% of U.S. adults surveyed were worried that the FDA would approve a COVID-19 vaccine without making sure it was safe and effective due to political influence.[386] Taken together, the opioid epidemic, aducanumab, and COVID-19 crises involved public debate on the FDA's science-based drug approval decisions between 2019 and 2023, and likely eroded public confidence in FDA drug approvals.[387]

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383 U.S. GOV'T ACCOUNTABILITY OFF., GAO-21-319, OPERATION WARP SPEED: ACCELERATED COVID-19 VACCINE DEVELOPMENT STATUS AND EFFORTS TO ADDRESS MANUFACTURING CHALLENGES (2021).

384 Donna Young, *US FDA Leaders Plead for Trust While Poll Shows Americans' Confidence Dwindling*, S&P GLOB. (Sept. 10, 2020), https://www.spglobal.com/marketintelligence/en/news-insights/latest-news-headlines/us-fda-leaders-plead-for-trust-while-poll-shows-americans-confidence-dwindling-60285178 [https://perma.cc/HFS3-PRA7] ("President Donald Trump has exerted political pressure on both the FDA and the CDC. . . . [by making] an unsubstantiated claim Aug. 22 that FDA scientists are 'deep state' operatives who are slowing down the regulatory process to harm him politically[,] . . . the administration was willing to put 'heat' on regulators if they 'don't see the light' . . . [and] the FDA has also disclosed little about how it is making decisions, 'squandering the chance to build up understanding and support . . . .'").

385 Sudhakar M. Pai et al., *Science and Evidence-Based Review and Approval of COVID-19 Vaccines: A Statement of Support for the US FDA*, 61 J. CLINICAL PHARMACOLOGY 277, 277 (2021); *see also* Robert M. Califf et al., *Seven Former FDA Commissioners: The FDA Should be an Independent Federal Agency*, 38 HEALTH AFFS. 84 (2019). This concern is not new: "The tension between politics and expertise raises difficult questions about the appropriate role of 'political reasons' in agency decision-making" and the role of science and policy in agency choices more generally. Glen Staszewski, *Public Engagement with Elected Representatives*, YALE J. ON REGUL. (Mar. 22, 2023), https://www.yalejreg.com/nc/public-engagement-with-elected-representatives-by-glen-staszewski [https://perma.cc/3WUS-5ZZT]; *see also* Reiner Grundmann, *The Problem of Expertise in Knowledge Societies*, 55 MINERVA 25, 37 (2017) ("The notion that the scientific component of decision-making can be separated from the political and entrusted to independent experts has effectively been dismantled by recent contributions of the political and social studies of science." (quoting SHEILA JASANOFF, THE FIFTH BRANCH: SCIENCE ADVISORS AS POLICY MAKERS 16 (1990))).

386 Law, *supra* note 372; *see also* Young, *supra* note 384; Angelis & Darrow, *supra* note 382, at 2330.

387 *See* Beth Snyder Bulik, *FDA Reputation Takes Another Hit After Scathing Aducanumab Advisory Panel Meeting*, FIERCE PHARMA (Nov. 9, 2020, 12:34 PM), https://www.fiercepharma.com/marketing/fda-reputation-takes-another-hit-after-scathing-alzheimer-s-drug-adcomm [https://perma.cc/ET7N-XQP7] ("The FDA's image is already under a cloud

B. *Connecting Power and Deference*

Trust in the FDA is important; FDA scholars have demonstrated the connections between regulatory flexibility, scientific expertise, and reputation: "The power afforded to the administrative state is heavily reliant on public trust and the perception of evidence-based agency decision-making. Organizational reputation is key to preserving regulatory power."[388] It follows that "[a] hit to the FDA's reputation isn't just about the agency . . . . [i]t bleeds onto the pharma industry, too."[389] This Section argues the "hits" from the three drug crises may have bled into courts as well; declining judicial deference to the FDA's longstanding science-based policy choices between 2019 and 2023 described in Part I may be related to the FDA's declining reputation and lost trust in the wake of a simultaneous public health crisis.

The suggestion that judicial deference to the FDA may be connected to its demonstrated scientific expertise draws on theoretical foundations in both the FDA and administrative law. Administrative law scholars have also noted the connection between public confidence in agency expertise and judicial concern over unfettered agency discretion.[390] As explained by Professor James T. O'Reilly, "[T]he media's negative portrayal of the politicized Agency may cast doubt on its legal arguments in the courtroom: judges are susceptible to the same human influences from past and current experiences and from information flows."[391]

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after this year's emergency authorizations of questionable COVID-19 treatments—under apparent political pressure."); *see also* Baden et al., *supra* note 87, at e148(2) ("Without a clear, transparent, and scientifically sound decision-making process, the trust the FDA has built and maintained over the past century is eroding.").

388 Christina Fuleihan, *Shattering the Mirage: The FDA's Early COVID-19 Pandemic Response Demonstrates a Need for Reform to Restore Agency Credibility*, 48 AM. J.L. & MED. 307, 307 (2022); *see also* CARPENTER, *supra* note 81, at 33 ("Reputations can expand or deflate the legal authority that agencies exercise by virtue of law and delegation."); Kowitt et al., *supra* note 372, at 1 ("Trust in government agencies plays a key role in advancing these organizations' agendas, influencing behaviors, and effectively implementing policies.").

389 Bulik, *supra* note 387, at 976.

390 *See* Wagner, *supra* note 91, at 2024–29 (noting that from the growth of the administrative state around the Civil War until the 1940s, "[t]he conception of the agency-as-expert[s] is one of the cornerstones of the U.S. administrative process . . . [such that] agencies in the United States were generally viewed as neutral experts who would resolve the nation's complex socio-political challenges").

391 Scholars have previously suggested a relationship between judicial deference and negative public perceptions of the FDA. *See* O'Reilly, *supra* note 12, at 940 ("[I]n recent years, the news media has disdained the Bush Administration's political manipulation of the FDA and has questioned the Agency's scientific integrity. This criticism of the Administration's political manipulations of the FDA (for the benefit of conservative political constituencies) may diminish the willingness of federal judges to defer to our nation's most distinguished regulatory Agency.");

In this specific case, the questions asked in the April 2023 dueling mifepristone cases,[392] decided about a month after the expiration of the federal COVID-19 public health emergency declaration,[393] were similar to the questions used in national surveys on controversial FDA COVID-19 drug approvals.[394] Like the courts,[395] newspapers also questioned which drugs should qualify for accelerated approval, what questions must be tested in clinical trials to demonstrate meaningful clinical benefit, and whether the conditions of approval were sufficiently close to the clinical trial conditions, among others with aducanumab.[396] Similar comparisons can be drawn to the other science-based policy questions debated by courts and the broader public. While far from conclusive, the timing and parallel questions raise the possibility that these public debates on science-based policy choices influenced courtrooms. If the shift in judicial deference to the Agency was due to the FDA's reputational damage, efforts to restore public trust may also restore judicial deference.

C. *Counterarguments*

However, judicial challenges to the FDA's longstanding science-based policy choices between 2019 and 2023 may not be fully explained by the FDA's declining reputation in these simultaneous drug crisis. This Section explores if the shift in judicial deference to the FDA may be part of a normal cyclic response to crisis, part of an expected trend in a national emergency, and part of broader trends in Agency deference.

First, it is possible that declining judicial deference to the FDA may be part of a cyclical pattern between the FDA, Congress, and courts

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see also Jody Freeman & Adrian Vermeule, Massachusetts v. EPA*: From Politics to Expertise*, 2007 SUP. CT. REV. 51, 54, 63–64 (2007) (observing the role of courts when politics interfere with decisions requiring an agency's scientific expertise).

392 *See supra* Section I.B.1 (discussing what types of drugs should qualify for accelerated approval, what outcomes must be tested in clinical trials to demonstrate meaningful clinical benefit, how data comparing the safety of alternative therapies should be collected and weighed, whether the conditions of approval are sufficiently close to the clinical trial conditions, whether the conclusion is consistent with the underlying data, whether the underlying data is reliable, etc.).

393 The public health emergency expired on May 11, 2023. *See OIG's COVID-19 Public Health Emergency Flexibilities End on May 11, 2023 upon Expiration of the COVID-19 Public Health Emergency Declaration*, U.S. DEP'T HEALTH & HUM. SERV. OFF. OF INSPECTOR GEN. (Mar. 10, 2023), https://oig.hhs.gov/coronavirus/covid-flex-expiration.asp [https://perma.cc/ZUA5-ASYG]; *End of the Federal COVID-19 Public Health Emergency (PHE) Declaration*, CTR. FOR DISEASE CONTROL & PREV. (Sept. 12, 2023), https://archive.cdc.gov/www_cdc_gov/coronavirus/2019-ncov/your-health/end-of-phe.html [https://perma.cc/P28U-7SDY].

394 *See supra* Section III.A.

395 *See supra* Sections I.B.1, III.A; All. for Hippocratic Med. v. FDA, 668 F. Supp. 3d 507, 549, 555 (N.D. Tex. 2023).

396 *See* sources cited *supra* note 322.

occurring over decades rather than years. Scholars have argued that trust in government institutions is cyclic.[397] The FDA, too, has had cycles of crisis that impact its reputation; in the HIV/AIDS crisis and Vioxx scandals, the Agency recovered after congressional action but new laws created new concerns.[398] For example, the heavily-criticized Accelerated Approval Program used for aducanumab was created as a response to perceived delays during the HIV/AIDS crisis as the FDA again faced significant criticism.[399] The REMS Program criticized by all three courts in the mifepristone litigation was created by a 2007 statute in response to questions of post-approval adverse event surveillance after Vioxx as the FDA also faced significant criticism.[400] After COVID-19, aducanumab and the opioid crisis, the FDA has been actively working to improve its reputation[401] and it is possible that further congressional efforts will

397 *See Public Trust in Government: 1958–2024*, PEW RSCH. CTR. (June 24, 2024), https://www.pewresearch.org/politics/2024/06/24/public-trust-in-government-1958-2024 [https://perma.cc/7TCY-9PE4] ("When the National Election Study began asking about trust in government in 1958, about three-quarters of Americans trusted the federal government to do the right thing almost always or most of the time. Trust in government began eroding during the 1960s . . . . [but c]onfidence in government recovered in the mid-1980s before falling again in the mid-'90s. But as the economy grew in the late 1990s, so too did trust in government. Public trust reached a three-decade high shortly after the 9/11 terrorist attacks but declined quickly after."); *see also* Betsey Stevenson & Justin Wolfers, *Trust in Public Institutions over the Business Cycle*, 101 AM. ECON. REV. 281, 281–87 (showing "that the public's confidence in each of these institutions [including Congress, banks, Supreme Court, big business, and newspapers] is pro-cyclical" through a time-series analysis); Felix Gille, Sarah Smith & Nicholas Mays, *Evidence-Based Guiding Principles to Build Public Trust in Personal Data Use in Health Systems*, 8 DIG. HEALTH, June 19, 2022, at 1–8; *cf.* Jack Citrin & Laura Stoker, *Political Trust in a Cynical Age*, 21 ANN. REV. POL. SCI. 49, 64 (2018) (noting declines in trust may not be able to be restored quickly).

398 *See supra* note 102; *see also* notes 33, 409, 449.

399 *The History of FDA's Role in Preventing the Spread of HIV/AIDS*, FDA (Mar. 14, 2019), https://www.fda.gov/about-fda/fda-history-exhibits/history-fdas-role-preventing-spread-hivaids [https://perma.cc/HUG2-9WWN]; *see also* John Carroll, *The Accelerated Approval Debate: Faster FDA Drug Approvals May Mean Less Efficacy Data*, 9 BIOTECH. HEALTHCARE 6 (2012) ("Twenty years ago, Congress set up the accelerated approval pathway for HIV and cancer medications to help speed new treatments that provided some measure of hope to patients in need."); Hwang et al., *supra* note 353 ("Although the FDA has increasingly used accelerated approval (with 278 accelerated approvals from 1992 to 2021), this pathway has been controversial, particularly because of these drugs' high cost, uncertain efficacy, and absence of completed confirmatory studies.").

400 Stephen Northrup, *Looking Back and Looking Ahead: Vioxx, Drug Safety, and the Legacy of Sen. Michael Enzi*, STAT NEWS (Dec. 21, 2020), https://www.statnews.com/2020/12/21/vioxx-drug-safety-legacy-senator-michael-enzi [https://perma.cc/38TP-SYWF] ("After 18 months of hearings and negotiations, Enzi and Kennedy formally introduced the risk evaluation and mitigation concept as the centerpiece . . . ."); Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, §§ 101–09, 121 Stat. 823, 825–42 (codified at 21 U.S.C. § 379g–j).

401 *See* FDA, SMG 9001.1, SCIENTIFIC INTEGRITY AT FDA, §§ 1–2 (2023), https://www.fda.gov/media/82932/download [https://web.archive.org/web/20250114113946/https://www.fda.gov/media/82932/download] ("Establishing and maintaining integrity of the scientific process and

increase trust in the FDA.[402] Already, Congress has passed legislation to address some underlying problems contributing to the aducanumab controversy.[403] If true, a cyclic pattern suggests there will not be wider successful challenges to longstanding FDA policies.

Second, judicial suspicion of executive actions may be an expected outcome of a national crisis.[404] As D.C. Circuit Chief Judge William Cranch wrote in 1807, judicial review takes on particular importance during national emergencies "when the public mind is agitated, when wars . . . conspiracies and treasons excite alarm, [i]t is the duty of a court to be peculiarly watchful."[405] While scholars argue if there is judicial skepticism or deference to federal government actions during national emergencies,[406] Professor Amanda L. Tyler has argued that the Supreme Court was inconsistent when examining public health questions during the COVID-19 pandemic, having "applied increasingly rigorous scrutiny to government regulations predicated upon public health" but also having "deferred to government decisions made in the context of the

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scientific data is crucial to the Agency's ability to arrive at sound decisions and to maintain public trust. . . . FDA has a long, and continuing, history of working to ensure integrity in its scientific and regulatory processes and, as a result, centers have put in place related policies, procedures, and initiatives."); *see also* B.L. Wilson, *FDA Commissioner Addresses Public Distrust and Social Media Impact on Decision Making*, GW TODAY (Feb. 8, 2024), https://gwtoday.gwu.edu/fda-commissioner-addresses-public-distrust-and-social-media-impact-decision-making [https://perma.cc/6DLN-N892] (discussing steps that FDA Commissioner Cardiff believes the Agency needs to take to restore trust).

402 *See supra* note 171, McClellan, *supra* note 88, at 514; Krumholz et al., *supra* note 88.

403 *See* Hwang et al., *supra* note 353; August T. Horvath, *2023 FDA Regulatory Developments*, FOOD & DRUG L. INST. (May 2024), https://www.fdli.org/2024/05/2023-fda-regulatory-developments [https://perma.cc/CYC7-PB8M] ("FDA can now require the sponsor to have confirmatory trials underway before being granted accelerated approval, and provides for expedited withdrawal of a previously granted approval if the confirmatory trials fail to confirm a clinical benefit.").

404 Steve Vladeck & Lindsay F. Wiley, *COVID-19 Reinforces the Argument for "Regular" Judicial Review—Not Suspension of Civil Liberties—In Times of Crisis*, HARV. L. REV. BLOG (Apr. 9, 2020), https://harvardlawreview.org/blog/2020/04/covid-19-reinforces-the-argument-for-regular-judicial-review-not-suspension-of-civil-liberties-in-times-of-crisis [https://perma.cc/D9VR-N5WY] ("[C]ourts entertaining challenges to these orders have stumbled into the central (and long-running) normative debate over emergency powers: Should constitutional constraints on government action be suspended in times of emergency (because emergencies are 'extraconstitutional'), or do constitutional doctrines forged in calmer times adequately accommodate exigent circumstances?"); *see also* Kenneth Lowande & Jon C. Rogowski, *Executive Power in Crisis*, 115 AM. POL. SCI. REV. 1406 (2021).

405 United States v. Bollman, 1 Cranch C.C. 373 (D.C. Cir. 1807).

406 *See* ERIC A. POSNER & ADRIAN VERMEULE, TERROR IN THE BALANCE: SECURITY, LIBERTY, AND THE COURTS 3 (2007) ("When national emergencies strike, the executive acts, Congress acquiesces, and courts defer."). *Contra* Fionnuala Ni Aoláin & Oren Gross, *A Skeptical View of Deference to the Executive in Times of Crisis*, 41 ISRAEL L. REV. 545 (2008).

pandemic in several other contexts."[407] It is possible that the Part I cases may reflect more rigorous scrutiny of the federal government during a national emergency.[408] If so, such scrutiny of health agencies during a national emergency would be expected to normalize after the emergency regardless of public trust. Like the cyclic pattern, this explanation also suggests there will not be wider successful challenges to longstanding FDA policies.

Finally and most importantly, challenges to the FDA cannot be considered separate from broader declines in deference to agency expertise, authority, and legitimacy.[409] FDA scholar-physicians had argued to the Supreme Court in *Loper Bright* that *Chevron* deference to the FDA was essential to the FDA's regulatory framework,[410] yet many of the cases cataloged here illustrate that courts have already begun questioning FDA policy choices with *Chevron* deference. Of the fifty-eight cases and ninety-four opinions viewed, twenty-seven cases (46.5% and forty opinions) cited *Chevron* deference directly. Courts sided with the FDA in nineteen cases (70% of the twenty-seven relevant cases).[411] The cluster of successful legal challenges described in Part I suggests that the FDA may have been subject to some of the same scrutiny facing other agencies rather than broader deference or exceptionalism. Unlike cyclic patterns or national emergencies, this explanation suggests there will be wider successful challenges to longstanding FDA policies.

The role of agency deference is even more compelling after the Supreme Court's decision in *Loper Bright* overruled the second step of the *Chevron* doctrine.[412] Using the "traditional tools of statutory construction," courts now resolve ambiguities in statutes to find the "best meaning."[413] *Loper Bright* explicitly rejects deference in cases involving "technical statutory questions,"[414] holding that the APA requires courts

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407 Amanda L. Tyler, *Judicial Review in Times of Emergency: From the Founding Through the Covid-19 Pandemic*, 109 VA. L. REV. 489, 494–95 (2023); *see also* Whelan, *supra* note 373, at 1867–68.

408 *See supra* Section I.B.

409 *See generally* Gillian E. Metzger, *The Roberts Court and Administrative Law*, 2019 SUP. CT. REV. 1 (2020).

410 Brief of Dr. Reshma Ramachandran & Dr. Joseph S. Ross as Amici Curiae in Support of Respondents at 5–6, Relentless, Inc. v. Dep't of Com., 144 S. Ct. 325 (2023) (No. 22-1219), 2023 WL 9000700.

411 *See infra* Appendix I.

412 *See* Loper Bright Enters. v. Raimondo, 603 U.S. 369, 395 (2024); *cf.* Wendy E. Parmet, Loper Bright *and the Death of Deference in the Administration of Health Policy*, HEALTH AFFS. (July 18, 2024), https://www.healthaffairs.org/content/forefront/loper-bright-and-death-deference-administration-health-policy [https://perma.cc/ZH45-Q876] ("*Loper Bright* may be less significant than first meets the eye.").

413 *Loper Bright*, 603 U.S. at 400–01.

414 *Id.* at 402.

to exercise independent judgment in determining whether an agency action aligns with its statutory authority.[415] Many scholars predicted that these and other recent changes in administrative law will lead to increased judicial review, uncertainty, and unpredictability in drug approvals.[416] Professors Erin C. Fuse Brown and Rachel E. Sachs suggested that the "FDA may also face new legal challenges," including over the classification of products like laboratory-development tests.[417] Other scholars predicted that litigation may involve high-profile issues like non-discrimination, the Affordable Care Act, and reproductive health.[418]

The cases examined in this Article suggest that future challenges may not be limited to highly politically controversial topics.[419] If new challenges follow the Part I cases, there may be increasing litigation on both politically charged and lucrative products for that company. That is, litigants might question agencies' science-based policy choices to gain competitive advantages including by challenging classifications of products as drugs or devices, as well as challenges to the application of commonly accepted manufacturing requirements and exclusivities. Historically, in an industry that "thrives on predictability,"[420] challenges to settled practices may be disfavored as lawsuits are expensive, time-consuming, and unpredictable.[421] However, if challenges are likely to succeed and extend monopolies, more litigation may be forthcoming after *Loper*. Therefore, understanding judicial deference to longstanding FDA policies is particularly timely.

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415 *Id.* at 384.

416 *See* CTR. FOR HEALTH L. & POL'Y INNOVATION, HARVARD L. SCH.,"HUBRIS SQUARED": WHAT SCOTUS DECISION GUTTING DEFERENCE TO PUBLIC AGENCIES MEANS FOR HEALTH CARE PROTECTIONS (July 17, 2024), https://chlpi.org/wp-content/uploads/2024/07/HCIM-Loper-Bright-SCOTUS_FINAL.pdf [https://perma.cc/4HBB-Z2CA].

417 Rachel E. Sachs & Erin C. Fuse Brown, *Supreme Power—The Loss of Judicial Deference to Health Agencies*, 391 NEW ENG. J. MED. 777, 778 (2024).

418 *See* Sections I.B.2–4.

419 The role of politics in judicial review of drug determinations is beyond the scope of this Article. *See id.*

420 *For Industry That Thrives on Predictability, Health Law Uncertainty Provokes Frustration*, KFF HEALTH NEWS (Apr. 3, 2017), https://kffhealthnews.org/morning-breakout/for-industry-that-thrives-on-predictability-health-law-uncertainty-provokes-frustration [https://perma.cc/TQL9-6ALQ]; *see supra* Section I.A.

421 *See* Halpern, *supra* note 195 ("[I]t costs a lot of money to sue the federal government—actually, to sue anyone in the health care system." (quoting Interview by Pharmacy Times with Ron Lanton III, *supra* note 195)); *see also* Wagner, *supra* note 22, at 97 ("[I]f the courts' scientific competency is less than that of the party they are reviewing, it is unclear what the courts are contributing to the exercise."); Sutter, *supra* note 268 ("[H]aving deference for agency rulemaking provides a more reliable, uniform, regulatory regime that companies can make investment decisions based around.").

D. *Implications*

As Elizabeth Fisher, Pasky Pascual, and Wendy Wagner insightfully explain, the optimal role of judicial review is unclear as

> courts do not have the expertise of the agencies they are reviewing; they are legal institutions. They are also not political and need to restrain from becoming amateur policy makers in the course of their review. By granting courts authority to review science-based regulatory decisions, there is a risk they will unravel layers of careful scientific work as a result of their combined ignorance and judicial second-guessing.[422]

The potential negative outcomes that have been predicted are dire: delays, increased drug costs, and industry unpredictability.[423] FDA scholars have predicted that substantive judicial review can threaten scientific integrity and public health.[424] Lawsuits against the FDA inevitably divert scarce judicial and agency resources[425] and may limit the

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422 Fisher et al., *supra* note 90, at 1682.

423 *See* Andrew M. London & Kian Azimpoor, *Loper Bright's Potential Impact on the U.S. Department of Health and Human Services*, BLOOMBERG L. (June 2024), https://www.bloomberglaw.com/external/document/X3EH5278000000/litigation-professional-perspective-loper-bright-s-potential-imp [https://perma.cc/3WG2-LGPH] (discussing uncertainty on reliance on new or existing regulations); Parmet, *supra* note 412 (providing that rulings "stand as a symbol of the Court's hostility to the administrative state . . . make it far more difficult for agencies to protect the nation's health"); David A. Simon & Michael J. Young, *The Supreme Court's* Loper Bright *Ruling: Implications for Clinical Testing, Innovation, and Public Health*, 332 JAMA 1325, 1325–26 (2024); Halpern, *supra* note 195 ("On the day *Chevron* was overturned, the American Cancer Society, American Heart Association, American Lung Association, and 13 other associations released a joint statement claiming that the Court's decision 'threatens to disrupt [the] public health care system.' . . . Many observers are expecting a wave of challenges ultimately leading to self-regulation in the pharmaceutical industry." (first alteration in original) (first quoting Press Release, Am. Acad. Pediatrics et al., Supreme Court Decision to Overturn 'Chevron Deference' Threatens to Disrupt Public Health Care System (June 28, 2024), https://newsroom.heart.org/news/supreme-court-decision-to-overturn-chevron-deference-threatens-to-disrupt-public-health-care-system [https://perma.cc/F7LD-WSSD]; then quoting Interview by Pharmacy Times with Ron Lanton III, *supra* note 195)).

424 *See* Nikhil Chaudhry, Reshma Ramachandran & Joseph Ross, *Overruling* Chevron *and FDA Decision-Making*, YALE J. ON REGUL. (Feb. 9, 2024), https://www.yalejreg.com/nc/overruling-chevron-and-fda-decision-making-by-nikhil-chaudhry-dr-reshma-ramachandran-and-dr-joseph-ross [https://perma.cc/3SRW-8ADB]; *see also* O'Reilly, *supra* note 12, at 940 ("[I]f the FDA loses its legacy of deference, its ability to regulate efficiently will diminish significantly.").

425 *See* Samidh Guha & Kelly McGee, *In Loper Bright's Shadow: An Overworked Judiciary Becomes Further Burdened*, THOMSON REUTERS (Oct. 3, 2024), https://www.thomsonreuters.com/en-us/posts/government/loper-bright-judiciary-impact [https:/perma.cc/ 5UYC-2EHW] ("[T]he Supreme Court's decisions in four major cases . . . together shift review of decision-making from administrative and regulatory forums into federal courts. Now the judicial system, already overtaxed and plagued by delays, faces an unavoidable deluge of litigation in areas requiring

FDA's ability to adjust to changing circumstances.[426] Disagreeing experts risk a "new battle of expertise" where "courts play a role in sorting and validating the claims of competing experts,"[427] which creates the risk of putting "an official imprimatur on the junk science."[428]

Scholars disagree on the optimal role of judicial review of drug approvals. Some scholars have gone so far as to imply FDA drug approval decisions should be beyond reproach.[429] They dismissed the role judicial scrutiny of drug approvals and raised doubts regarding the potential for corrective benefits.[430] This response has appeal: no one wants a system where deliberative FDA scientists are replaced by lawyers arguing over which drugs should be approved before judges untrained in biostatistics, while patients who need those medications suffer in wait depending on which circuit they reside. Challengers, however, point out that the FDA is subject to judicial review under the APA for much needed good governance,[431] and there is "nothing untoward about judicial scrutiny of FDA drug approval decisions even if in [the mifepristone] case it proceeded in an over-the-top manner."[432] As explained by Fifth Circuit Judge James Ho during oral arguments on May 17, 2023, "[i]f the FDA didn't consider an important part of the problem, it is [the court's] role"

subject-matter expertise with no increase in capacity or resources."); Sutter, *supra* note 268 ("Stacy Cline Amin, a partner at Morrison Foerster in Washington DC and a former FDA chief counsel, said the agency will have to divert a lot more resources into how it documents its decisions, including decision memos that take a lot of time and effort, going forward.").

426 *See generally* sources cited *supra* note 406.

427 Aziza Ahmed, *Abortion Experts*, 2022 U. CHI. LEGAL F. 1, 20 (2023). Experts often disagree about where to draw the line in any particular decision, even if there is a general consensus on broad principles. *See* Jonathan J. Koehler & John B. Meixner, *Decision Making and the Law: Truth Barriers*, *in* THE WILEY-BLACKWELL HANDBOOK OF JUDGMENT AND DECISION MAKING 749 (Gideon Keren & George Wu eds., 2015).

428 Posting of Edward P. Richards, richards@lsu.edu, to adminlaw@listserv.lsu.edu (Aug. 17, 2023, 7:58 PM) (on file with author).

429 *See* Aaron et al., *supra* note 9, at 1736 ("To reduce the uncertainty that these courts have created, Congress could explicitly give the FDA the final say in approving abortion drugs—or drugs more generally.").

430 *See* Whelan, *supra* note 372, at 1866–73; *see also* Califf et al., *supra* note 385, at 84–85. *But see* Troy et al. *supra* note 145.

431 *See* Noah, *supra* note 14, at 924 ("[O]ver the course of a century of struggling to protect the public health with its limited statutory powers and often inadequate resources, the FDA evidently has institutionalized a practice of cavalierly ignoring legal constraints."); 21 C.F.R. § 314.235 (1985).

432 Noah, *supra* note 9, at 62; *see also* Donley & Zettler, *supra* note 9, at 66 ("We did not assert . . . that judges should not or cannot review FDA decisions, including drug approvals. Indeed, our prior published work describes the necessity of such review." (footnote omitted)); O'Reilly, *supra* note 12, at 962 ("Given that the FDA can be buffeted on both sides by those with political motives, the Judiciary may not wish to maintain deference to the FDA's scientific choices.").

to review.[433] The opioid litigation discussed in Section III.A illustrates how judicial review adds meaningful value to the post-drug approval regulatory market through transparency and promoting equitable, safe access to medications.[434] Judicial review has an important role when agencies err, and the FDA does not always get the science or law correct. There are decades of examples that call the FDA's decision-making and oversight process into question, including the non-steroidal anti-inflammatory drug,[435] suicide risks of antidepressants in teenagers,[436] and even asthma treatments for children.[437]

Rather than continuing the "major trope of modern administrative law [that j]udicial review cures all,"[438] the benefits of judicial review in FDA drug approvals require nuanced consideration. With declining trust

433 Oral Argument at 32:06, All. for Hippocratic Med. v. FDA., 78 F.4th 210 (5th Cir. 2023) (No. 23-10362), https://www.ca5.uscourts.gov/OralArgRecordings/23/23-10362_5-17-2023.mp3 [https://perma.cc/LFS4-TCP5]; All. for Hippocratic Med. v. FDA, 78 F.4th 210, 256–57 (5th Cir. 2023); Tierney Sneed, *Takeaways from the 5th Circuit Arguments Over Abortion Drug Access*, CNN POLITICS (May 17, 2023, 8:26 PM), https://www.cnn.com/2023/05/17/politics/abortion-drug-mifepristone-5th-circuit-hearing-takeaways/index.html [https://perma.cc/HDS8-VWU3].

434 PATRICIA J. ZETTLER ET AL., EXTERNAL REVIEW OF FDA REGULATION OF OPIOID ANALGESICS FINAL REPORT 2, 12 (2023), https://www.fda.gov/media/165238/download [https://web.archive.org/web/20250213015030/https://www.fda.gov/media/165238/download]; *supra* note 434; *see supra* Section III.A. For further discussion on this argument, please see Anjali D. Deshmukh, Justly Judging Prescriptions (unpublished manuscript) (on file with author) (describing the role of courts in the broad post-approval "pseudo-regulatory" system between FDA approval and patients taking a drug).

435 *See* Krumholz et al., *supra* note 88, at 120 ("Rofecoxib (Vioxx) was introduced by Merck in 1999 as an effective, safer alternative to non-steroidal anti-inflammatory drugs for the treatment of pain associated with osteoarthritis. It was subsequently found to increase the risk of cardiovascular disease and withdrawn from the worldwide market."); Jeanne Lenzer, *FDA Is Incapable of Protecting US "Against Another Vioxx,"* 329 BRITISH MED. J. 1253, 1253 (2004) (reporting that an agency expert described Vioxx approval as the "single greatest drug safety catastrophe in the history of this country or the history of the world," and demonstrating that Vioxx had billions of sales over its five-year life span between 1998 and 2003, but misleading studies obscured increased risks of myocardial infarction and stroke—88,000 Americans had heart attacks from taking Vioxx, and 38,000 of them died); Peter Jüni et al., *Risk of Cardiovascular Events and Rofecoxib: Cumulative Meta-Analysis*, 364 LANCET 2021 (2004).

436 The FDA required a black box warning for antidepressant drugs for young adults following multiple media reports about the link between antidepressant usage and suicide in 2004, which some regard as overcautious. *See* Michele Fornaro et al., *The FDA "Black Box" Warning on Antidepressant Suicide Risk in Young Adults: More Harm Than Benefit?*, 10 FRONTIER PSYCH., May 3, 2019, at 1; Richard A. Friedman, *Antidepressants' Black-Box Warning—10 Years Later*, 371 NEW ENG. J. MED. 1666, 1667 (2014).

437 *See* Christina Jewett & Benjamin Mueller, *The F.D.A. Warned an Asthma Drug Could Induce Despair. Many Were Never Told*, N.Y. TIMES (Jan. 9, 2024), https://www.nytimes.com/2024/01/09/health/fda-singulair-asthma-drug-warning.html [https://web.archive.org/web/20240306082407/https://www.nytimes.com/2024/01/09/health/fda-singulair-asthma-drug-warning.html].

438 Thomas W. Merrill, *Article III, Agency Adjudication, and the Origins of the Appellate Review Model of Administrative Law*, 111 COLUM. L. REV. 939, 976 (2011).

in the FDA,[439] growing questions of independence,[440] and national debates on access and costs, the role of judicial review in the Agency's future is worth considering especially if litigation accelerates after *Loper Bright*. Drawing from the potential benefits of judicial review of agency actions that have been meticulously researched for other agencies may illuminate benefits to the FDA. Professor Jerry L. Mashaw's 1978 landmark report of judicial review of Social Security Administration decisions lays out a taxonomy of the many beneficial functions of judicial review.[441] He points out that courts provide a corrective function that serves to fix incorrect agency decisions, in addition to a public information function to increase transparency of agency decision-making amongst others.[442]

Part of the benefits of judicial review of drug approval may lie in transparency. Former FDA Commissioner Dr. Mark McClellan has explained "[t]hat transparency is especially important in areas where there is the most controversy."[443] Transparency can potentially address both perceptions of scientific miscalculations as well as perceptions of improper influence on the FDA from either politics or industry.[444] First, transparency can ensure confidence in the FDA's substantive scientific decisions. Former FDA Commissioner Robert Califf has said that "[w]hen the FDA's decisions generate controversy, it is often when the system fails to produce reliable evidence that clarifies an intervention's risks and benefits during a relevant time frame."[445] For example, the FDA's stop/start approach with "the Janssen COVID-19 vaccine may have ultimately reduced confidence in the Janssen vaccine but simultaneously prevented further erosion of the public's trust in the greater COVID-19 vaccination campaign."[446] Other researchers have

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439 *See supra* Section III.A.2.

440 *See generally* sources cited *supra* note 22.

441 JERRY L. MASHAW, CHARLES J. GOETZ, FRANK I. GOODMAN, WARREN F. SCHWARTZ & PAUL R. VERKUIL, SOCIAL SECURITY HEARINGS AND APPEALS: A STUDY OF THE SOCIAL SECURITY ADMINISTRATION HEARING SYSTEM 146–47 (1978).

442 *Id.*; *see also* Rand et al., *supra* note 78, at S65 (discussing the importance of transparency for trust in the FDA).

443 Schneider, *supra* note 80.

444 *See, e.g.*, O'Reilly, *supra* note 11, at 977 ("It would be incorrect to presume that judges are impervious to the media, and also incorrect to presume that judges do not pay attention to coverage of government agencies, such as the FDA, that affect them and their families. . . . News coverage of White House involvement in FDA decision making may undercut any presumption of detached, scientific objectivity that the Agency will plead in those briefs seeking deference, as can be seen by the recent rise in cases refusing deference to FDA decisions.").

445 Robert M. Califf, *The FDA and the Clinical Community*, 328 JAMA 1043, 1044 (2022).

446 Benjamin Rader, Molly E. Chiang, Douglas L. Kriner, Rebecca L. Weintraub & John S. Brownstein, *Persistent Drop in Confidence Following US Recommended Pause of Ad26.Cov2.S*

shown the same pattern: Transparency from the Agency in the setting of controversies and uncertainty underlying data may have decreased confidence in the specific product but bolstered confidence in the system as a whole.[447]

However, transparency to address improper industry or political influence is complex. Congress and courts can identify process missteps, as exemplified by the judicial and congressional investigations in both the opioid and aducanumab decisions, but former FDA Commissioner Robert Califf expressed concerns for the shift from litigation over procedural errors to litigation over substantive questions on January 16, 2024, and declared he was "very worried" about judges overruling agency decisions.[448] He feared that further cases would destabilize the industry.[449] Moreover, the fear of improper political interference leading to approval of an unsafe or ineffective therapy, while real, reflects questions on

Vaccine Administration, 41 VACCINE 5, 9 (2023); *see also id.* at 8 ("The broad and persistent rejection of the Janssen vaccine also fits with our understanding of how sensationalism of adverse events can cause dramatic and long-tailed hesitation, even when individual risks are minimal."). Janssen received FDA Emergency Use Authorization in February 2021 as the first single-dose non-mRNA formula for use in the United States, but concerns grew with reports of rare but serious adverse events. The FDA recommended a ten-day pause of the one-dose vaccine four months later. The FDA held nine meetings to review Janssen's safety data between June 2020 and 2022, all of which received negative press. Sara E. Oliver et al., *Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine: Updated Interim Recommendations from the Advisory Committee on Immunization Practices—United States, December 2021*, 71 MORBIDITY & MORTALITY WKLY. REP. 90, 90 (2022); *see* Press Release, FDA, FDA and CDC Lift Recommended Pause on Johnson & Johnson (Janssen) COVID-19 Vaccine Use Following Thorough Safety Review (Apr. 23, 2021), https://www.fda.gov/news-events/press-announcements/fda-and-cdc-lift-recommended-pause-johnson-johnson-janssen-covid-19-vaccine-use-following-thorough [https://web.archive.org/web/20241229004434/https://www.fda.gov/news-events/press-announcements/fda-and-cdc-lift-recommended-pause-johnson-johnson-janssen-covid-19-vaccine-use-following-thorough]; *see also* Memorandum from Peter Marks, Dir., Ctr. for Biologics Evaluation & Rsch., to Janssen COVID-19 Vaccine EUA 27205 (June 11, 2021), https://www.fda.gov/media/150081/download [https://perma.cc/QN8D-TYZQ]; Rader et al., *supra* note 446, at 5.

447 *See* Kyle Thomson & Herschel Nachlis, *Emergency Use Authorizations During the COVID-19 Pandemic: Lessons from Hydroxychloroquine for Vaccine Authorization and Approval*, 324 JAMA 1282, 1283 (2020).; Pai et al., *supra* note 385, at 277; *see also* O'Reilly, *supra* note 12, at 949 ("This confidence in the FDA exists because of the Agency's reputation for superior science and expertise—not for its doctrinal or political policies.").

448 Brenda Sandburg, *FDA's Califf Is 'Very Worried' About Judges Overruling Agency Decisions*, CITELINE: PINK SHEET (Jan. 26, 2024), https://pink.citeline.com/PS149674/FDAs-Califf-Is-Very-Worried-About-Judges-Overruling-Agency-Decisions [https://perma.cc/G57M-NCN9].

449 *See id.* (reporting that Califf stated: "[R]ecently, more judges have stepped in and, I don't know, acted like they were FDA. . . . I'm worried about that because if we ended up with every decision of FDA ending up with a judge potentially overruling the FDA, this would be extremely disruptive to the entire system.").

executive control over agencies. "The role of politics and expertise is one of the defining tensions in administrative law."[450]

Ensuring executive control and capturing the benefits of judicial review without incentivizing anticompetitive litigation abuse, deteriorating trust, or disrupting relied-upon policy choices is a difficult needle to thread. It might benefit from the development of appropriate "yardsticks"[451] with clear standards of review of science-based policy choices from both courts and Congress. Accordingly, this Article's analysis of the last ten years of litigation against the FDA signals the need for a broader conversation on deference to FDA drug approval determinations, especially given the inherent uncertainty. Debates on the best way to improve trust are ongoing,[452] but this Article adds that there may be an underappreciated benefit to restoring trust in the FDA: judicial deference.

CONCLUSION

Tracing the last ten years of litigation against the FDA related to drugs suggests that courts have overturned multiple decades-old, science-based FDA policy decisions related to pharmaceuticals between 2020 and 2023. The cases have been brought predominantly by smaller pharmaceutical companies and may be anticompetitive. These concerning outcomes may be connected to both eroding public confidence in the FDA and broader changes in agency deference. Although this cluster of cases may be part of a cycle, it may also be a canary in a coal mine of broader implications of declining trust in the FDA. Dr. Daniel Carpenter noted the connection between the FDA's

450 Staszewski, *supra* note 385; *see also* Sid Shapiro, *Government, Expertise, and a "Fair Chance in the Race of Life,"* YALE J. ON REGUL. (Mar. 21, 2023), https://www.yalejreg.com/nc/government-expertise-and-a-fair-chance-in-the-race-of-life-by-sid-shapiro [https://perma.cc/KMN3-44PP] ("The American public has lost faith in expertise. . . . Citizen distrust of government became the norm when the country embraced globalization and abandoned its commitment to promote a 'fair chance in the race of life.'").

451 Fisher et al., *supra* note 90, at 1684–85.

452 *See supra* Section III.A.2; Chris P. Long & Sim B. Sitkin, *Contradictions That Erode Institutional Trust & Opportunities for Addressing Them*, 9 BEHAVIORAL SCI. & POL'Y, issue 2, 2023, at 1; Carl Latkin et al., *An Assessment of the Rapid Decline of Trust in US Sources of Public Information About COVID-19*, 25 J. HEALTH COMMC'N 764 (2021); Patrick Boyle, *Why Do So Many Americans Distrust Science?*, ASS'N AM. MED. COLLS. (May 4, 2022), https://www.aamc.org/news/why-do-so-many-americans-distrust-science [https://perma.cc/BK6H-W9WC] ("*The forces and factors behind distrust*, which include a public overwhelmed by too much information, growing polarization, disinformation campaigns by domestic or foreign corporations and governments, a media environment that rewards outrage and outlandishness, and the increasingly public nature of scientific research.").

management of politically charged issues involving tobacco and abortion drugs, oversights in drug safety and efficacy regulations, and the breakdown in trust in Agency's role in scientific regulation.[453] Broader conversations on the role of courts in ensuring safe and effective drugs alongside improving trust and transparency in scientific agencies are overdue.

453 CARPENTER, *supra* note 81, at 748–50; *see also* Christina Fuleihan, *Shattering the Mirage: The FDA's Early COVID-19 Pandemic Respnse Demonstrates a Need for Reform to Resotre Agency Credibility*, 48 AM. J. L. & MED. 307, 323 (2022).

APPENDIX I

Case	Outcome	*Chevron* Deference Applied? (Yes/No)	Are the Litigants Challenging a Competitor Product? (Yes/No)	Related to FDA Awarding Exclusivities	Related to Classification of Product as Drug, Device, Compound, Etc.
Norwich Pharms., Inc. v. Becerra, 703 F. Supp. 3d 1 (D.D.C. 2023)	Favors FDA	Yes	Yes	No	No
Vanda Pharms., Inc. v. FDA, No. 22-cv-014322023, 2023 U.S. Dist. LEXIS 165379 (D.D.C. Aug. 2, 2023)	Favors FDA	No	No	Yes	No
United States v. Vepuri, 74 F.4th 141 (3d Cir. 2023)	Does Not Favor FDA	No	No	No	No
United States v. Vepuri, No. 21-132, 2022 WL 541772 (E.D. Pa. Feb. 23, 2022)	Does Not Favor FDA	No	No	No	No
Ipsen Biopharmaceuticals, Inc. v. Becerra, 678 F. Supp. 3d 20 (D.D.C. 2023)	Favors FDA	Yes	No	No	Yes
Ipsen Biopharmaceuticals, Inc. v. Becerra, No. 20-cv-2437, 2021 WL 4399531 (D.D.C. Sept. 24, 2021)	Favors FDA	No	No	No	Yes
Sandoz Inc. v. Becerra, 57 F.4th 272 (D.C. Cir. 2023)	Favors FDA	No	Yes	Yes	No

Sandoz Inc. v. Becerra, 2022 WL 2904262 (D.D.C. July 22, 2022)	Favors FDA	No	Yes	Yes	No
Avadel CNS Pharms., LLC v. Becerra, 638 F. Supp. 3d 23 (D.D.C. 2022)	Favors FDA	No	Yes	No	No
Melinta Therapeutics, LLC v. FDA, 2022 WL 6100188 (D.D.C. Oct. 7, 2022)	Does Not Favor FDA	No	Yes	No	No
Nostrum Pharms., LLC v. FDA, 35 F.4th 820 (D.C. Cir. 2022)	Favors FDA	No	No	No	No
Wedgewood Vill. Pharmacy, LLC v. FDA, No. 22-cv-02649, 2022 WL 1591787 (D.N.J. May 19, 2022)	Favors FDA	No	No	No	No
Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299 (11th Cir. 2021)	Does Not Favor FDA	Yes	Yes	Yes	No
Catalyst Pharms., Inc. v. FDA, 19-cv-22425, 2020 WL 5792595 (S.D. Fla. Sept. 29, 2020)	Favors FDA	Yes	Yes	Yes	No
Catalyst Pharms., Inc. v. Azar, No. 19-cv-22425, 2020 WL 5514187 (S.D. Fla. July 30, 2020)	Favors FDA	Yes	Yes	Yes	No
Catalyst Pharms., Inc. v. Azar, No. 19-cv-22425, 2020 WL 4573068 (S.D. Fla. May 1, 2020)	Both Favors and Disfavors	No	Yes	Yes	No

Wellness Pharmacy, Inc. v. Becerra, No. 20-cv-3082, 2021 WL 4284567 (D.D.C. Sept. 21, 2021)	Does Not Favor FDA	Yes	No	No	No
MediNatura, Inc. v. FDA, 998 F.3d 931 (D.C. Cir. 2021)	Favors FDA	No	No	No	No
MediNatura, Inc. v. FDA, No. 20-2066, 2021 WL 1025835 (D.D.C. Mar. 16, 2021)	Favors FDA	No	No	No	No
MediNatura, Inc. v. FDA, No. 20-2066, 2020 U.S. Dist. LEXIS 252453 (D.D.C. Dec. 15, 2020)	Favors FDA	No	No	No	No
MediNatura, Inc. v. FDA, 496 F. Supp. 3d 416 (D.D.C. 2020)	Favors FDA	No	No	No	No
Vanda Pharms., Inc. v. FDA, 539 F. Supp. 3d 44 (D.D.C. 2021)	Does Not Favor FDA	No	No	No	No
Vanda Pharms., Inc. v. FDA, 436 F. Supp. 3d 256 (D.D.C. 2020)	Favors FDA	No	No	No	No
Vanda Pharms., Inc. v. FDA, No. 19-301, 2019 WL 1198703 (D.D.C. Mar. 14, 2019)	Favors FDA	No	No	No	No
Genus Med. Techs., LLC v. FDA, 994 F.3d 631 (D.C. Cir. 2021)	Does Not Favor FDA	Yes	No	No	Yes

Genus Med. Techs., LLC v. FDA, 427 F. Supp. 3d 74 (D.D.C. 2019)	Does Not Favor FDA	Yes	No	No	Yes
Arbor Pharms., LLC v. Cochran, No. 21-cv-00810, 2021 WL 2451541 (N.D. Ga. Mar. 4, 2021)	Favors FDA	No	Yes	No	No
Genus Lifesciences, Inc. v. Azar, No. 20-cv-00211, 2021 WL 270409 (D.D.C. Jan. 27, 2021)	Does Not Favor FDA	No	Yes	Yes	No
Genus Lifesciences, Inc. v. Azar, 486 F. Supp. 3d 450 (D.D.C. 2020)	Both Favors and Disfavors	Yes	Yes	Yes	No
United Therapeutics Corp. v. U.S. Dep't of Health & Hum. Servs., No. 17-01577, 2020 WL 6498619 (D.D.C. Sept. 2, 2020)	Does Not Favor FDA	No	No	Yes	No
United States v. Innovative Biodefense, Inc., SA cv 18-0996, 2020 WL 5035857 (C.D. Cal. May 4, 2020).	Favors FDA	No	No	No	No
United States v. Innovative Biodefense, Inc., No. SA cv 18-006, 2019 WL 7195332 (C.D. Cal. Nov. 15, 2019)	Favors FDA	No	No	No	No

Pharm. Mfg. Rsch. Servs. v. FDA, 957 F.3d 254 (D.C. Cir. 2020)	Favors FDA	No	No	No	No
Pharm. Mfg. Rsch. Servs. v. FDA, No. 17-04898, 2019 WL 285970 (E.D. Pa. Jan. 22, 2019)	Favors FDA	No	Yes	No	No
Athenex Inc. v. Azar, No. 19-cv-00603, 2019 WL 4316139 (D.D.C. Sept. 6, 2019)	Favors FDA	No	No	No	No
Athenex Inc. v. Azar, 397 F. Supp. 3d 56 (D.D.C. 2019)	Favors FDA	Yes	No	No	No
Braeburn Inc. v. FDA, 389 F. Supp. 3d 1 (D.D.C. 2019)	Does Not Favor FDA	Yes	Yes	Yes	No
Teva Pharms. USA, Inc. v. FDA, 514 F. Supp. 3d 66 (D.D.C. 2020)	Favors FDA	Yes	Yes	No	Yes
Teva Pharms. USA, Inc. v. Azar, 369 F. Supp. 3d 183 (D.D.C. 2019)	Favors FDA	No	No	Yes	No
Breckenridge Pharm., Inc. v. FDA, 754 F. App'x 1 (D.C. Cir. 2018)	Favors FDA	No	No	No	No
Eagle Pharms., Inc. v. Azar, 952 F.3d 323 (D.C. Cir. 2020)	Does Not Favor FDA	yes	No	Yes	No
Eagle Pharms., Inc. v. Azar, No. 16-790, 2018 U.S. Dist. LEXIS 218098 (D.D.C. Aug. 1, 2018)	Does Not Favor FDA	No	No	Yes	No

Eagle Pharms., Inc. v. Azar, No. 16-790, 2018 U.S. Dist. LEXIS 101735 (D.D.C. June 8, 2018)	Does Not Favor FDA	Yes	No	Yes	No
Eagle Pharm., Inc. v. Price, 322 F.R.D. 48 (D.D.C. 2017)	Neither	No	No	Yes	No
Eagle Pharms. v. Burwell, No. 16-790, 2016 U.S. Dist. LEXIS 200543 (D.D.C. Dec. 30, 2016)	Favors FDA	No	No	No	No
In re Cantrell Drug Co., 585 B.R. 555 (Bankr. E.D. Ark. 2018)	Favors FDA	No	No	No	No
Ferring Pharms., Inc. v. Azar, 296 F. Supp. 3d 166 (D.D.C. 2018)	Favors FDA	Yes	No	Yes	No
Ferring Pharms., Inc. v. Burwell, No. 15-0802, 2016 U.S. Dist. LEXIS 121826 (D.D.C. Sept. 9, 2016)	Does Not Favor FDA	Yes	No	Yes	No
Ferring Pharms., Inc. v. Burwell, 169 F. Supp. 3d 199 (D.D.C. 2016)	Favors FDA	Yes	No	Yes	No
Amneal Pharms. LLC v. FDA, 285 F. Supp. 3d 328 (D.D.C. 2018)	Favors FDA	Yes	No	Yes	No
Perrigo Rsch. & Dev. Co. v. FDA, 290 F. Supp. 3d 51 (D.D.C. 2017)	Favors FDA	No	Yes	Yes	No

Lannett Co. v. FDA, 300 F. Supp. 3d 34 (D.D.C. 2017)	Favors FDA	Yes	No	No	No
In re New England Compounding Pharmacy, Inc., No. 13-2419, 2015 U.S. Dist. LEXIS 199090 (D. Mass. July 31, 2015)	Favors FDA	No	No	No	No
In re New England Compounding Pharmacy, Inc. Prods. Liab. Litig., 251 F. Supp. 3d 294 (D. Mass. 2017)	Favors FDA	No	No	No	No
Sheller, P.C. v. U.S. Dep't of Health & Hum. Servs., 663 F. App'x 150 (3d Cir. 2016)	Favors FDA	No	No	No	No
Sheller, P.C. v. U.S. Dep't of Health & Hum. Servs., 119 F. Supp. 3d 364 (E.D. Pa. 2015)	Favors FDA	No	No	No	No
Otsuka Pharm. Co. v. Price, 869 F.3d 987 (D.C. Cir. 2017)	Favors FDA	Yes	Yes	Yes	No
Otsuka Pharm. Co. v. Burwell, 302 F. Supp. 3d 375 (D.D.C. 2016)	Favors FDA	Yes	Yes	Yes	No
AstraZeneca Pharms. LP v. Burwell, 197 F. Supp. 3d 53 (D.D.C. 2016)	Both Favors and Disfavors	No	Yes	Yes	No

Boehringer Ingelheim Pharma GmbH & Co. KG v. FDA, 195 F. Supp. 3d 366 (D.D.C. 2016)	Favors FDA	Yes	No	No	No
Spectrum Pharms., Inc. v. Burwell, 824 F.3d 1062 (D.C. Cir. 2016)	Favors FDA	Yes	Yes	Yes	No
Spectrum Pharms., Inc. v. Burwell, 107 F. Supp. 3d 23 (D.D.C. 2015)	Favors FDA	Yes	Yes	Yes	No
United States v. Dessart, 823 F.3d 395 (7th Cir. 2016)	Favors FDA	No	No	No	No
United States v. Dessart, No. 12-CR-85, 2013 U.S. Dist. LEXIS 190405 (E.D. Wis. Sept. 16, 2013)	Favors FDA	No	No	No	No
Amarin Pharms. Ir. Ltd. v. FDA, 106 F. Supp. 3d 196 (D.D.C. 2015)	Does Not Favor FDA	Yes	No	Yes	No
Amarin Pharms. Ir., Ltd. v. FDA, 139 F. Supp. 3d 437 (D.D.C. 2015)	Neither	No	Yes	Yes	No
Amarin Pharms. Ir. Ltd. v. FDA, No. 15-5214, 2015 U.S. App. LEXIS 21333 (D.C. Cir. Dec. 9, 2015)	Favors FDA	No	No	Yes	No
Eisai, Inc. v. FDA, 134 F. Supp. 3d 384 (D.D.C. 2015)	Favors FDA	No	No	Yes	No
Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196 (S.D.N.Y. 2015)	Does Not Favor FDA	No	No	No	No

Mallinckrodt Inc. v. FDA, No. DKC 14-3607, 2015 U.S. Dist. LEXIS 193019 (D. Md. July 29, 2015)	Favors FDA	No	No	No	No
Veloxis Pharms., Inc. v. FDA, 109 F. Supp. 3d 104 (D.D.C. 2015)	Favors FDA	Yes	No	Yes	No
United States v. Scully, 108 F. Supp. 3d 59 (E.D.N.Y. 2015)	Neither	Yes	No	No	No
Otsuka Pharm. Co. v. Burwell, No. GJH-15-852, 2015 WL 1579127 (D. Md. Apr. 8, 2015)	Does Not Favor FDA	No	Yes	Yes	No
Otsuka Pharm. Co. v. Burwell, No. GJH-15-852, 2015 WL 1962240 (D. Md. Apr. 29, 2015)	Favors FDA	Yes	Yes	Yes	No
Otsuka Pharm. Co. v. Burwell, No. GJH-15-852, 2015 WL 3442013 (D. Md. May 27, 2015)	Favors FDA	Yes	Yes	Yes	No
Ranbaxy Lab'ys., Ltd. v. Burwell, No. 14-1923, 2015 U.S. Dist. LEXIS 183425 (D.D.C. Feb. 27, 2015)	Favors FDA	No	No	Yes	No
Ranbaxy Lab'ys., Ltd. v. Burwell, 82 F. Supp. 3d 159 (D.D.C. 2015)	Favors FDA	Yes	No	Yes	No
Takeda Pharms., U.S.A., Inc. v. Burwell, 78 F. Supp. 3d 65 (D.D.C. 2015)	Favors FDA	Yes	Yes	Yes	No

Takeda Pharms. U.S.A., Inc. v. Burwell, 691 F. App'x 634 (D.C. Cir. 2016) (mem.)	Favors FDA	No	Yes	No	No
Mylan Pharms., Inc. v. FDA, 23 F. Supp. 3d 631 (N.D.W. Va. 2014)	Favors FDA	Yes	Yes	Yes	No
Mylan Pharms., Inc. v. FDA, No. 14cv75, 2014 U.S. Dist. LEXIS 176242 (N.D.W. Va. June 16, 2014)	Favors FDA	Yes	Yes	Yes	No
Mylan Pharms., Inc. v. FDA, 594 F. App'x 791 (4th Cir. 2014)	Does Not Favor FDA	Yes	Yes	Yes	No
Prevor v. FDA, 67 F. Supp. 3d 125 (D.D.C. 2014)	Does Not Favor FDA	Yes	No	No	Yes
Hospira, Inc. v. Burwell, No. GJH-14-02662, 2014 WL 4182398 (D. Md. Aug. 19, 2014)	Does Not Favor FDA	No	Yes	Yes	No
Hospira, Inc. v. Burwell, No. GJH-14-02662, 2014 WL 4406901 (D. Md. Sept. 5, 2014)	Favors FDA	Yes	Yes	No	No
Depomed, Inc. v. U.S. Dep't of Health & Hum. Servs., 66 F. Supp. 3d 217 (D.D.C. 2014)	Does Not Favor FDA	Yes	Yes	Yes	No
Teva Pharm. Indus. v. Sebelius, No. 14-0786, 2014 U.S. Dist. LEXIS 188256 (D.D.C. May 14, 2014)	Favors FDA	No	Yes	Yes	No

United States v. Regenerative Scis., LLC, 741 F.3d 1314 (D.C. Cir. 2014)	Favors FDA	No	No	No	Yes
Carik v. U.S. Dep't of Health & Hum. Servs., 4 F. Supp. 3d 41 (D.D.C. 2013)	Favors FDA	No	No	No	No
Cumberland Pharms. Inc. v. FDA, 981 F. Supp. 2d 38 (D.D.C. 2013)	Favors FDA	No	Yes	No	No
Cook v. FDA, 733 F.3d 1 (D.C. Cir. 2013)	Does Not Favor FDA	No	No	No	No
Astrazeneca Pharms. LP v. FDA, 713 F.3d 1134 (D.C. Cir. 2013)	Favors FDA	Yes	Yes	Yes	No
Hill Dermaceuticals, Inc. v. FDA, 709 F.3d 44 (D.C. Cir. 2013)	Favors FDA	No	Yes	Yes	No
ViroPharma, Inc. v. Hamburg, 916 F. Supp. 2d 76 (D.D.C. 2013)	Favors FDA	Yes	Yes	Yes	No