

Exasperated But Not Exhausted: Unlocking the Trap Set by the Exhaustion Doctrine on the FDA’s REMS Petitioners

When health is at stake, bureaucratic delays can be disastrous. This is especially true in the field of pharmaceutical regulation. Fortunately, concerned parties—ranging from research institutions and universities to doctors and pharmaceutical companies—can file citizen petitions to urge the Food and Drug Administration (“FDA”) to regulate potentially risky drugs through Risk Evaluation and Mitigation Strategies (“REMS”) programs. But despite submitting comprehensive citizen petitions calling for changes to REMS determinations, petitioners regularly await the FDA’s response for years. When these petitioners, still awaiting an FDA determination, have sought recourse in the courts, the agency has argued that these petitioners have not yet exhausted the FDA’s mandatory administrative remedy. In accepting this argument, courts across the country have misapplied the exhaustion doctrine in FDA cases, depriving potential petitioners of judicial review and leaving the FDA’s original REMS decisions without any oversight. All the while, societal costs of unaccountable drug decisions continue to climb.

This Note examines the dilemma of REMS petitioners, the “exhaustion trap,” wherein petitioners cannot seek legal remedy until the FDA allows them to exhaust their administrative remedy. Through original empirical analysis, this Note finds the FDA responds to fewer than one-third of REMS petitions before its own 180-day deadline, with petitioners languishing for an average of 937.6 days (2.56 years) before the FDA lets them exhaust this administrative remedy. So, petitioners frequently remain trapped and exasperated, while their remedies—by no fault of their own—remain unexhausted.

*This exhaustion trap is superable, however, and this Note proposes three potential escape routes. First, the plain language of the APA’s statutory provision codifying the exhaustion doctrine—5 U.S.C. § 704, as interpreted by the Supreme Court in the landmark case *Darby v. Cisneros*—prohibits the exhaustion trap. Second, this Note proposes an amendment to the Food, Drug, and Cosmetic Act that would waive the FDA’s exhaustion requirement when the FDA disregards its own deadline of 180 days. Finally, this Note suggest that courts should waive the FDA’s exhaustion requirement more readily in these cases. Given the stakes for public health, the American people deserve remedies that are actually exhaustible.*

| | |
|--------------------------------------------------------------------------------------------------------|-----|
| INTRODUCTION..... | 938 |
| I. BACKGROUND: SETTING THE TRAP..... | 942 |
| A. <i>The FDA and the Drug Approval Process: An Overview</i> | 942 |
| B. <i>The Pre-REMS FDA: Powerless to Limit the Risks of Already-Approved Drugs</i> | 946 |
| C. <i>A New Tool for Fighting Risk: Introducing REMS</i> | 948 |
| D. <i>Exhaustion of Administrative Remedies</i> | 951 |
| E. <i>Exhaustion, Meet the FDA: Citizen Petitions</i> | 955 |
| II. ANALYSIS: SPRINGING THE TRAP | 957 |
| A. <i>The View from the Ground: Delayed Decisions Leave Petitioners in the Lurch</i> | 958 |
| 1. An Overview of the Data: Poor Performance by the FDA | 958 |
| 2. Serious Petitions Go Unanswered for Years | 963 |
| B. <i>The View from the Law: Without First Receiving a Response, Petitioners Are Out of Luck</i> | 966 |
| 1. Most Petitioners Are Trapped | 967 |
| 2. Judicial Waiver in Unusual Circumstances: Mifepristone Litigation | 972 |
| III. SOLUTIONS: UNLOCKING THE FDA'S EXHAUSTION TRAP..... | 976 |
| A. <i>Requiring Inoperativeness Is the Best Reading of Section 704 and Darby</i> | 976 |
| B. <i>Statutory Waiver</i> | 983 |
| C. <i>Judicial Waiver</i> | 984 |
| CONCLUSION..... | 985 |
| APPENDIX..... | 987 |

INTRODUCTION

Is the cure for male-pattern baldness worse for men than the condition itself? The Post-Finasteride Syndrome Foundation (“the Foundation”) believes so. This nonprofit formed in 2012 to support men who developed a wide variety of symptoms after taking finasteride to

treat male-pattern baldness.¹ Widely available under the brand names Propecia and Proscar² and as the generic Hims,³ finasteride garnered such a following that as of 2017, even President Trump was using it.⁴

But all was not sunshine and thicker hair for finasteride users. According to the Foundation, patients suffering from Post-Finasteride Syndrome (“PFS”) experience “erectile dysfunction (ED), loss of libido, depression, suicidal ideation, anxiety, panic attacks, insomnia and cognitive dysfunction.”⁵ Even worse, the Foundation estimates that “tens of thousands of men” have already developed PFS from these drugs, making risk-reducing measures necessary to protect public health.⁶ The Foundation determined that it not only needed to raise awareness among the public but also needed to get the government’s attention.

Fortunately for the Foundation, concerned citizens may submit a written citizen petition to the Food and Drug Administration (“FDA” or “the Agency”) to persuade it to take or refrain from taking any kind of action.⁷ Citizens may request that the FDA require a Risk Evaluation and Mitigation Strategies (“REMS”) program for drugs they fear are too risky without stronger safeguards.⁸ On September 18, 2017, the Foundation took advantage of this program, submitting a 120-page citizen petition outlining its support for requiring a REMS on finasteride.⁹ The FDA’s response? Crickets. After more than five years,

1. *About the Post-finasteride Syndrome Foundation*, POST-FINASTERIDE SYNDROME FOUND., <https://www.pfsfoundation.org/about-post-finasteride-syndrome-foundation/> (last visited Apr. 17, 2024) [<https://perma.cc/MPQ3-ZD3Z>].

2. Citizen Petition from Post-Finasteride Syndrome Found. to Comm’r, FDA 1 (Sept. 18, 2017) (on file with FDAPetitions.com) [hereinafter PFSF Petition]. As described in Part II, FDAPetitions.com maintains the most accessible database of all citizen petitions for drugs, and specifically REMS. *See generally FDA Petitions Home*, FDAPETITIONS.COM, <https://fdapetitions.com/> (last visited Apr. 17, 2024) [<https://perma.cc/7QPH-QCRA>] [hereinafter *Home*, FDAPETITIONS.COM].

3. *Topical Finasteride and Minoxidil Spray*, HIMS, <https://www.forhims.com/shop/hair-top-fin-minox-spray> (last visited Apr. 17, 2024) [<https://perma.cc/8JGD-2MZ7>].

4. *See* Daniel Marchalik, *Potential Side Effects of the Drug Trump Reportedly Takes for Hair Loss*, WASH. POST (Feb. 3, 2017, 3:03 PM), <https://www.washingtonpost.com/news/to-your-health/wp/2017/02/03/side-effects-of-the-drug-trump-reportedly-takes-for-hair-loss/> [<https://perma.cc/H74T-NJDN>].

5. PFSF Petition, *supra* note 2, at 5.

6. *Id.*

7. 21 C.F.R. §§ 10.25-10.45 (2023).

8. *See id.* § 10.30 (delineating the procedures for a citizen petition); *Risk Evaluation and Mitigation Strategies | REMS*, FDA, <https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rem> (last updated May 16, 2023) [<https://perma.cc/GQF8-YWEB>] [hereinafter FDA, *REMS Description*] (explaining REMS programs).

9. *See* PFSF Petition, *supra* note 2.

the Foundation still awaits an answer. Meanwhile, the costs of unmitigated finasteride risk¹⁰ have continued to build.¹¹

One might expect the Foundation to take its case to court, but until the FDA responds to its petition, the Foundation has not fully exhausted its administrative remedies, meaning that a court would dismiss such a suit.¹² Thus, the Foundation has fallen into what this Note calls the “exhaustion trap.” It cannot be sure the FDA has considered its petition to enhance finasteride’s safeguards, but it also cannot get a second look from the judiciary until the FDA has responded to the petition. In other words, until the FDA responds, its determination is unchallengeable, creating a perverse incentive for the FDA to delay responding to petitioners in perpetuity.

This Note evaluates the FDA’s citizen-petition process, the current state of the exhaustion doctrine, and how these factors converge to trap REMS petitions. The exhaustion doctrine is a judicially created rule requiring that parties seeking to challenge an agency’s action first pursue that agency’s internal resolution procedures before resorting to the judiciary. With regard to the FDA specifically, these procedures mandate that parties first file a citizen petition detailing their request—only after which will the FDA provide a final response confirming the exhaustion of its internal remedies.¹³ If the would-be plaintiff has not yet received a final response but decides to file suit, the FDA will move to dismiss and, citing the FDA’s exhaustion regulations, the court will grant the Agency’s motion.

This common-sense doctrine has several benefits—such as utilizing agency expertise, allowing the agency to correct its own errors, and compiling a full record prior to judicial resolution, among others—but its misuse has major costs, as exemplified by its application to the FDA’s REMS determinations and the resulting exhaustion trap. Despite providing in its regulations that the Agency will respond to all citizen petitions within 180 days,¹⁴ this Note finds the FDA meets this

10. Although finasteride is only available with prescriptions, the FDA has never required a REMS program on it. See *FDA Risk Evaluation and Mitigation Strategy (REMS) Public Dashboard*, FDA, <https://fis.fda.gov/sense/app/ca606d81-3f9b-4480-9e47-8a8649da6470/sheet/dfa2f0ce-4940-40ff-8d90-d01c19ca9c4d/state/analysis> (last updated Jan. 16, 2024) [<https://perma.cc/PD8M-2KN8>] [hereinafter *REMS Public Dashboard*] (displaying all REMS approved by the FDA).

11. This Note takes no position on the riskiness of any drugs mentioned throughout the Note; rather, it seeks to highlight the legal and administrative failure that occurs when these petitions are left unanswered for unreasonable periods. From these petitioners’ perspective, grievous harms can occur to the public for every day that their petitions languish without any path toward achieving the change the petitioners believe is necessary.

12. See *infra* Section II.B.

13. 21 C.F.R. § 10.45 (2023).

14. *Id.* § 10.30(e)(2).

deadline with less than one-third of REMS petitions.¹⁵ The other two-thirds of petitioners languish, making the average wait time for all REMS petitioners 937.6 days and the median 575.5 days.¹⁶ Illustrating how extreme these wait times can be, a petition from Kaiser Permanente continues collecting dust after nearly fourteen years.¹⁷ And yet, under the current exhaustion regime, the Agency's REMS determination is invulnerable until the Agency has responded to the petition, leaving petitioners trapped without recourse.

But what if this is unnecessary? Congress codified the exhaustion doctrine in the Administrative Procedure Act ("APA") at 5 U.S.C. § 704, specifically providing that exhaustion is required in two scenarios: (1) when a statute requires it or (2) when an agency requires exhaustion "by rule and provides that the [contested agency] action meanwhile is inoperative."¹⁸ As discussed below, the United States Supreme Court held exactly this in the authoritative case on exhaustion under the APA, *Darby v. Cisneros*.¹⁹ Nonetheless, courts across the country have misinterpreted *Darby* to allow an agency to require exhaustion by rule without rendering its contested action inoperative. This misinterpretation has real-world consequences because every day that serious petitions languish in the exhaustion trap, the costs to Americans' health continue to climb.

While this Note advocates for increasing the judicial accountability of the FDA, it does not wish to merely criticize the Agency. The FDA indisputably has limited time and resources to allocate to any petition.²⁰ Rather, this Note and the Agency share the same mission: "protecting the public health by ensuring the safety" of potentially risky drugs.²¹ To that end, this Note neither argues that all REMS petitioners are right nor that judges are better qualified than

15. See *infra* Subsection II.A.1.

16. See *infra* Subsection II.A.1.

17. Ironically, this long-waiting petition itself calls for improvements in the REMS determination process. Citizen Petition from Kaiser Permanente to Comm'r, FDA (Dec. 22, 2009) (on file with FDAPetitions.com).

18. 5 U.S.C. § 704.

19. 509 U.S. 137, 154 (1993) ("But where the APA applies, an appeal to 'superior agency authority' is a prerequisite to judicial review *only* when expressly required by statute or when an agency rule requires appeal before review and the administrative action is made inoperative pending that review." (quoting 5 U.S.C. § 704)).

20. See Bradley Merrill Thompson, *Unpacking Averages: FDA's Extraordinary Delay in Resolving Citizen Petitions*, EPSTEIN BECKER GREEN: HEALTH L. ADVISOR (Oct. 3, 2023), <https://www.healthlawadvisor.com/unpacking-averages-fdas-extraordinary-delay-in-resolving-citizen-petitions> [<https://perma.cc/JW4V-WL5X>] ("FDA's excuse typically is based on resources, but how often does FDA accept an excuse of too few resources from a company regarding its compliance?").

21. *What We Do*, FDA, <https://www.fda.gov/about-fda/what-we-do> (last updated Nov. 21, 2023) [<https://perma.cc/5HJZ-7ANP>] [hereinafter FDA, *What We Do*].

agency experts to determine a drug's riskiness. But the exhaustion trap creates a dearth of accountability and stifles petitioners' ability to give meaningful input to our nation's regulators—leaving petitioners exasperated, but their remedies not exhausted. While potential exhaustion traps in other agencies' regulatory schemes are beyond the scope of this Note, the current state of the exhaustion doctrine incentivizes all agencies to behave like the FDA.²²

This Note proceeds through the following four Parts. Part I provides an overview of the FDA's regulation of potentially risky drugs and then details how the exhaustion doctrine works in theory. Part II brings this theory into practice and evaluates how the current state of the exhaustion doctrine traps REMS petitioners. Part III provides several potential solutions, arguing first that we return to a truer interpretation of § 704 of the APA, as elicited by the Supreme Court in *Darby*.²³ Alternatively, this Note proposes a statutory amendment to the FDA's exhaustion regime that would automatically waive the Agency's exhaustion requirement if the Agency has failed to respond within its stipulated timeframe of 180 days.²⁴ This Part also weighs each proposal's potential drawbacks. Following the Conclusion, an Appendix provides this Note's data.

I. BACKGROUND: SETTING THE TRAP

A. The FDA and the Drug Approval Process: An Overview

Congress established the FDA in 1906 through the Pure Food and Drugs Act to counter “long-standing, serious abuses in the consumer product marketplace.”²⁵ Today, the Agency operates under and enforces several statutes, including the Food, Drug, and Cosmetic Act of 1938 (“FD&C Act”),²⁶ which was amended by the Food and Drug Administration Amendments Act of 2007 (“FDAAA”).²⁷ These statutes authorize the FDA to promote the public health by regulating a wide variety of the products Americans interact with daily, including “drugs, biological products, and medical devices . . . our nation's food supply,

22. See *Conservation Force v. Salazar*, 919 F. Supp. 2d 85, 90–92 (D.D.C. 2013) (dismissing plaintiffs' complaint against the U.S. Fish and Wildlife Service under the Service's regulations requiring exhaustion but not rendering its original decision inoperative pending review).

23. See *infra* Sections III.A–B.

24. See *infra* Section III.C.

25. *When and Why Was FDA Formed?*, FDA, <https://www.fda.gov/about-fda/fda-basics/when-and-why-was-fda-formed> (last updated Mar. 28, 2018) [<https://perma.cc/EW9W-U9E8>].

26. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-399i.

27. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

cosmetics, and products that emit radiation.”²⁸ Of the FDA’s broad set of responsibilities, some of its most important work is its regulation of the pharmaceutical industry.

The broad availability and constant innovation of medications have led to tremendous improvements in living standards.²⁹ Nonetheless, the high stakes of public health, the scientific complexity of the medications, and the industry’s leviathan production capacity necessitate careful oversight. The FDA, therefore, must approve all prescription drugs before they can be marketed to American consumers.³⁰ While this Note focuses only on the FDA’s decisions regarding whether a REMS program is necessary for a specific drug, it is helpful to understand the overall drug approval process and the all-sided pressure the Agency faces throughout this gauntlet.

The typical approval process is lengthy and expensive, often taking ten to twelve years³¹ and costing hundreds of millions of dollars from the start of research to patient use.³² A drug developer (referred to as a “sponsor”) begins the process by submitting an Investigational New Drug (“IND”) application, asking the FDA to clear the IND for human trials.³³ Upon gaining IND approval, the sponsor conducts three phases of clinical trials over the course of multiple years.³⁴ The sponsor submits

28. FDA, *What We Do*, *supra* note 21.

29. See Sundee Mishra, *Does Modern Medicine Increase Life-Expectancy: Quest for the Moon Rabbit?*, 68 INDIAN HEART J. 19, 20 (2016) (observing that global life-expectancy doubled between 1900 and 1980, largely due to “global drug and chemical innovations”).

30. See Kevin M. Fain, Keeve E. Nachman & Lainie Rutkow, *An Analysis of FDA’s Drug Safety Authorities: Challenges and Opportunities Under a New Regulatory Framework*, 17 N.Y.U. J. LEGIS. & PUB. POL’Y 1, 2 (2014) (describing the application and approval process).

31. Compare Emma Wysocki, *What Does It Take to Get a Medication Approved Through the FDA?*, NATIONWIDE CHILD.’S HOSP.: 700 CHILD.’S (Jan. 7, 2021), <https://www.nationwidechildrens.org/family-resources-education/700childrens/2018/03/what-does-it-take-to-get-a-drug-approved-through-the-fda> [<https://perma.cc/TD4D-P8CU>] (stating it takes an average of ten years to get a drug approved), with Jen Christensen, *Nearly a Third of FDA-Approved Drugs Had Problems, Study Finds*, CNN (May 9, 2017, 5:25 PM), <https://www.cnn.com/2017/05/09/health/fda-approval-drug-events-study/index.html> [<https://perma.cc/U8GC-EBDZ>] (stating that “[o]n average, it takes about 12 years to get a drug from the research phase to patient”). For a helpful overview of the drug approval process, see *FDA Case Study: Drug Approval—Bringing a New Drug to Market*, FDA, <https://www.fda.gov/media/94428/download> (last visited Apr. 17, 2024) [<https://perma.cc/6E7J-ZSJJ>].

32. Wysocki, *supra* note 31.

33. Fain et al., *supra* note 30, at 3; see Wysocki, *supra* note 31 (describing this process).

34. See Wysocki, *supra* note 31 (delineating the three trial phases). For example, while phase one trials only require twenty to one hundred participants, who need not all have the disease or condition the drug is designed to target, phase three trials require between three hundred and three thousand participants, all of whom must have the disease or condition. *Id.* The INDs’ pass rates decrease with each phase, from approximately seventy percent at phase one to approximately twenty-five percent at phase three. *Id.*

the trials' data in a New Drug Application ("NDA"),³⁵ and the Agency then weighs the drug's risks and benefits.³⁶ Since the FD&C Act does not provide a rigid formula for determining drug safety, the Agency bases its decision on the context of each application, including factors such as the "nature and severity of the disease the drug will treat and the availability of alternative treatments."³⁷ The Agency not only approves the drug itself but also its labeling, which includes all information on the drug's uses and risks.³⁸ This final review process usually takes six to ten months,³⁹ with only about ten percent of potential drugs gaining approval.⁴⁰

Given the duration of the above process, the FDA offers several routes to expedited approval when quick action is "in everyone's interest."⁴¹ One such method that recently gained publicity is the Emergency Use Authorization, which the FDA used to rapidly approve the COVID-19 vaccines during the pandemic.⁴² Additionally, Fast Track or Breakthrough Therapy designations can be used to expedite development and testing of drugs that fill unmet needs or offer a strong improvement over existing alternatives.⁴³ The FDA can likewise designate a drug for "Accelerated Approval" if it is designed to fill an unmet medical need regarding a serious condition,⁴⁴ allowing the drug to be approved upon less rigorous testing than what is typically required.⁴⁵ Finally, the Agency can use Priority Review to lift a drug's

35. *Id.*

36. Fain et al., *supra* note 30, at 2.

37. *Id.* at 2–3.

38. *Id.* at 3.

39. Wysocki, *supra* note 31.

40. *Id.*

41. *Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review*, FDA, <https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review> (last updated June 12, 2023) [<https://perma.cc/7NTV-SYY3>].

42. *See COVID-19 Vaccine Emergency Use Authorization (EUA) Fact Sheets for Recipients and Caregivers*, CTRS. FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/vaccines/covid-19/eua/index.html> (last updated Sept. 28, 2023) [<https://perma.cc/88PM-A3X9>]; Wysocki, *supra* note 31 (describing the Emergency Use Authorization as a tool to allow "non-FDA approved medications to be used when certain criteria are met" in emergency situations).

43. Wysocki, *supra* note 31. For more explanation of how these two designations work, see *Fast Track*, FDA, <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track> (last updated Jan. 4, 2018) [<https://perma.cc/NP6E-8NNT>]; and *Breakthrough Therapy*, FDA, <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy> (last updated Jan. 4, 2018) [<https://perma.cc/PL2J-SA6F>].

44. *But see* 21 C.F.R. § 314.500 (2023) (stating the Accelerated Approval program applies to drugs meant to treat "serious or life-threatening illnesses" (emphasis added)).

45. Wysocki, *supra* note 31; *Accelerated Approval Program*, FDA, <https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program> (last updated Nov. 27, 2023) [<https://perma>

NDA to the top of the application pile and provide an answer within six months.⁴⁶

Longstanding debates surround the rate and pace at which the FDA approves new drugs, with critics arguing both that the Agency approves too many drugs too quickly as well as too few too slowly.⁴⁷ For example, in 1995, then-Speaker of the House Newt Gingrich referred to the FDA as a “job killer[],” claiming the Agency’s “excessive reviews” unnecessarily delayed the approval of new drugs and stymied the growth of the pharmaceutical industry.⁴⁸ Another worthy consideration underlies this rationale for unhobbling the pharmaceutical industry: more industry growth means more innovation and distribution, which therefore means more cures to diseases and access to better treatments for suffering patients.⁴⁹ These arguments moved the needle. By 1998, the FDA was approving a higher volume of drugs at a faster pace than ever before.⁵⁰ But the recalls of three new drugs between 1997 and 1998 led other critics to claim that pressure from the pharmaceutical industry was inducing the Agency to approve new drugs without sufficient research.⁵¹ Nonetheless, some scholars defended the Agency’s new pace, calling the rising number of recalls a “statistically inevitable” result of progress in the field.⁵² These defenders concluded that while

.cc/WDL3-FJT7] [hereinafter FDA, *Accelerated Approval Program*] (explaining that to “considerably shorten” the time required to test the drug, the FDA allows a sponsor to use “surrogate endpoint[s],” or markers that are reasonably likely to predict clinical benefit from the drug while not themselves being true measures of clinical benefit, such as x-ray results showing tumor shrinkage as a surrogate for longer survival).

46. See Wysocki, *supra* note 31 (“Priority Review designation means the FDA will aim to provide a decision on an NDA within 6 months . . .”).

47. See J.D. Kleinke & Scott Gottlieb, *Is the FDA Approving Drugs Too Fast?*, 317 *BMJ* 899, 899 (1998) (claiming this debate goes back to 1962, when Congress first established the drug approval process).

48. *Id.*

49. See Peter J. Pitts, *Too Fast or Too Slow: Is the FDA Moving at the Right Speed?*, HEALTH AFFS. BLOG (Mar. 19, 2021), <https://www.healthaffairs.org/content/forefront/too-fast-too-slow-fda-moving-right-speed> [<https://perma.cc/5JHG-ALGG>] (“Speedier review has resulted in more drugs for serious and life-threatening diseases, with solid benefit/risk profiles. In short, the speed with which the FDA moves saves lives.”).

50. See Kleinke & Gottlieb, *supra* note 47, at 899 (mentioning that the average number of drugs approved per year doubled from twenty to forty between 1990 and 1998).

51. See *id.* (“The FDA’s critics cite these recalls as evidence that pressure from the pharmaceutical industry and other special interest groups has accelerated the drug review process to the point of endangering public health.”).

52. *Id.* They further posited four reasons for the Agency’s acceleration at the end of the twentieth century: First, Congress passed the Prescription Drug User Fee Act in 1992, requiring sponsors to pay a fee for each drug application submitted, and the Agency had invested these fees to hire six hundred more reviewers. *Id.*; *Prescription Drug User Fee Amendments*, FDA, <https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments> (last updated Dec. 14, 2023) [<https://perma.cc/ZHF2-ETKQ>]. Second, the pharmaceutical industry developed highly profitable drugs in the 1980s, allowing it to invest more into research and development of new drugs. Kleinke & Gottlieb, *supra* note 47, at 899. Third, activists persuaded

individual tragedies associated with these recalls were indeed tragic, the Agency was still moving at the right pace.⁵³

This debate continues today. The FDA is now approving drugs at a pace of approximately forty-one new drugs per year,⁵⁴ and postmarket problems have likewise risen in frequency. In 2017, for example, a study found that nearly one-third of the drugs the FDA had approved between 2001 and 2010 later exhibited safety problems.⁵⁵

This landscape of risk raises two questions: First, prior to a drug's approval, what happens when the FDA determines that it is risky but still merits approval? Second, what happens when the trials are insufficient, such that a drug's dangers appear only postapproval, after it has already reached patients? These questions bring us to the topic of the FDA's REMS programs.

B. The Pre-REMS FDA: Powerless to Limit the Risks of Already-Approved Drugs

Prescription medications are ubiquitous today.⁵⁶ This widespread availability of drugs would not be possible without a massive pharmaceutical infrastructure to research, develop, manufacture, and distribute these products throughout the country.

the Agency to start fast-tracking potentially life-saving treatments for AIDS and cancer. *Id.* Fourth, experience sharpened both the industry and the Agency, making them more efficient. *Id.*

53. See Kleinke & Gottlieb, *supra* note 47, at 899 (providing rationale for the increased pace).

54. *FDA Is Approving Drugs Faster than Ever—but Is This a Good Thing?*, ADVISORY BD.: DAILY BRIEFING, <https://www.advisory.com/daily-briefing/2020/01/21/fda-reviews> (last updated Mar. 20, 2023) [<https://perma.cc/VV4C-U9SF>].

55. See Christensen, *supra* note 31 (citing a 2017 study finding that seventy-one out of 222 novel therapeutics approved between 2001 and 2010 required FDA action). During this period, the FDA approved 222 novel therapeutic drugs, and the study found that seventy-one of them were associated with 123 post-market adverse safety events requiring FDA action. *Id.* Of these seventy-one products, three were withdrawn, and extra warning labels were added to the boxes of sixty-one others. *Id.* These problems were most common among drugs treating mental illness and drugs that underwent Accelerated Approval, thereby facing less stringent testing criteria. See *id.* While these numbers are alarming, the majority of the drugs exhibiting safety problems were “niche drugs used for specialty-type diseases.” *Id.* It is also important to remember Accelerated Approval is for serious and life-threatening conditions without existing alternative treatments. See FDA, *Accelerated Approval Program*, *supra* note 45 (explaining this program is meant “to allow for earlier approval of drugs that treat serious conditions, and fill an unmet medical need”). Drugs treating common conditions and used by larger portions of the population, on the other hand, undergo the longer pre-approval testing process laid out *supra*. See Christensen, *supra* note 31. Nonetheless, all patient populations—no matter how great or small—deserve diligent protection.

56. See *Therapeutic Drug Use*, CTRES. FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/nchs/fastats/drug-use-therapeutic.htm> (last updated Sept. 19, 2023) [<https://perma.cc/4MHM-TE4F>] (noting that between 2015 and 2018, nearly half of all Americans used at least one prescription drug within the previous thirty days, and nearly a quarter used at least three prescription drugs during the same period).

Indeed, Americans spent \$573 billion on pharmaceuticals in 2021,⁵⁷ and five of the ten largest pharmaceutical companies in the world are based in the United States.⁵⁸

Constant innovation and the impossibility of having perfect clinical trials make drugs inherently risky, and the industry's capacity to distribute these drugs to huge portions of the population makes the consequences of mistakes devastating. Vioxx provides a harrowing example. The FDA approved Vioxx in 1999, but its manufacturer withdrew the painkiller from the market only five years later.⁵⁹ During that time, Vioxx had already caused an estimated 88,000 heart attacks and 38,000 deaths in America alone.⁶⁰ This calamity showcased the need for the FDA to strengthen its ability to ensure a drug's benefits outweighed its risks.⁶¹

At that time, the Agency's power to require extra safety measures from the industry as conditions for a drug's approval was limited to three weak methods.⁶² First, the FDA could require drug sponsors to provide medication guides, providing information on "serious safety risks associated with a drug's use" directly to patients.⁶³ Second, the FDA could ask a sponsor to issue "Dear Health Care Professional" letters, informing physicians and pharmacists of the drug's serious health hazards.⁶⁴ Finally, the FDA could request that a sponsor submit a Risk Minimization Action Plan ("RiskMAP"), which could include a combination of the prior two methods as well as "restricted distribution conditions" like education programs for physicians and patients and even prescription tracking.⁶⁵ Under the FD&C Act, the Agency was authorized to require enhanced labeling from drug sponsors only as a condition for initial approval.⁶⁶ But once a drug gained approval, the Agency lacked the authority to require any

57. Matej Mikulic, *Total Nominal Spending on Medicines in the U.S. from 2002 to 2022*, STATISTA (Sept. 15, 2023), <https://www.statista.com/statistics/238689/us-total-expenditure-on-medicine/> [<https://perma.cc/3SAQ-LTF5>].

58. Matej Mikulic, *U.S. Pharmaceutical Industry – Statistics & Facts*, STATISTA (Aug. 31, 2023), <https://www.statista.com/topics/1719/pharmaceutical-industry> [<https://perma.cc/L56Y-L4E7>].

59. Snigdha Prakash & Vikki Valentine, *Timeline: The Rise and Fall of Vioxx*, NPR (Nov. 10, 2007, 2:40 PM), <https://www.npr.org/2007/11/10/5470430/timeline-the-rise-and-fall-of-vioxx> [<https://perma.cc/5UBE-5S8D>].

60. *Id.*

61. *See* FDA, *REMS Description*, *supra* note 8 (explaining this goal of REMS).

62. *See* Fain et al., *supra* note 30, at 5–7 (delineating these three measures).

63. *Id.* at 5–6.

64. *Id.* at 7.

65. *Id.* at 7–8.

66. *See id.* at 8 ("Before marketing began, FDA could condition a drug's approval upon certain indications, warnings, and directions in the product labeling . . .").

of the above methods, making nearly all industry cooperation on approved drugs voluntary.⁶⁷ If the FDA determined that new information on an already-approved drug necessitated additional safety measures, the strongest method for attaining the necessary change was to either enjoin the drug's marketing through a federal enforcement proceeding or withdraw the Agency's approval and require the sponsor to apply again, this time requiring the additional measures.⁶⁸ Both methods were cumbersome and inappropriate when only minor adjustments (e.g., stronger warning labels) were necessary.⁶⁹

C. A New Tool for Fighting Risk: Introducing REMS

Within three years of Vioxx's withdrawal from the market, Congress passed the FDAAA, amending the FD&C Act to enhance the Agency's ability to protect the public from risky drugs.⁷⁰ The FDAAA authorized the Agency to require more rigorous safety measures from drug sponsors both pre- and post-approval. Essentially, the Act codified the Agency's use of medication guides, "Dear Health Care Professional" letters, and RiskMAPs, bundling and repackaging these methods as Risk Evaluation and Mitigation Strategies—or REMS.⁷¹

Stated simply, the FDA requires a REMS for a medication the Agency has determined presents "serious safety concerns" in order to ensure the medication's benefits "outweigh its risks."⁷² The amended FD&C Act now requires the Commissioner to determine whether a REMS is necessary for a drug awaiting approval based on the following six factors:

(A) the estimated size of the population expected to use the drug;⁷³

67. *See id.* at 7–9 (stating that "after approval, there was no clear statutory authority for FDA to require a drug sponsor to amend the drug's labeling with new safety information").

68. *Id.* at 9; *see also* 21 U.S.C. § 355-1 (authorizing the FDA to require a drug developer to institute a REMS).

69. *See* Fain et al., *supra* note 30, at 7–8 (describing how the sponsor of Lotronex had to withdraw and reintroduce the drug with increased restrictions because the previously approved conditions were not preventing serious adverse events).

70. FDA, REMS: FDA'S APPLICATION OF STATUTORY FACTORS IN DETERMINING WHEN A REMS IS NECESSARY: GUIDANCE FOR INDUSTRY 2 (2019), <https://www.fda.gov/media/100307/download> [<https://perma.cc/47LR-MQQE>] [hereinafter FDA, REMS GUIDANCE] (explaining that the FDA's REMS authority was established by the FDAAA).

71. *See id.* at 2–3 ("Many of the principles described in the RiskMAP Guidance are reflected in the REMS provisions . . .").

72. FDA, *REMS Description*, *supra* note 8.

73. 21 U.S.C. § 355-1(a)(1)(A); *see also* FDA, REMS GUIDANCE, *supra* note 70, at 9 (advising that the FDA not only considers the size of the population, but also whether that population can be expected to use the drug for unapproved uses).

- (B) “[t]he seriousness of the disease or condition” the drug will treat;⁷⁴
- (C) the drug’s expected benefit regarding such disease or condition;⁷⁵
- (D) the duration of treatment;⁷⁶
- (E) the “seriousness” of related adverse events and the frequency of such events in the population expected to use the drug;⁷⁷ and
- (F) “[w]hether the drug is a new molecular entity.”⁷⁸

Additionally, the Commissioner also considers a REMS’s potential burden on the healthcare system and patient access to the drug, seeking to decrease such burdens as much as practicable.⁷⁹ Once the FDA has determined a REMS is necessary, the drug’s sponsor develops a REMS plan and submits it for Agency approval.⁸⁰ Under the new REMS regime, a drug application cannot be approved until the Agency has approved the sponsor’s REMS plan.⁸¹

The FDA can require much of a sponsor through REMS. Specific requirements can include obligating sponsors to communicate with patients through patient-friendly medication guides and with healthcare providers directly.⁸² These communications should highlight

74. 21 U.S.C. § 355-1(a)(1)(B); *see also* FDA, REMS GUIDANCE, *supra* note 70, at 8 (“[T]he more serious the disease or condition to be treated, the greater the potential benefit of the drug’s measured effect in the benefit-risk assessment.”).

75. 21 U.S.C. § 355-1(a)(1)(C); *see also* FDA, REMS GUIDANCE, *supra* note 70, at 7 (“FDA may evaluate information about the drug’s effectiveness, whether the drug treats a serious disease or condition, whether it fills an unmet medical need, and whether it can cure the disease or alleviate its symptoms.”).

76. 21 U.S.C. § 355-1(a)(1)(D); *see also* FDA, REMS GUIDANCE, *supra* note 70, at 9 (advising that REMS may be required for both drugs with long and short duration treatments depending on the other factors).

77. 21 U.S.C. § 355-1(a)(1)(E); *see also* FDA, REMS GUIDANCE, *supra* note 70, at 6–7 (“While a high frequency of adverse events may necessitate a REMS to mitigate this risk, FDA may also require a REMS for an infrequent adverse event, if the adverse event is particularly severe.”).

78. 21 U.S.C. § 355-1(a)(1)(F); *see also* FDA, REMS GUIDANCE, *supra* note 70, at 8 (explaining that information may be limited regarding a new molecular entity’s safety, thus increasing uncertainty about its risks).

79. *See* FDA, REMS GUIDANCE, *supra* note 70, at 5, 9 (delineating how the FDA takes these burdens into account).

80. *See* Debbie Cheslow & Kristen Veley, *Four Common Missed Opportunities When Designing and Developing a REMS Program*, EVIDERA 2 (2021), https://www.evidera.com/wp-content/uploads/2021/05/EFSpr21_A11_CheslowD-REMS.pdf [<https://perma.cc/4YG9-GKHK>] (“The FDA requires, reviews, and approves REMS programs, but sponsors must design and develop their own REMS programs.”).

81. *See id.* (explaining how delays in REMS program development can lead to delayed approval).

82. *What’s in a REMS?*, FDA, <https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/whats-rems> (last updated Jan. 26, 2018) [<https://perma.cc/WA98-6HDH>] [hereinafter FDA, *What’s in a REMS?*].

“specific serious risk[s] associated”⁸³ with the medications and “steps to take to reduce” those risks.⁸⁴ More active requirements, known as Elements to Assure Safe Use (“ETASU”), may attach if the Agency has found the drug effective but believes that it is too risky to approve unless changes are made to the drug’s labeling or additional measures are carried out in practice.⁸⁵ For example, ETASU may require the drug’s prescribers and dispensers to undergo training, gain certification, and agree to conduct activities designed to lessen the drug’s risks.⁸⁶ Some ETASU require physicians, pharmacists, or patients to document a “safe use condition” (e.g., a monthly lab test) before the drug is dispensed.⁸⁷ Other ETASU may require that the drug be dispensed to patients only in certain settings (e.g., hospitals) or only when patients are placed under monitoring or in a registry.⁸⁸ Some ETASU require the developer to establish implementation systems to facilitate monitoring and improvement of the elements’ execution, such as websites, call centers, or electronic databases.⁸⁹ Finally, a REMS typically includes a timetable for the sponsor to submit mandatory assessments of the REMS program’s implementation so the Agency may track the drug’s safety over time.⁹⁰

Crucially, the amended FD&C Act not only authorizes the Agency to require a REMS for new drugs but also empowers the Agency to require a REMS program if new safety information on the drug becomes available after its approval.⁹¹ Such safety information can arise from a variety of sources, including postapproval adverse event reports, clinical trials, and studies.⁹² Most importantly, the amended Act prohibits failure to comply with any of the conditions of a REMS and also authorizes the FDA to take enforcement action through either civil or criminal proceedings, dramatically raising the sponsors’ stakes for noncompliance.⁹³ Of course, the Agency may withdraw the

83. *Id.*; see also Fain et al., *supra* note 30, at 11 (defining serious risks as “adverse drug experiences resulting in death, immediate risk of death, inpatient hospitalization, persistent or significant incapacity, or a congenital anomaly or birth defect”).

84. FDA, *What’s in a REMS?*, *supra* note 82.

85. FDA, REMS GUIDANCE, *supra* note 70, at 2.

86. *Id.*

87. *Id.*

88. *Id.*

89. *Id.*

90. *Id.* at 3. The sponsor must submit such assessments at eighteen months, three years, and seven years from the date the FDA approves the sponsor’s REMS. *Id.*

91. 21 U.S.C. § 355-1(a)(2); see also FDA, REMS GUIDANCE, *supra* note 70, at 2 (“ETASU may be required for approved drug products that were initially approved without ETASU when other elements are not sufficient to mitigate a serious risk.”).

92. *Id.* at 4–5.

93. See Fain et al., *supra* note 30, at 10.

requirement for a REMS program if it determines one is no longer necessary.⁹⁴ Although REMS programs are required for only a small minority of all FDA-approved drugs,⁹⁵ the public health stakes make REMS a vital part of the regulatory scheme.

Thus, if a party disagrees with the Agency's REMS decision, the party may wish to have a neutral court provide a second look. But before the court can get to the merits of the plaintiff's case, the court must first determine whether the plaintiff was obligated to exhaust its administrative remedies before suing,⁹⁶ and if so, whether the plaintiff had indeed exhausted them.⁹⁷

D. Exhaustion of Administrative Remedies

Citizens challenge agency actions in court with great frequency.⁹⁸ Not every agency action, however, is reviewable in court.⁹⁹ In fact, there are several potential roadblocks on the route to judicial review of agency actions, and to get past them, a plaintiff must demonstrate both constitutional¹⁰⁰ and prudential standing;¹⁰¹ that

94. See *id.* at 12 (“REMS may be modified or withdrawn by FDA based on new safety or effectiveness information.”).

95. See FDA, REMS GUIDANCE, *supra* note 70, at 4 (stating “routine risk mitigation measures . . . are sufficient to preserve benefits while minimizing risks” for most drugs); see also *REMS Public Dashboard*, *supra* note 10 (stating there are currently sixty-six active REMS and 311 ever approved).

96. See *Darby v. Cisneros*, 509 U.S. 137 (1993) (considering applicability of exhaustion doctrine in actions brought under the Administrative Procedures Act).

97. See *Ass’n of Am. Physicians & Surgeons v. FDA*, 539 F. Supp. 2d 4, 21 (D.D.C. 2008) (finding dismissal appropriate in part because plaintiffs had failed to exhaust administrative remedies).

98. See Joel Beauvais, Steven P. Croley & Elana Nightingale Dawson, *Judicial Challenges to Federal Agency Action*, in *ENVIRONMENTAL LITIGATION: LAW AND STRATEGY 1* (Kegan A. Brown & Andrea M. Hogan eds., 2d ed. 2019) (noting that “most major environmental regulatory decisions at the federal level are challenged in court”).

99. JARED P. COLE, CONG. RSCH. SERV., R44699, AN INTRODUCTION TO JUDICIAL REVIEW OF FEDERAL AGENCY ACTION 2 (2016), <https://crsreports.congress.gov/product/pdf/R/R44699> [<https://perma.cc/2T5J-MQHN>].

100. See *id.* at 6–7 (delineating requirements for constitutional standing). Standing ensures the suit is brought by the right person. Specifically, constitutional standing requires a plaintiff to show he or she has suffered an “injury in fact” that is “fairly traceable” to the defendant’s actions, and that a favorable decision will “likely . . . redress[]” this injury. *Id.* at 7 (quoting *Bennett v. Spear*, 520 U.S. 154, 162 (1997)).

101. See *Ass’n of Data Processing Serv. Orgs. v. Camp*, 397 U.S. 150, 153 (1970) (holding that a party challenging an agency’s action under a statute must show that the “interest sought to be protected . . . is arguably within the zone of interests to be protected or regulated by the statute . . . in question”).

judicial review of the issue is not precluded,¹⁰² and that the case is properly timed.¹⁰³

Among the other timing doctrines of finality,¹⁰⁴ ripeness,¹⁰⁵ and mootness,¹⁰⁶ courts dealing with administrative issues must often evaluate whether the doctrine of exhaustion of administrative remedies applies and, if so, whether it has been satisfied.¹⁰⁷ The doctrine is relatively straightforward: courts typically expect parties challenging agency actions to have already gone through the agency's apparatus for resolving such challenges.¹⁰⁸ Rooted in the common law,¹⁰⁹ the exhaustion doctrine rests upon the wisdom that where Congress has delegated the authority to answer certain questions to certain agencies, those agencies—rather than Article III courts—should get the first crack at answering them.¹¹⁰ This requirement serves several purposes. Specifically, exhaustion utilizes the agency's expertise, allows the agency the opportunity to correct its own errors, and ensures the compilation of a full record before the case reaches the judiciary.¹¹¹ It also maintains agency authority by preventing would-be plaintiffs from dodging Congress's intended mechanism for resolving an

102. See COLE, *supra* note 99, at 11 (stating that review under the APA may be precluded via statute or “when the agency’s action is legally com[m]itted to an agency’s discretion”); see also Laura Dolbow, *Barring Judicial Review*, 77 VAND. L. REV. 307, 312 (2024) (finding Congress has expressly precluded judicial review in 190 different provisions across the U.S. Code).

103. See COLE, *supra* note 99, at 7–8 (discussing proper timing for a case, including ripeness, mootness, and failure to exhaust remedies).

104. *Id.* at 11. The APA limits review to “final” agency actions, meaning actions representing the “‘consummation’ of the agency’s decisionmaking process” and creating “rights or obligations” or legal consequences. *Id.* (quoting *Bennett*, 520 U.S. at 178).

105. *Id.* at 7–8. Ripeness ensures that the plaintiff is not bringing a premature case but rather a case in which the parties would face “hardship” if the court does not hear the case. *Id.* at 8 (citing *Abbott Lab’s v. Gardner*, 387 U.S. 136, 149 (1967)).

106. *Id.* at 8. A case is moot if the original controversy no longer exists, for instance, if the agency ceased the action of which the plaintiff originally complained. See *id.* (noting that a “change in the law” can moot a case).

107. See *id.* (“[A] court might deny review because a party failed to exhaust its administrative remedies before suing in federal court.”).

108. 33 CHARLES ALAN WRIGHT, CHARLES H. KOCH & RICHARD MURPHY, FEDERAL PRACTICE AND PROCEDURE § 8363, at 214 (2d ed. 2018).

109. See Jeffrey S. Lubbers, *Fail to Comment at Your Own Risk: Does Issue Exhaustion Have a Place in Judicial Review of Rules?*, 70 ADMIN. L. REV. 109, 110 (2018) (describing the origins of exhaustion as a “prudential judicial construct”); *United States v. Sing Tuck*, 194 U.S. 161, 169–70 (1904) (dismissing an immigrant’s lawsuit for failing to appeal his immigration denial through the statutorily-prescribed process prior to filing suit); *United States v. Consol. Mines & Smelting Co.*, 455 F.2d 432, 439 (9th Cir. 1971) (crediting *Sing Tuck* with “formulat[ing]” the exhaustion doctrine).

110. See *Smith v. Berryhill*, 139 S. Ct. 1765, 1779 (2019) (“Fundamental principles of administrative law . . . teach that a federal court generally goes astray if it decides a question that has been delegated to an agency if that agency has not first had a chance to address the question.”).

111. 33 WRIGHT ET AL., *supra* note 108, § 8363, at 214 n.2 (citing *Weinberger v. Salfi*, 422 U.S. 749, 765 (1975)).

administrative issue.¹¹² Finally, exhaustion preserves judicial and administrative efficiency by preventing unnecessary suits from burdening both the courts and agencies.¹¹³

Presumably observing the exhaustion doctrine's common-law benefits, Congress codified it in the APA.¹¹⁴ Section 10 of the APA provides for judicial review of agency actions.¹¹⁵ The first section provides a right of judicial review to people "suffering [a] legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of a relevant statute."¹¹⁶ Section 704, the provision known for codifying the exhaustion doctrine,¹¹⁷ deserves careful consideration. It provides that "[a]gency action made reviewable by statute and final agency action for which there is *no other adequate remedy* in a court are subject to judicial review,"¹¹⁸ thereby reserving review for actions in which all other appropriate remedies have been exhausted. The final sentence of this provision provides the following:

Except as otherwise expressly required by statute, agency action otherwise final is final for the purposes of this section whether or not there has been presented or determined an application for a declaratory order, for any form of reconsideration, or, unless the agency otherwise requires by rule and provides that the action meanwhile is inoperative, for an appeal to superior agency authority.¹¹⁹

This longwinded provision essentially stipulates that an agency action is judicially reviewable regardless of whether a plaintiff has asked "for any form of reconsideration," with two exceptions: (1) where a statute expressly declares the action not final or (2) where the agency requires by rule that the plaintiff appeal the original action to "superior agency authority" *and* renders the original action inoperative while the appeal is pending.¹²⁰ This seemingly straightforward doctrine is not

112. *Id.* at 214 (quoting *McCarthy v. Madigan*, 503 U.S. 140, 145 (1992)).

113. *Id.* (quoting *McCarthy*, 503 U.S. at 145); *see also* Nicholas Bagley, *The Puzzling Presumption of Reviewability*, 127 HARV. L. REV. 1285, 1287 (2014) (arguing against the presumption of judicial review partly because it "diverts agency resources").

114. 5 U.S.C. § 704; *see also* *Darby v. Cisneros*, 509 U.S. 137, 153 (1993) ("[W]ith respect to actions brought under the APA, Congress effectively codified the doctrine of exhaustion of administrative remedies in § 10(c).").

115. Because the relevant provisions of the APA were codified at 5 U.S.C. §§ 701-706, this Note refers to their location in the U.S. Code instead of their original placement in the statute to avoid confusion. *Darby*, however, refers to the statutory placement. *See, e.g.*, 509 U.S. at 152 (referring to the review of agency action provision codified at 5 U.S.C. § 704 as "§ 10(c)").

116. 5 U.S.C. § 702.

117. *See Darby*, 509 U.S. at 153 (stating that § 704 of the APA "effectively codified" the exhaustion doctrine).

118. 5 U.S.C. § 704 (emphasis added).

119. *Id.*

120. *Id.*; *see also* William Funk, *Exhaustion of Administrative Remedies – New Dimensions Since Darby*, 18 PACE ENV'T L. REV. 1, 4 (2000).

without its issues, however,¹²¹ and courts throughout the country have struggled to determine when a court should require exhaustion and when exhaustion is unnecessary.¹²²

The leading case on exhaustion under the APA is *Darby v. Cisneros*.¹²³ In *Darby*, the Plaintiff Petitioner sought judicial review of a decision by the Department of Housing and Urban Development (“HUD”) to debar him from making mortgage insurance deals with HUD for eighteen months after it had found him liable for violating HUD’s regulations.¹²⁴ As the first administrative step, HUD held an adjudication in which an Administrative Law Judge (“ALJ”) heard the Petitioner’s case and issued an “Initial Decision and Order,” finding him liable.¹²⁵ HUD’s regulations provided that any party to the administrative adjudication could file for review within thirty days of the ALJ’s decision, but neither chose to do so.¹²⁶ Notably, the regulations did not explicitly require administrative appeal.¹²⁷ But because the Petitioner could have appealed within the agency, HUD argued he could not bring his suit in court for failure to exhaust available administrative remedies.¹²⁸

The Supreme Court disagreed, however, stating that the availability of appeal within an agency does not by itself force a plaintiff to exhaust that remedy before resorting to the judiciary.¹²⁹ Section 704, insisted the Court, was meant to “remove obstacles to judicial review of agency action,”¹³⁰ not to serve as “a trap for unwary litigants.”¹³¹ Indeed, the Court held that § 704 prohibits courts from requiring exhaustion beyond “the extent that it is required by statute or by agency rule as a prerequisite to judicial review.”¹³² As this Note discusses below, courts and scholars across the country have seized on this line to

121. See Marcia R. Gelpe, *Exhaustion of Administrative Remedies: Lessons from Environmental Cases*, 53 GEO. WASH. L. REV. 1, 3 (1985) (calling exhaustion caselaw “complex and confusing” and arguing that it leads to decisions that are “confusing and poorly reasoned”).

122. See *Darby*, 509 U.S. at 137; *Ctr. for Food Safety v. Hamburg*, 142 F. Supp. 3d 898 (N.D. Cal. 2015), *vacated and remanded on other grounds*, 696 F. App’x 302 (9th Cir. 2017) (holding exhaustion required in a challenge to FDA approval of a drug for use in animals); *Cody Lab’ys, Inc. v. Sebelius*, 446 F. App’x 964, 966 (10th Cir. 2011) (holding exhaustion required in a challenge to FDA refusal to exempt a drug from regulation under a “grandfather clause”).

123. 509 U.S. 137 (1993).

124. *Id.* at 140–42.

125. *Id.*

126. *Id.* at 141–42.

127. *Id.* at 141.

128. *Id.*

129. *Id.* at 147–50.

130. *Id.* at 147 (quoting *Bowen v. Massachusetts*, 487 U.S. 879, 904 (1988)).

131. *Id.*

132. *Id.* at 153.

show agencies can make exhaustion mandatory by promulgating a regulation.¹³³ While true, this takeaway comes with a significant caveat regarding how agencies may require exhaustion.

On the next page of the opinion, the Court elaborated on how an agency may go about requiring exhaustion: “[W]here the APA applies, an appeal to ‘superior agency authority’ is a prerequisite to judicial review *only* when expressly required by statute or when an agency rule requires appeal before review *and the administrative action is made inoperative pending that review.*”¹³⁴ According to this holding, a party need not exhaust its administrative remedies, therefore, unless (1) a statute expressly requires so or (2) an agency rule expressly requires exhaustion, and the complained-of action becomes inoperative while the appeal is pending.¹³⁵ The Court even instructed agencies as such, stating they can require exhaustion and avoid finality “first, by adopting a rule that an agency appeal be taken before judicial review is available, and, second, by providing that the initial decision would be ‘inoperative’ pending appeal.”¹³⁶ And since no such statutory nor regulatory requirement existed, the Petitioner was free to sue.¹³⁷

In the years following *Darby*, many agencies—seeking shelter from judicial review—have promulgated rules requiring parties to exhaust their administrative remedies prior to filing suit. The FDA has joined in this practice,¹³⁸ but as shown below, the FDA’s regulations notably lack the “inoperative” part of § 704’s framework.

E. Exhaustion, Meet the FDA: Citizen Petitions

The FDA provides its administrative remedies in Title 21, Part 10 of the Code of Federal Regulations (“CFR”).¹³⁹ Section 10.25(a) states that interested citizens “may petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking

133. *See infra* Section II.B.

134. *Darby*, 509 U.S. at 154 (second emphasis added) (quoting 5 U.S.C. § 704).

135. *Id.*

136. *Id.* at 152. While the quotation refers specifically to finality, and the two concepts are supposed to remain distinct, scholars have noted that exhaustion under the APA is “largely subsumed within the finality requirement of § 704.” Admin. Conf. of the U.S., *Judicial Review of Agency Action*, FED. ADMIN. PROC. SOURCEBOOK, https://sourcebook.acus.gov/wiki/Judicial_Review_of_Agency_Action/view (last updated Aug. 15, 2023, 7:22 PM) [<https://perma.cc/RYG7-V74B>].

137. *Darby*, 509 U.S. at 144, 154.

138. *See* *Ctr. for Food Safety v. Hamburg*, 142 F. Supp. 3d 898, 903 (N.D. Cal. 2015) (“The FDA regulations, therefore, ‘require that a request’ be made to the Commissioner before filing a complaint in court complaining of an administrative action or failure to act.” (quoting *Ass’n of Am. Physicians & Surgeons v. FDA*, 539 F. Supp. 2d 4, 21 (D.D.C. 2008))).

139. 21 C.F.R. § 10 (2023).

any other form of administrative action.”¹⁴⁰ While there are several types of citizen petitions, someone challenging a REMS determination would file one under §§ 10.25 and 10.30.¹⁴¹ Section 10.30(e) lays out how the citizen petition process should end. The Agency promises the Commissioner “shall” respond “to each petitioner within 180 days of receipt of the petition.”¹⁴² The Commissioner has three end-of-the-line options: approve the petition, deny the petition, or dismiss the petition if the Commissioner believes changes in law or circumstance have rendered the petition moot.¹⁴³ Alternatively, the Commissioner may issue a tentative response, kicking the petition down the road until a better time.¹⁴⁴

While the language of § 10.25(a) may sound optional, § 10.45 clarifies that this process is mandatory: any “request that the Commissioner take or refrain from taking any form of administrative action must first be the subject of a final administrative decision based on a petition submitted under § 10.25(a)”¹⁴⁵ If a plaintiff files in court complaining of the FDA’s action or inaction before the Agency has submitted a final decision on the plaintiff’s petition, “the Commissioner shall request dismissal of the court action . . . for failure to exhaust administrative remedies”¹⁴⁶ Due to this requirement, courts across the country have dismissed plaintiffs’ claims for failure to exhaust administrative remedies when they failed to file citizen petitions with the FDA or failed to wait until the Agency responded to the petition before suing.¹⁴⁷

But what if this system is failing Americans? While there is value in letting the agency with expertise take the first pass at resolving a party’s complaint, this Note shows that REMS petitions spend years trapped in the FDA’s docket before receiving a final administrative decision.¹⁴⁸ During this time, the FDA’s original determination goes

140. *Id.* § 10.25(a).

141. *Id.* (providing the citizen petition as one of two options for interested parties); *id.* § 10.30 (providing the nuts and bolts of the citizen petition process, including where to file, proper formatting of petitions, and the framework for the Commissioner’s decisions).

142. *Id.* § 10.30(e)(2).

143. *Id.* § 10.30(e)(i)-(iii).

144. *Id.* § 10.30(e)(iv). Because tentative decisions do not exhaust a petitioner’s remedies in the way final decisions do, *id.* § 10.45(d)(1)(i), this Note does not consider them in the analysis of how long petitioners wait in the exhaustion trap.

145. *Id.* § 10.45(b).

146. *Id.*

147. *See* *Ctr. for Food Safety v. Hamburg*, 142 F. Supp. 3d 898, 903 (N.D. Cal. 2015) (holding that “[t]he FDA regulations, therefore, ‘require that a request’ be made to the Commissioner before filing a complaint in court complaining of an administrative action or failure to act” (quoting *Ass’n of Am. Physicians & Surgeons v. FDA*, 539 F. Supp. 2d 4, 21 (D.D.C. 2008))).

148. *See infra* Section II.A.

unchallenged, deteriorating the legitimacy of the citizen petition process. The next Part analyzes this problem in greater detail.

II. ANALYSIS: SPRINGING THE TRAP

The FDA's regulations lay out a straightforward process for petitioning the Agency to reassess or alter its REMS determinations.¹⁴⁹ But reality proves to be much more tortuous. This Part evaluates the Agency's citizen petition docket, focusing on REMS petitions and finding that the Agency routinely fails to adhere to its promised 180-day response window.¹⁵⁰ Instead, these petitions can await decisions for years, often without receiving any indication that the Agency has even considered the petitioners' claims.¹⁵¹ Thus, requiring these petitioners to exhaust their remedies leaves them without recourse, trapped in an administrative purgatory without hope of any future consideration.

As courts understand the FDA's exhaustion requirement today, parties seeking to challenge a REMS determination must file a citizen petition and receive a final decision from the Agency before taking their case to court.¹⁵² But as *Darby* says, an appeal to superior agency authority is not required under the APA unless (1) a statute so requires or (2) a regulation so requires, and the agency action is rendered inoperative pending the resolution of the dispute.¹⁵³ No statute requires submission of a citizen petition prior to judicial review of a REMS determination by the FDA, nor does the FDA ever hold its REMS determinations inoperative pending the resolution of a citizen petition on those specific issues.¹⁵⁴ Thus, a straightforward reading of the APA and *Darby* suggests that the FDA must render its challenged REMS decisions inoperative while agency resolution is pending in order to require exhaustion. Nonetheless, courts across the country have applied *Darby* to FDA cases without mentioning inoperativeness.¹⁵⁵ This Note argues they should reconsider.

149. *See supra* Section I.E.

150. *See infra* Section II.A (finding the FDA only responds to 30.61% of REMS petitions within 180 days).

151. *See infra* Section II.A (finding the average REMS petition wait time is 937.6 days).

152. *See* 21 C.F.R. §§ 10.25(a), 10.30, 10.45 (2023) (describing the process required to challenge a REMS determination).

153. *Darby v. Cisneros*, 509 U.S. 137, 154 (1993).

154. *See, e.g.*, *All. for Hippocratic Med. v. FDA*, 2:22-CV-223-Z, 2023 WL 2825871, at *2–3 (N.D. Tex. Apr. 7, 2023) (noting the FDA maintained its REMS determination for several years after the Plaintiffs filed their citizen petition challenging the REMS program).

155. *See Ass'n of Am. Physicians & Surgeons v. FDA*, 539 F. Supp. 2d 4, 21 (D.D.C. 2008), *aff'd*, 358 F. App'x 179 (D.C. Cir. 2009); *Ctr. for Food Safety v. Hamburg*, 142 F. Supp. 3d 898, 903 (N.D. Cal. 2015); *Cody Lab'ys, Inc. v. Sebelius*, 446 F. App'x 964, 969 (10th Cir. 2011) (applying *Darby* to FDA cases).

A. The View from the Ground: Delayed Decisions Leave Petitioners in the Lurch

Delay has stifled the FDA's citizen petition process for decades. In 1998, the Department of Health and Human Services published a report that found the FDA had a backlog of nearly 250 petitions, some of which had awaited responses for two decades.¹⁵⁶ To its credit, the Agency has improved this process dramatically in the twenty-first century, but petitioners still have a bleak outlook. A petition tracker published by the FDA-specializing law firm Hyman, Phelps & McNamara noted that on June 14, 2021, forty-eight of the 180 citizen petitions filed with the FDA in 2018 were still pending.¹⁵⁷ As of the same date, seventy-nine of the 155 citizen petitions filed in 2019 were still pending.¹⁵⁸ This means the unanswered petitions filed in 2018 were waiting at least 896 days (2.45 years) and the unanswered petitions filed in 2019 had been waiting a minimum of 531 days (1.45 years)—far exceeding the FDA's own self-imposed 180-day maximum.¹⁵⁹ While these delays impact a variety of citizen petitions, they are particularly acute for REMS petitions.¹⁶⁰

1. An Overview of the Data: Poor Performance by the FDA

Because government resources do not make citizen petition data easily accessible to the public,¹⁶¹ this Note's data come from two private

156. OFF. OF INSPECTOR GEN., U.S. DEP'T. OF HEALTH & HUM. SERVS., REVIEW OF THE FOOD AND DRUG ADMINISTRATION'S CITIZEN PETITION PROCESS 3 (1998), <https://oig.hhs.gov/oas/reports/phs/c9750002.pdf> [<https://perma.cc/4NR4-8NXX>].

157. *FDA Citizen Petition Tracker*, FDALAWBLOG: HYMAN, PHELPS & MCNAMARA, <https://www.thefdalawblog.com/wp-content/uploads/CPTracker.xls> (last updated June 14, 2021) [<https://perma.cc/NEZ3-GEZT>] [hereinafter *Citizen Petition Tracker*]; cf. *FDAPetitions.com Statistics -- January 1, 2004 to December 31, 2021*, FDAPETITIONS.COM (Dec. 31, 2021), <https://fdapetitions.com/wp-content/uploads/2006/08/Stats-Table-2021.pdf> [<https://perma.cc/EL79-9T4T>] [hereinafter *FDAPetitions Stats Table*] (finding that thirty-four of the 124 petitions filed in 2018 regarding pharmaceuticals were still pending as of December 31, 2021).

158. *Citizen Petition Tracker*, *supra* note 157; cf. *FDAPetitions Stats Table*, *supra* note 157 (finding that forty-four of the 107 citizen petitions regarding pharmaceuticals filed in 2019 were still pending as of December 31, 2021).

159. Eight hundred and ninety-six days elapsed between December 31, 2018 and June 14, 2021, and 531 days between December 31, 2019 and June 14, 2021. *Days Between Dates*, CALENDAR12.COM, https://www.calendar-12.com/days_between_dates (last visited Apr. 17, 2024) [<https://perma.cc/3PPY-JAEX>].

160. For a discouraging analysis of the FDA's response times to citizen petitions on medical devices, see Thompson, *supra* note 20 ("FDA is just sitting on petitions. Not just a little bit past 180 days. Think of the order of magnitude. 900 days would be way past 180, 5 times beyond. But we are talking about almost 45 times that. We're talking about over 8000 days.").

161. While members of the public can look up individual citizen petitions on the government website [regulations.gov](https://www.regulations.gov), the site is cumbersome and does not allow for easy tracking of wait times. See Michael A. Carrier, *Five Actions to Stop Citizen Petition Abuse*, 118 COLUM. L. REV. ONLINE

research services: Parry Ashford, Inc.'s FDAPetitions.com and Hyman, Phelps & McNamara's FDALawBlog.net. The two sources are each helpful, but incomplete, in different ways. For example, while FDALawBlog lists all kinds of petitions, including those regarding food, animal products, and medical devices, it describes them in less detail and does not categorize REMS petitions. To find REMS petitions, a reader must scour all the petitions within the table and identify those related to REMS. On the other hand, FDAPetitions.com provides thorough summaries of petitions and the Agency's response and categorizes REMS petitions, but it focuses solely on pharmaceutical products.¹⁶² This Note, therefore, primarily utilizes FDAPetitions.com due to its greater ease of access.

Before diving into the specifics of this Note's findings, it is helpful to understand the boundaries of this research and which petitions are and are not included. First, only petitions that came up in a search for the term "REMS" in the FDAPetitions.com database are listed;¹⁶³ this produced a list of fifty-three petitions filed between 2006¹⁶⁴ and 2023, not counting supplements, replies, and other accompanying documents.¹⁶⁵ Second, this Note excludes a few petitions prudentially, such as two petitions that were quickly withdrawn by the petitioner,¹⁶⁶ one duplicate petition,¹⁶⁷ and the most recently filed

82, 85 (2018) (calling the government website "difficult to navigate" and explaining that this difficulty breeds public dependence on sources like FDALawBlog instead).

162. *Home*, FDAPETITIONS.COM, *supra* note 2.

163. *Search Results for 'REMS'*, FDAPETITIONS.COM, <https://fdapetitions.com/forums/search/REMS/> (last visited Apr. 17, 2024) [<https://perma.cc/LG45-YB5H>] [hereinafter *Search Results for 'REMS'*, FDAPETITIONS.COM]. In addition to all petitions explicitly mentioning REMS, Parry Ashford, Inc., included a couple petitions discussing risk and safety concerns of drugs in general. *See, e.g.*, Citizen Petition from Physicians for Responsible Opioid Prescribing to Comm'r, FDA (Sept. 1, 2017) (on file with FDAPetitions.com) (asking the FDA to completely remove ultra-high-dose opioids from the market instead of just placing a REMS on them).

164. While REMS programs were created by the passage of the FDAAA in 2007, prior petitions discussing REMS's predecessors like RiskMAPs and "Dear Health Care Professional" letters are included going back to the database's creation in 2006.

165. *Search Results for 'REMS'*, FDAPETITIONS.COM, *supra* note 163.

166. *See, e.g.*, Citizen Petition from Joseph Dedvukaj, Attorney, the Joseph Dedvukaj Firm, P.C., to Comm'r, FDA (July 9, 2012) (on file with FDAPetitions.com); Withdrawal Notice from Joseph Dedvukaj, Attorney, the Joseph Dedvukaj Firm, P.C., to Comm'r, FDA (July 12, 2012) (on file with FDAPetitions.com); Second Citizen Petition from Joseph Dedvukaj, Attorney, the Joseph Dedvukaj Firm, P.C., to Comm'r, FDA (July 12, 2012) (on file with FDAPetitions.com) (replacing the previous petition); *see also* Citizen Petition from Ieuan G. Mahony, Attorney, Holland & Knight, to Comm'r, FDA (Nov. 1, 2011) (on file with FDAPetitions.com) (withdrawn by petitioner after 72 days).

167. The public interest group National Advocates for Pregnant Women submitted two identical petitions on opioids on October 7, 2013. Citizen Petition from Nat'l Advocs. for Pregnant Women to Comm'r, FDA (Oct. 7, 2013) (on file with FDAPetitions.com) [hereinafter NAPW Petition 1]; Citizen Petition from Nat'l Advocs. for Pregnant Women to Comm'r, FDA (Oct. 7, 2013) (on file with FDAPetitions.com) [hereinafter NAPW Petition 2]. While FDAPetitions.com reports

petition, which had been awaiting a response for only ninety-four days on December 31, 2023.¹⁶⁸ Finally, this Note recognizes that petitioners may not always have upright intentions. Petitions filed under § 505(q) of the FDAAA have gained a particular reputation as a tool that name-brand pharmaceutical companies sometimes use to stifle generic competition.¹⁶⁹ Rather than attempting to discern ulterior motives and filter out potentially anticompetitive 505(q) petitions, this Note includes all 505(q) petitions in the sample and labels them as 505(q) petitions in the appendix.¹⁷⁰

Thus, this Note's dataset consists of forty-nine petitions. In the grand scheme of things, this number may feel insignificant.¹⁷¹ But recall that while the FDA only requires REMS programs on a fraction of all drugs, their high-stakes nature makes them worthy of careful consideration.

the FDA filed two identical responses on April 16, 2014, this Note treats these as probably accidental duplicates, thus only considering one petition and one response in the dataset. Response from Comm'r, FDA, to Nat'l Advocs. for Pregnant Women (Apr. 16, 2014) (on file with FDAPetitions.com) [hereinafter FDA Response to NAPW 1]; Response from Comm'r, FDA, to Nat'l Advocs. for Pregnant Women (Apr. 16, 2014) (on file with FDAPetitions.com) [hereinafter FDA Response to NAPW 2].

168. Citizen Petition from David Melvin, Linda Martin & Michael Mendoza, to Comm'r, FDA (Sept. 26, 2023) (on file with FDAPetitions.com) (pending 94 days as of 12/31/2023).

169. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 914, 121 Stat. 823, 953-57 (2007) (codified at 21 U.S.C. § 355(q)). Section 505(q) petitions pertain to Abbreviated New Drug Applications ("ANDAs"), which allow generic sponsors to utilize brand drugs' already-existing safety and efficacy studies. *Id.* Congress created § 505(q) petitions to reduce delays in the generic approval process. *Id.* Specifically, § 505(q) mandates that the Agency issue a final response to the petition within 150 days, and it also requires petitioners to certify that they are not filing their petition merely to delay the generic drug's approval. *Id.* Unfortunately, however, scholars have found that these petitions have been weaponized by brand-name drug companies to stymie the approval of generic competitors, filing last-minute petitions questioning a generic's ANDA and forcing the FDA to quickly respond to the petitioners' charges. *See id.* Despite the statutorily required certifications to the contrary, it is difficult to ensure the petitioner is not attempting to throw a wrench in the generic's ANDA. For more discussion of anticompetitive § 505(q) petitions, see Michael A. Carrier & Carl Minniti, *Citizen Petitions: Long, Late-Filed, and At-Last Denied*, 66 AM. U. L. REV. 305 (2016), and Carrier, *supra* note 161.

170. *See, e.g.*, Citizen Petition from Otsuka to Comm'r, FDA (Aug. 27, 2019) (on file with FDAPetitions.com); Citizen Petition from Jazz Pharms., Inc., to Comm'r, FDA (May 18, 2012) (on file with FDAPetitions.com); Citizen Petition from Jazz Pharms., Inc., to Comm'r, FDA (July 10, 2012) (on file with FDAPetitions.com); Citizen Petition from Reckitt Benckiser Pharms., Inc., to Comm'r, FDA (Sept. 25, 2012) (on file with FDAPetitions.com); Citizen Petition from Hyman, Phelps & McNamara, PC, to Comm'r, FDA (Aug. 12, 2013) (on file with FDAPetitions.com); Petition for Stay of Action from Mylan Lab'ys to Comm'r, FDA (Aug. 26, 2009) (on file with FDAPetitions.com); *see also* Citizen Petition from Pharm. Mfg. Rsch. Servs. to Comm'r, FDA (May 11, 2017) (on file with FDAPetitions.com) (not explicitly a § 505(q) petition, but it appears possibly anticompetitive).

171. *See Comment on Proposed Regulations and Submit Petitions*, FDA, <https://www.fda.gov/regulatory-information/dockets-management/comment-proposed-regulations-and-submit-petitions> (last updated Mar. 22, 2023) [<https://perma.cc/8H9V-NWDC>] (noting that the FDA receives "about 200 petitions" per year).

TABLE 1: TYPES OF REMS PETITIONERS

| Type of Petitioner | Number of Petitions |
|----------------------------------------|---------------------|
| Public Interest Groups | 17 |
| Pharmaceutical Companies | 18 |
| Law Firms | 4 |
| Individual Physicians | 4 |
| Universities and Research Institutions | 2 |
| Healthcare Providers | 2 |
| State and Local Government | 2 |
| Total | 49 |

As shown in Table 1, these petitions come from a variety of sources.¹⁷² Their content and arguments vary widely, with some petitioning the FDA to increase the severity of REMS programs and other restrictions on certain drugs,¹⁷³ and others seeking to relax

172. While it can be presumed law firms represent a client when petitioning the FDA, the petitions labeled here as “Law Firm” do not identify their clients, so the clients’ identities can only be surmised by context clues. *See, e.g.*, Citizen Petition from Ieuan G. Mahony, *supra* note 166, at 1 (identifying Holland & Knight’s client as a manufacturer of “research materials”); Citizen Petition from Michael H. Hinckle, Attorney, K&L Gates LLP, to Comm’r, FDA 1 (on file with FDAPetitions.com) (identifying its client as a “generic drug manufacturer”); Citizen Petition from David B. Clissold, Attorney, Hyman, Phelps & McNamara, PC, to Comm’r, FDA (Dec. 2, 2011) (on file with FDAPetitions.com) [hereinafter HPM Suboxone Petition 1] (not mentioning its client but presumably on behalf of Reckitt Benckiser, the producer of Suboxone, because it is asking FDA to deny any NDA for a new form of Suboxone); Citizen Petition from David B. Clissold, Attorney, Hyman, Phelps & McNamara, PC, to Comm’r, FDA (Aug. 12, 2013) (on file with FDAPetitions.com) [hereinafter HPM Suboxone Petition 2] (same); Citizen Petition from Deborah L. Livornese, Attorney, Hyman, Phelps & McNamara, PC, to Comm’r, FDA (Nov. 21, 2018) (on file with FDAPetitions.com) (similarly requesting that the FDA not approve any new applications for Zelnorm, so possibly on behalf of Novartis, the original manufacturer of Zelnorm). Thus, to avoid misidentifying the “true” petitioner, this Note leaves these petitions in the “Law Firm” category. Although the Joseph Dedvukaj Firm is clearly a personal injury law firm, *see* THE JOSEPH DEDVUKAJ FIRM, P.C., <https://www.1866hirejoe.com> (last visited Apr. 17, 2024) [<https://perma.cc/UPS4-YK4H>], its petition better fits into the “Public Interest” category because the petitioner self-identifies as “a consumer advocacy law firm,” and urges the FDA to deny the Qnexa NDA as “not safe.” Second Citizen Petition from Joseph Dedvukaj, *supra* note 166, at 1, 9.

173. *See, e.g.*, Citizen Petition from Pub. Citizen to Comm’r, FDA (Apr. 16, 2019) (on file with FDAPetitions.com) [hereinafter Public Citizen Prolia Petition] (asking the FDA to require a REMS for Prolia due to heightened risks of vertebral fractures when patients stop taking the drug too abruptly); PFSF Petition, *supra* note 2 (asking the FDA to immediately remove Propecia from the market, or else require the immediate revision of the product label).

certain drugs' REMS programs.¹⁷⁴ Still other petitions take more general approaches, like asking the FDA to clarify its testing procedures and to ensure name-brand companies cannot use REMS programs to stymie competition from generics.¹⁷⁵ Opioids were the most common topic, comprising seventeen of the forty-nine petitions.¹⁷⁶

TABLE 2: RESPONSE TIME MEASUREMENTS

| Response Time Measurements | Number of Days |
|------------------------------------------|-------------------------------------------------------------|
| Maximum | 5,122 (Petitioner: Kaiser Permanente, pending) |
| Mean | 937.6 |
| Median | 575.5 |
| Minimum | 37 (Hyman, Phelps & McNamara's Second Petition on Suboxone) |
| Percentage Answered Within 180 Days | 30.61% (15 petitions) |
| Percentage Receiving Tentative Decisions | 7.84% (4 petitions) |

Some summary statistics are enlightening. At 5,122 days and counting, Kaiser Permanente holds the longest-waiting petition.¹⁷⁷ In that thirteen-year-old petition, Kaiser asked the FDA to bring the REMS development and evaluation processes into compliance with the FDAAA by, among other things, allowing healthcare providers to give input on a drug's proposed REMS program and reevaluating existing REMS programs regularly to see if they were still necessary.¹⁷⁸ Most petitions, fortunately, do not await responses for thirteen years, instead

174. See, e.g., Citizen Petition from Genesee Health Sys. to Comm'r, FDA (Sept. 3, 2014) (on file with FDAPetitions.com) (asking the FDA to amend the clozapine REMS to permit patients with benign ethnic neutropenia to begin using clozapine at a lower white blood cell count); Citizen Petition from Am. Coll. of Obstetricians & Gynecologists to Comm'r, FDA (Oct. 4, 2022) (on file with FDAPetitions.com) (asking the FDA to designate miscarriage management as an indication for the abortion drug Mifeprex and to remove the drug's REMS insofar as it prevents such a use).

175. Citizen Petition from Dr. Reddy's Lab's to Comm'r, FDA (June 10, 2009) (on file with FDAPetitions.com).

176. Page 15 of Search Results for 'REMS', FDAPETITIONS.COM, <https://fdapetitions.com/forums/search/REMS/page/15/> (last visited Apr. 17, 2024) [<https://perma.cc/4DG9-R66T>] [hereinafter Page 15 of Search Results for 'REMS', FDAPETITIONS.COM] (showing seventeen petitions regarding opioids in general); Page 17 of Search Results for 'REMS', FDAPETITIONS.COM, <https://fdapetitions.com/forums/search/REMS/page/17/> (last visited Apr. 17, 2024) [<https://perma.cc/V7N9-MVLF>] [hereinafter Page 17 of Search Results for 'REMS', FDAPETITIONS.COM] (showing three petitions on the opioid fentanyl alone).

177. Citizen Petition from Kaiser Permanente, *supra* note 17.

178. *Id.* at 1–2.

waiting for an average of 937.6 days, with a median of 575.5 days. Finally, the FDA's fastest response came in at thirty-seven days.¹⁷⁹

This record must be considered against the FDA's own regulations: the Commissioner *shall* respond within 180 days.¹⁸⁰ Of these forty-nine REMS petitions, only fifteen received an answer before the 180-day clock had run. The Agency meeting its self-set deadlines less than one-third of the time is not a strong record. Of course, the subject matter of the petitions is a relevant factor; if the petitions were mere prank mail, then the FDA need not waste scarce time and resources thoroughly analyzing and responding to them. But serious petitions deserve serious consideration. The next Section describes a few of the longer-languishing petitions to shed light on what the Agency is—slowly—dealing with.

2. Serious Petitions Go Unanswered for Years

As stated above, the decision to restrict access to drugs based on evidence of their outsized risks to the public is not a matter to take lightly. The FDA is not the only entity that understands this, and members of the public have petitioned the FDA on these REMS issues.

Several pertinent examples arise among the opioid petitions. As the tragedy of the Opioid Epidemic has made clear, these pharmaceutical drugs are highly addictive and capable of causing overdose and death.¹⁸¹ In 2009, the National Center on Addiction and Substance Abuse at Columbia University recognized the dangers these drugs posed and submitted an eighteen-page petition asking the FDA to impose across-the-board REMS programs on all opioid drugs, requesting that each drug come with safety components including “medication guides, package inserts,” and other ETASU.¹⁸² The FDA issued a tentative response on November 18, 2009—just over the 180-day deadline.¹⁸³ Columbia's petition then waited for nearly two-and-a-

179. HPM Suboxone Petition 2, *supra* note 172; Response from FDA to Hyman, Phelps & McNamara (Sept. 18, 2013) (on file with FDAPetitions.com).

180. 21 C.F.R. § 10.30(e) (2023).

181. See *Commonly Used Drugs Charts*, NAT'L INST. ON DRUG ABUSE (Sept. 19, 2023), <https://nida.nih.gov/research-topics/commonly-used-drugs-charts#PrescriptionOpioidsOxyPercs> [<https://perma.cc/D77L-H3D6>]; see also Karen Feldscher, *What Led to The Opioid Crisis—and How to Fix It*, HARV. T.H. CHAN SCH. OF PUB. HEALTH (Feb. 9, 2022), <https://www.hsph.harvard.edu/news/features/what-led-to-the-opioid-crisis-and-how-to-fix-it/> [<https://perma.cc/2AU2-MH2E>] (“The current opioid crisis ranks as one of the most devastating public health catastrophes of our time.”).

182. Citizen Petition from Columbia Univ. to Comm'r, FDA (May 15, 2009) (on file with FDAPetitions.com) [hereinafter Columbia Petition].

183. *Page 15 of Search Results for 'REMS'*, FDAPETITIONS.COM, *supra* note 176.

half years until the FDA issued a final response on June 17, 2013.¹⁸⁴ The Agency denied the university's requests as overly broad, instead opting to tailor REMS approaches to each drug.¹⁸⁵ In the meantime, however, tens of thousands of people had died from prescription opioid drug overdoses.¹⁸⁶ This Note does not pass judgment on the wisdom of the FDA's decision on how to regulate opioids nor any other drugs; rather, this Note merely argues that input from concerned members of the public deserves timely attention from the government.¹⁸⁷

Another opioid petition of note landed at the FDA on September 1, 2017, this one authored by the organization Physicians for Responsible Opioid Prescribing.¹⁸⁸ While this petition does not explicitly mention REMS, FDAPetitions.com categorized it as a REMS petition because it concerns the riskiness of certain opioids.¹⁸⁹ This group of physicians presented the case for removing ultra-high-dose oral and transmucosal opioids from the market altogether, claiming their risks outweigh their benefits.¹⁹⁰ The petitioners highlight how easy it is for a patient to rapidly surpass the CDC's recommended maximum daily dosage using these hyperpotent opioids, greatly increasing the patient's risk of overdose and death.¹⁹¹ Thus, the petitioners suggest a patient could simply take a higher quantity of lower-dosage pills when doses this large are appropriate.¹⁹² While this request may or may not be apt, the FDA has not communicated either way to the petitioners. Thus, the petition sits unanswered at 2,239 days and counting.¹⁹³

Concerned citizens do not limit themselves to only filing citizen petitions on opioids. In fact, the well-known consumer advocacy

184. Response from FDA to Columbia Univ. (June 17, 2013) (on file with FDAPetitions.com).

185. *Id.* at 3.

186. *Press Release: Opioids Drive Continued Increase in Drug Overdose Deaths*, CTRS. FOR DISEASE CONTROL & PREVENTION (Feb. 20, 2013), https://www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.html [<https://perma.cc/NJZ7-SF7Q>] ("In 2010, nearly 60 percent of the drug overdose deaths (22,134) involved pharmaceutical drugs. Opioid analgesics, such as oxycodone, hydrocodone, and methadone, were involved in about 3 of every 4 pharmaceutical overdose deaths (16,651), confirming the predominant role opioid analgesics play in drug overdose deaths.").

187. See Cary Coglianese, Heather Kilmartin & Evan Mendelson, *Transparency and Public Participation in the Federal Rulemaking Process: Recommendations for the New Administration*, 77 GEO. WASH. L. REV. 924, 927 (2009) (noting that in the rulemaking context, "transparency and public participation inevitably help to achieve democratic goals" and "help produce better, more informed policy decisions").

188. Citizen Petition from Physicians for Responsible Opioid Prescribing, *supra* note 163.

189. *Page 15 of Search Results for 'REMS'*, FDAPETITIONS.COM, *supra* note 176.

190. Citizen Petition from Physicians for Responsible Opioid Prescribing, *supra* note 163, at 1.

191. *Id.*

192. *Id.* at 5.

193. *Page 15 of Search Results for 'REMS'*, FDAPETITIONS.COM, *supra* note 176.

organization Public Citizen submitted a petition on October 4, 2012 about the allegedly dangerous combination of three drug classes: “angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), and aliskiren.”¹⁹⁴ According to Public Citizen, combining these three types of drugs could cause “renal failure, symptomatic hypotension, and hyperkalemia, with no countervailing clinical benefit compared with any of the drug classes used alone.”¹⁹⁵ Therefore, their petition argued, the FDA should strengthen the REMS program on these three drugs to include warning labels, medication guides, and “Dear Doctor” letters, alerting readers to the risks posed by combining these drugs.¹⁹⁶ On one of the drugs specifically, Public Citizen also asked the FDA to remove the existing labeling, finding it misleading and dangerous.¹⁹⁷ The Agency denied the petition on April 3, 2015—two-and-a-half years later.¹⁹⁸

While most REMS petitioners seek enhanced restrictions, other petitioners seek a relaxation of a drug’s required REMS program.¹⁹⁹ On April 9, 2012, Dr. David Behar, a psychiatrist, petitioned for a targeted relaxation of the REMS on clozapine, a drug used to treat schizophrenia.²⁰⁰ Specifically, the petitioner noted that clozapine’s REMS only allowed providers to prescribe the drug to patients with a white blood cell (“WBC”) count above 3500 WBC per microliter to prevent neutropenia, a potentially dangerous condition in which a patient has too few white blood cells.²⁰¹ But because many patients of African and Mediterranean heritage have naturally and benignly lower WBC counts than Caucasians, many of these patients are inappropriately barred from receiving the drug’s benefits.²⁰² The

194. Citizen Petition from Pub. Citizen to Comm’r, FDA 1 (Oct. 4, 2012) (on file with FDAPetitions.com).

195. *Id.* at 2.

196. *Id.*

197. *Id.*

198. Response from FDA to Pub. Citizen (Apr. 3, 2015) (on file with FDAPetitions.com).

199. *See, e.g.*, Citizen Petition from David Behar, M.D., to Comm’r, FDA (Apr. 9, 2012) (on file with FDAPetitions.com) (asking the FDA to create a national registry for patients suffering from both treatment-resistant schizophrenia and benign ethnic neutropenia to facilitate treatment of such patients with clozapine); Citizen Petition from Genesee Health Sys., *supra* note 174 (asking the FDA to amend the clozapine REMS to permit patients with benign ethnic neutropenia to begin clozapine at a lower white blood cell count); *see also* Citizen Petition from Am. Coll. of Obstetricians & Gynecologists, *supra* note 174 (asking the FDA to designate miscarriage management as an indication for the abortion drug Mifeprex and to remove the drug’s REMS insofar as it prevents such a use).

200. Citizen Petition from David Behar, *supra* note 199; *see also* Citizen Petition from Genesee Health Sys., *supra* note 174 (a public health provider in Michigan requesting a similar relaxation on clozapine’s REMS for people with naturally lower WBC).

201. Citizen Petition from David Behar, *supra* note 199, at 3.

202. *Id.*

petition therefore called the Agency to drop the REMS's minimum by 500 WBC per microliter to allow patients diagnosed with a benign, low WBC count to still receive the drug.²⁰³ After waiting ten months for a response, Dr. Behar followed up with the Agency to check on its progress and to ask questions regarding his petition,²⁰⁴ but the Agency did not reply for three more years.²⁰⁵ When the Agency finally got around to the petition in 2016, it could no longer locate Behar's current address and therefore considered the petition voluntarily withdrawn.²⁰⁶ Fortunately, however, the FDA had essentially granted the petition's request in 2015 by issuing an amended REMS program that accounted for some patients' naturally lower WBC counts.²⁰⁷ While this is indeed a happy ending for patients needing clozapine, the Agency notably missed its deadline by some two-and-a-half years, and it never responded to Behar directly.

B. The View from the Law: Without First Receiving a Response, Petitioners Are Out of Luck

The petitioners are in a bind. They have found what they believe to be significant issues regarding the FDA's determinations on the riskiness of certain drugs, but no one has answered them. How do they ensure the FDA's decisions regarding these drugs' level of risk-reducing measures have any oversight? Perhaps they could sue and ask a court to enjoin an FDA decision until it provides a satisfactory answer to the petitioner. But as § 10.45 stipulates and this Note outlines below, a court will likely dismiss any complaint that has not already received a final Agency response for failure to exhaust administrative remedies.²⁰⁸ Herein lies the FDA's exhaustion trap: petitioners cannot gain judicial review until they have exhausted their remedies, but they cannot exhaust said remedies if the Agency refuses to respond. Absent extraordinary circumstances, the FDA's REMS decisions are thus

203. *Id.* at 2.

204. Follow-up Letter from David Behar to Comm'r, FDA (Feb. 3, 2013) (on file with FDAPetitions.com).

205. Notice of Voluntary Withdrawal from FDA to David Behar (Apr. 7, 2016) (on file with FDAPetitions.com) (explaining that the FDA had sent a letter in February 2016 to Behar only to have it returned as undeliverable and unforwardable).

206. *Id.*

207. *FDA Drug Safety Communication: FDA Modifies Monitoring for Neutropenia Associated with Schizophrenia Medicine Clozapine; Approves New Shared REMS Program for All Clozapine Medicines*, FDA (Sept. 15, 2015), <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-modifies-monitoring-neutropenia-associated-schizophrenia-medicine> [<https://perma.cc/6MT7-3XPY>].

208. *See infra* Subsection II.B.2.

apparently unchallengeable. Meanwhile, the costs of zero oversight continue to climb interminably.²⁰⁹

But this need not be the case. This Note advocates that § 704 and *Darby* show a potential escape route for petitioners seeking accountability.²¹⁰ Specifically, *Darby*'s "inoperativeness" rule requires that if an agency wishes to mandate exhaustion based only on an administrative rule, it must render the agency's challenged decision inoperative while the administrative appeal is still pending.²¹¹ If the agency prefers not to render its original decision inoperative, then exhaustion cannot be required based on administrative rule alone.²¹² Because *Darby*'s rule applies to citizen petitions, parties wishing to get a second look at the FDA's REMS decisions should be free to file in court. But if the FDA prefers to make petitioners address the Agency before turning to the judiciary, it may do so by rendering its original decision inoperative. While this escape hatch has promise, as described below, courts across the country have dismissed it.

1. Most Petitioners Are Trapped

While very few cases have been filed specifically challenging the FDA's decision to require or not to require a REMS,²¹³ several close analogs discuss exhaustion and citizen petitions. The most relevant of these is *Association of American Physicians & Surgeons, Inc. v. FDA*, in which several public interest groups attempted to challenge the FDA's approval of the emergency contraceptive Plan B for over-the-counter ("OTC") distribution to anyone over eighteen.²¹⁴ Preceding this suit was a winding process in which the drug's sponsors sought approval of Plan B first for prescription-only ("Rx-Only") use, and then for OTC availability.²¹⁵ The FDA declined the sponsors' first application for OTC approval, citing concerns regarding consumers under sixteen and their ability to safely administer the drug without professional supervision.²¹⁶ At one point, the FDA intended to resolve the issue through the rulemaking process, issuing an Advance Notice of Proposed Rulemaking requesting comments on the issue, and the Plaintiffs

209. See PFSF Petition, *supra* note 2, at 5 (positing that tens of thousands of men suffer from PFS).

210. See *infra* Part III.

211. *Darby v. Cisneros*, 509 U.S. 137, 154 (1993).

212. See *id.* ("Courts are not free to impose an exhaustion requirement as a rule of judicial administration where the agency action has already become 'final' under § 10(c).").

213. See *infra* Subsection II.B.2.

214. *Ass'n of Am. Physicians & Surgeons v. FDA*, 539 F. Supp. 2d 4, 11 (D.D.C. 2008).

215. *Id.* at 10.

216. *Id.*

participated in the 47,000 comments sent to the Agency.²¹⁷ The rulemaking was jettisoned, however, and the sponsors submitted a Supplemental NDA (“SNDA”) presenting strategies to ensure only consumers eighteen and up could access the drug OTC.²¹⁸ The Agency approved the SNDA and the Plaintiffs sued.²¹⁹ Critically, the Plaintiffs never filed a citizen petition under § 10.25(a).²²⁰

The Defendants moved to dismiss for lack of standing and failure to exhaust administrative remedies, and the court granted the Defendants’ motion on both grounds.²²¹ On the exhaustion issue, the district court found each of the Plaintiffs’ two arguments wanting.²²² And while the court correctly explained the FDA’s regulations, its application of *Darby* was wobbly at best.²²³

The court first aptly analyzed the FDA’s regulatory scheme when it rejected the Plaintiffs’ reading of § 10.45(e). Essentially, the Plaintiffs argued that they had satisfied the exhaustion requirement because § 10.45(e) simply states that “interested persons” may seek judicial review of a final decision by the Commissioner without first needing to appeal that decision to the Commissioner.²²⁴ The Plaintiffs contended that the FDA’s approval of the SNDA was a final decision by the Commissioner, and since the Plaintiffs were interested persons, they were clear to sue.²²⁵ As the court pointed out, however, this interpretation would fly in the face of the FDA’s overarching administrative scheme, given that the regulations, taken together, required interested persons to submit a citizen petition under § 10.25 and receive a final decision upon it.²²⁶ Had the court determined that the Plaintiffs had relieved their administrative obligations here, it would have allowed interested persons to challenge every final decision by the Agency, regardless of whether that decision dealt with the interested person particularly.²²⁷ A single comment on the public rulemaking does not substitute for a citizen petition; thus, the proper

217. *Id.* at 10, 21.

218. *Id.* at 11. Such measures included labeling the drug as Rx-Only for anyone seventeen and under, only supplying the drug to legitimate pharmacies and clinics, and requesting that pharmacists keep it behind the counter. *Id.*

219. *Id.*

220. *Id.* at 23.

221. *Id.* at 11.

222. *Id.*

223. *Id.* at 21–24.

224. *Id.* at 22; see 21 C.F.R. § 10.45(e) (2023) (“An interested person may request judicial review of a final decision of the Commissioner in the courts without first petitioning the Commissioner for reconsideration or for a stay of action . . .”).

225. 539 F. Supp. 2d at 22.

226. *Id.*

227. *Id.*

interpretation of § 10.45(e) is that the final decision in question must be one particularly focused on the plaintiff's citizen petition.²²⁸ Once the plaintiff has received said decision, § 10.45(e) allows the plaintiff to appeal to the judiciary without petitioning the Agency for reconsideration.²²⁹ While the court's analysis correctly reflects how the FDA's regulatory scheme functions, that does not mean the scheme itself is good—or even that it is compatible with other governing statutes. As this Note has highlighted, the odds that a plaintiff receives a final decision within the regulatory time frame are slim.²³⁰ Moreover, correctly interpreting the regulations only does so much if the regulations themselves violate § 704 of the APA by skirting its inoperativeness requirement.²³¹

Notably, the Plaintiffs contested exactly that under *Darby*, arguing that they were only required to exhaust their remedies so long as the complained-of decision was rendered inoperative. The court, however, dismissed this argument in just two sentences.²³² Without mentioning *Darby*'s inoperativeness discussion, the court characterized that Supreme Court decision as only prohibiting federal courts from requiring “plaintiffs seeking judicial review under the APA to exhaust *optional* administrative remedies.”²³³ But since § 10.45 mandates the submission of citizen petitions, the court sent the Plaintiffs packing, specifically quoting *Darby*: “[T]he exhaustion doctrine continues to exist under the APA to the extent that it is required by statute or by *agency rule* as a prerequisite to judicial review.”²³⁴

The next year, the Court of Appeals for the D.C. Circuit affirmed the district court's decision on essentially the same grounds, using the same quotation from *Darby*.²³⁵ Both the district and circuit courts highlighted *Darby*'s holding that agencies may require exhaustion through a rule, but they failed to mention the inoperativeness that § 704 provides as a necessary component of that route.²³⁶ As is seen in the

228. *Id.* at 21–22.

229. *Id.* at 22.

230. *See supra* Section II.A (presenting statistics demonstrating that citizen petitions are often subject to lengthy delays before the FDA responds).

231. *See infra* Section III.A (arguing that courts should meaningfully enforce § 704's inoperativeness requirement); 5 U.S.C. § 704 (stating that “agency action otherwise final is final for the purposes of this section” even if there was no application “for an appeal to superior agency authority” unless “the agency otherwise requires by rule and provides that the action meanwhile is inoperative”).

232. 539 F. Supp. 2d at 21–22.

233. *Id.* at 22.

234. *Id.* (quoting *Darby v. Cisneros*, 509 U.S. 137, 153 (1993)).

235. *Ass'n of Am. Physicians & Surgeons v. FDA*, 358 F. App'x 179, 180–81 (D.C. Cir. 2009).

236. 539 F. Supp. 2d at 22; 358 F. App'x at 180–81.

next cases, this has become a well-worn rut, allowing the Agency to guide courts to conclude exhaustion is mandatory while it elides the inoperativeness requirement.²³⁷

A district court in the Ninth Circuit also enforced the FDA's exhaustion requirement in a 2015 case called *Center for Food Safety v. Hamburg*.²³⁸ There, several public interest groups sued to challenge the FDA's approval of an animal drug called ractopamine, used to fatten livestock, claiming the drug's approval violated the National Environmental Policy Act ("NEPA") and the APA.²³⁹ Specifically, the Plaintiffs alleged the FDA had violated NEPA by failing to consider ractopamine's potential environmental impact.²⁴⁰

Although the Plaintiffs had not filed a citizen petition, they argued that the FDA could not require them to do so because the Agency would not render its approval of ractopamine inoperative in the meantime.²⁴¹ Nonetheless, the court took the same tack as the district court in *Association of American Physicians and Surgeons*,²⁴² swiftly rejecting the Plaintiff's argument and holding that *Darby* shows § 704's "'inoperative' exception applies only to *optional* administrative remedies."²⁴³ But this begs the question: how can an optional administrative remedy be mandatory? This will be analyzed in greater depth below.²⁴⁴

The court moved next to the Plaintiffs' call to waive the requirement.²⁴⁵ Under the Supreme Court case *McCarthy v. Madigan*, a court may waive administratively required exhaustion because either: (1) requiring the plaintiffs to exhaust their remedies would cause the plaintiffs undue prejudice or (2) exhaustion would be futile given that the agency is biased or has already determined the issue.²⁴⁶ The court found that the Plaintiffs did not make an effective showing through

237. See, e.g., *Cody Lab's, Inc. v. Sebelius*, 446 F. App'x 964, 969 (10th Cir. 2011) (citing *Ass'n of Am. Physicians & Surgeons*, 539 F. Supp. 2d at 21–24, as authority for dismissing the claim of a plaintiff who had failed to file a citizen petition without mentioning inoperativeness).

238. 142 F. Supp. 3d 898 (N.D. Cal. 2015), *vacated and remanded on other grounds*, 696 F. App'x 302 (9th Cir. 2017) (vacating the district court's judgment with instructions that the district court stay the action to provide the plaintiffs an opportunity to file a citizen petition with the FDA).

239. *Id.* at 901.

240. *Id.*

241. *Id.* at 906.

242. *Id.*; *Ass'n of Am. Physicians & Surgeons*, 539 F. Supp. 2d at 22.

243. *Ctr. for Food Safety*, 142 F. Supp. 3d at 906.

244. See *infra* Section III.A.

245. *Ctr. for Food Safety*, 142 F. Supp. 3d at 907.

246. *Id.* (citing *McCarthy v. Madigan*, 503 U.S. 140, 146–49 (1992)). A third reason for waiver is that the agency lacks power to grant effective relief to the plaintiffs' claim. *Id.* This Note does not analyze this factor because the FDA can grant the relief REMS petitioners seek since it decides whether to require a REMS.

either route, showcasing how rarely courts waive exhaustion under the APA.²⁴⁷ Regarding undue prejudice, the court rejected the Plaintiffs' evidence that the FDA had taken years to respond to two of the Plaintiffs' previous petitions—one of which dealt specifically with ractopamine—insisting that they were “unrelated.”²⁴⁸ Instead, the court held that the “[P]laintiffs ha[d] not shown that FDA would unduly delay its response to *this . . .* petition.”²⁴⁹ Regarding bias, the Plaintiffs provided a document in which the Agency essentially stated it would not require environmental assessments from applicants “regardless of whether extraordinary circumstances exist.”²⁵⁰ While the court “recognize[d] the troubling nature of this document,” it still found the Plaintiffs had not provided sufficient evidence to show the Agency's decision was predetermined,²⁵¹ evidently setting a high bar for proving bias. When the Plaintiffs appealed, the Court of Appeals for the Ninth Circuit briefly endorsed the district court's analysis.²⁵² And to ensure the Plaintiffs would have to file a citizen petition rather than seek judicial review via appeal, the Court of Appeals vacated the lower court's decision and stayed judicial proceedings while administrative resolution was pending.²⁵³ Thus, the Court of Appeals forced these petitioners back into the exhaustion trap.

247. *Id.* at 907–09 (“Plaintiffs are only able to cite a single APA case post-*Darby* where a court waived an exhaustion requirement.”).

248. *Id.* at 908; Plaintiff's Opposition to Intervenor-Defendant's Motion to Dismiss at 13, *Ctr. for Food Safety*, 142 F. Supp. 3d 898 (No. 4:14-cv-4932), 2015 WL 7774387 (“Plaintiffs CFS and Animal Legal Defense Fund filed a citizen petition related to ractopamine—the content of which is not at issue in this case—with FDA on December 20, 2012. Two and a half years later, FDA has yet to substantively respond.”).

249. 142 F. Supp. 3d at 908; *cf.* *Cody Lab's, Inc. v. Sebelius*, 446 F. App'x 964, 970 (10th Cir. 2011) (holding that requiring exhaustion would not unduly prejudice the plaintiff although “the FDA is sometimes dilatory in substantively responding to citizen petitions” because the plaintiff already had an NDA for the drug it hoped to sell pending before the Agency).

250. 142 F. Supp. 3d at 909.

251. *Id.*

252. *See Ctr. for Food Safety v. Hamburg*, 696 F. App'x 302, 303 (9th Cir. 2017):

The district court properly held that, under the facts of this case, the FDA should be afforded an opportunity to apply its expertise to assess [the plaintiff's] claims in the first instance “prior to possible judicial intervention.” Requiring [the plaintiff] to file a citizen petition “prevents[s] premature interference with agency processes so that the agency may function efficiently and so that it may have an opportunity to correct its own errors, to afford the parties and the courts the benefit of its experience and expertise, and to compile a record which is adequate for judicial review.”

(citations omitted).

253. *Id.* at 304.

2. Judicial Waiver in Unusual Circumstances: Mifepristone Litigation

Two courts waived exhaustion in a developing and controversial²⁵⁴ topic of litigation, but the exceptional nature of this litigation signals petitioners should not hang their hats on waiver. In *Alliance for Hippocratic Medicine v. FDA*, the U.S. District Court for the Northern District of Texas waived the Plaintiffs' exhaustion requirement in a case challenging the FDA's allegedly lax treatment of the chemical abortion drug mifepristone.²⁵⁵ On the same day, the U.S. District Court for the Eastern District of Washington also waived exhaustion for several Plaintiff States who were challenging the Agency's allegedly harsh treatment of the same drug.²⁵⁶

The long story of the Texas case's two citizen petitions merits brief description. The FDA first approved mifepristone in 2000.²⁵⁷ This approval came with hefty safety requirements that later evolved into a REMS.²⁵⁸ The Plaintiffs, groups of doctors and medical associations,

254. On the same day as the Texas ruling enjoining the FDA's approval of mail distribution of mifepristone, the Eastern District of Washington issued a countervailing order enjoining the FDA from changing the status quo. See *Washington v. FDA*, No. 1:23-CV-3026, 2023 WL 2825861, at *10 (E.D. Wash. Apr. 7, 2023) ("Defendants are preliminarily enjoined from altering the status or rights of the parties under the operative Mifepristone REMS Program until a determination on the merits."). The Supreme Court issued a stay in April 2023, and the Court of Appeals for the Fifth Circuit ruled under the stay in August 2023. Melissa Quinn, *Appeals Court Upholds FDA's 2000 Approval of Abortion Pill, but Would Allow Some Limits*, CBS NEWS, <https://www.cbsnews.com/news/abortion-pill-mifepristone-fda-approval-5th-circuit-appeals-court> (last updated Aug. 16, 2023, 9:40 PM) [<https://perma.cc/9RFC-ABCF>]. The Supreme Court recently agreed to hear an appeal of the Fifth Circuit's decision. Andrew Chung, *US Supreme Court to Decide Access to Abortion Pill in Major Case*, REUTERS, <https://www.reuters.com/legal/us-supreme-court-decide-access-abortion-pill-major-case-2023-12-13/> (last updated Dec. 14, 2023, 2:49 AM) [<https://perma.cc/LF4W-MBDY>].

255. No. 2:22-CV-223-Z, 2023 WL 2825871, at *13–15 (N.D. Tex. Apr. 7, 2023).

256. *Washington*, 2023 WL 2825861, at *5–6.

257. *All. for Hippocratic Med.*, 2023 WL 2825871, at *1. This petition predates this Note's dataset and the list available at FDAPetitions.com, so it was not included in the statistical analysis. See *supra* Subsection II.A.1 (noting the FDAPetitions.com list started in 2006). It is helpful to note, however, that the FDA regulations requiring a citizen petition and an agency response within 180 days have existed substantially unchanged since 1979. Compare Administrative Practices and Procedures Amendments, 44 Fed. Reg. 22318, 22326, 22330 (Apr. 13, 1979) (to be codified at 21 C.F.R. pt. 10) ("The Commissioner shall furnish a response to each petitioner within 180 days of receipt of the petition A request that the Commissioner take or refrain from taking any form of administrative action must first be the subject of a final administrative decision based on a petition"), with 21 C.F.R. § 10.30(e)(2) (2023) ("Except as provided in paragraphs (e)(4) and (5) of this section, the Commissioner shall furnish a response to each petitioner within 180 days of receipt of the petition."), and *id.* § 10.45(b) ("A request that the Commissioner take or refrain from taking any form of administrative action must first be the subject of a final administrative decision based on a petition").

258. *All. for Hippocratic Med.*, 2023 WL 2825871, at *2. Remember that the FDAAA created REMS in 2007. See *supra* Section I.C. These safety measures included (1) prohibiting the drug's use after seven weeks' gestation; (2) requiring three visits to a doctor's office to (a) administer the drug, (b) administer its counterpart misoprostol, and (c) finally check for complications; and (3)

filed their first petition in 2002, contesting the Agency’s original approval of the drug and alleging that mifepristone’s risks still outweighed its benefits.²⁵⁹ The FDA did not respond until 2016—almost fourteen years later.²⁶⁰ Then, within twenty-four hours of rejecting the petition, the Agency substantially loosened mifepristone’s REMS requirements.²⁶¹ The Plaintiffs again filed a citizen petition in March 2019 challenging the reduced REMS program, which the FDA likewise rejected in December 2021.²⁶²

The Plaintiffs sued, challenging several of the FDA’s actions, ranging from the initial approval in 2000 and REMS reduction in 2016 to its approval of a generic version in 2019 and of mail distribution in 2021. The FDA argued that most of the Plaintiffs’ claims were barred as unexhausted because the claims were not present in either petition, citing *Darby* and *Association of Physicians*.²⁶³ But the Texas district court rebuffed this argument, finding waiver necessary because the FDA had failed to respond to the Plaintiffs’ petitions for a combined total of “nearly 6,000 days.”²⁶⁴ On a more granular level, the court found waiver necessary because, among reasons beyond the scope of this Note, the FDA’s remedies were “inadequate” and “futile.”²⁶⁵ The Court of

requiring providers to report all adverse events caused by the drug. *All. for Hippocratic Med.*, 2023 WL 2825871, at *2.

259. *All. for Hippocratic Med.*, 2023 WL 2825871, at *2.

260. *Id.*

261. *Id.* Specifically the Agency “(1) changed the dosage . . . ; (2) reduced the number of required in-person office visits from three to one; (3) allowed non-doctors to prescribe and administer chemical abortions; . . . (4) eliminated the requirement for prescribers to report non-fatal adverse events from chemical abortion”; and (5) raised the maximum gestational age to ten weeks. *Id.*

262. *Id.* at *3. In the meantime, the FDA also announced it would approve a generic form of the drug in April 2019 and its distribution via mail in April 2021. *Id.*; see also Pam Belluck, *F.D.A. Will Allow Abortion Pills by Mail During the Pandemic*, N.Y. TIMES (Apr. 13, 2021), <https://www.nytimes.com/2021/04/13/health/covid-abortion-pills-mailed.html> [<https://perma.cc/CRQ2-3VNV>] (explaining the FDA’s April 2021 decision not to require providers to administer mifepristone in person during the pandemic). Finally, the FDA accompanied its December rejection of the plaintiffs’ 2019 petition with the announcement that it would henceforth permanently allow mail distribution. Pam Belluck, *F.D.A. Will Permanently Allow Abortion Pills by Mail*, N.Y. TIMES (Dec. 16, 2021), <https://www.nytimes.com/2021/12/16/health/abortion-pills-fda.html> [<https://perma.cc/N2TS-7N92>].

263. Defendants’ Opposition to Plaintiffs’ Motion for a Preliminary Injunction at 16–17, *All. for Hippocratic Med.*, 2023 WL 3011645 (No. 2:22-CV-223-Z).

264. *All. for Hippocratic Med.*, 2023 WL 2825871, at *1.

265. *Id.* at *14–15; see also *McCarthy v. Madigan*, 503 U.S. 140, 146–47 (1992) (acknowledging that courts may waive exhaustion requirements due to an “unreasonable or indefinite timeframe for administrative action”). First, the court found the remedies inadequate because the FDA had effectively trapped the plaintiffs for years; all the while if they had chosen to sue, their claims within the petitions would still be unexhausted. *All. for Hippocratic Med.*, 2023 WL 2825871, at *15. Second, the court considered exhaustion futile because President Biden’s repeated statements championing access to mifepristone had implied that the Agency would not likely reconsider its position. *Id.*

Appeals for the Fifth Circuit echoed this reasoning and labeled the FDA's delays an "abuse of process" because it had "plainly and repeatedly refused to follow its own regulations" by not responding within the required 180-day window.²⁶⁶

Simultaneously, the district court in Washington waived exhaustion in the countervailing suit, *Washington v. FDA*.²⁶⁷ There, multiple states sued to reduce mifepristone's REMS requirements, calling the Agency's current stance arbitrary and capricious because the drug was safe, and arguing the REMS unnecessarily hampered the reproductive freedom of those states' citizens.²⁶⁸ The FDA noted that the states had "never filed a citizen petition challenging *any* FDA action regarding *any* restriction on mifepristone in the 22 years that the drug has been marketed."²⁶⁹ Nonetheless, the court found exhaustion futile.²⁷⁰ Despite having not received a citizen petition from the Plaintiffs, the FDA had heard and rejected similar arguments before, and therefore the court posited that the Agency could not "credibly argue that its decision on the Mifepristone REMS program would change upon another citizen petition."²⁷¹ The court cited two such rejections: First, the states had commented on a public docket regarding the FDA's March 2020 guidance stating the Agency was temporarily suspending enforcement of certain REMS due to the onset of the pandemic.²⁷² The comment unsuccessfully urged the FDA to remove the REMS on mifepristone because it hindered citizens' access to the drug at a time when many lived under shelter-in-place orders.²⁷³ Second, the court highlighted that while the Plaintiffs had not brought any of these

266. *All. for Hippocratic Med. v. FDA*, No. 23-10362, 2023 WL 2913725, at *15–16 (5th Cir. Apr. 12, 2023).

267. No. 1:23-CV-3026, 2023 WL 2825861, at *5–6 (E.D. Wash. Apr. 7, 2023).

268. *See* Plaintiff States' Reply in Support of Motion for Preliminary Injunction at 2–5, *Washington*, No. 1:23-cv-03026, 2023 WL 3540092.

269. Defendants' Response in Opposition to Plaintiff States' Motion for Preliminary Injunction at 15, *Washington*, No. 1:23-cv-03026, 2023 WL 7461672.

270. *Washington*, 2023 WL 2825861, at *5–6.

271. *Id.* at *6.

272. *See* Letter from the Attorneys General of Twenty-One States to Alex M. Azar II, Sec'y, U.S. Dep't of Health & Hum. Servs. and Stephen Hahn, Comm'r, FDA (Mar. 30, 2020), https://downloads.regulations.gov/FDA-2020-D-1106-0061/attachment_1.pdf [<https://perma.cc/R2QN-M9ZE>] [hereinafter Attorneys General Letter] ("[A]s the U.S. Food & Drug Administration (FDA) considers policy changes in response to the Coronavirus Disease 2019 (COVID-19) public health emergency, we urge you to waive its Risk Evaluation and Mitigation Strategy (REMS), or use FDA enforcement discretion, to allow certified prescribers to use telehealth for Mifepristone"); FDA, POLICY FOR CERTAIN REMS REQUIREMENTS DURING THE COVID-19 PUBLIC HEALTH EMERGENCY: GUIDANCE FOR INDUSTRY AND HEALTH CARE PROFESSIONALS (2020), https://downloads.regulations.gov/FDA-2020-D-1106-0018/attachment_1.pdf [<https://perma.cc/NB2U-7SS3>] (indicating that the FDA did not intend to enforce certain REMS during the pandemic).

273. Attorneys General Letter, *supra* note 272, at 4.

arguments via petition, the American College of Obstetricians and Gynecologists (“ACOG”) had in 2022 and the FDA rejected that petition.²⁷⁴ The Plaintiff States seemingly slid past the exhaustion trap.

Although the courts waived exhaustion in these two cases, the extraordinary circumstances of each show that the existing exhaustion regime should not rely on judges alone to unlock the trap. First, the petitioners in *Alliance for Hippocratic Medicine* had filed two petitions that languished for a total of sixteen years before a court was willing to call exhaustion futile and inadequate; of the long-waiting REMS petitions, only Kaiser Permanente’s thirteen-year-old petition rises to that level of delay.²⁷⁵ Second, the Plaintiff States in *Washington* altogether dodged the exhaustion requirement because they had commented on FDA guidance and because another organization had filed a similar petition.²⁷⁶ These waivers contrast starkly from *Association of Physicians*—in which a comment on a proposed rulemaking was not a sufficient substitute for a petition.²⁷⁷ They also differ greatly from *Center for Food Safety*—in which the court discounted the petitioner’s two prior rejected petitions as well as the Agency’s “troubling” statement that it would not change its position regardless of “extraordinary circumstances.”²⁷⁸ Thus, relying on waiver is a very weak bet.

While it is important to stipulate that of the above cases, only the Plaintiffs in *Alliance for Hippocratic Medicine* had filed a citizen petition, these cases’ overall implications for a would-be petitioner are dire. If these Plaintiffs were aware of the extremely long wait times for citizen petitions—as were the Plaintiffs in *Center for Food Safety*—why would they bother filing one?²⁷⁹ The exhaustion doctrine is necessary and beneficial if properly applied, but setting an exhaustion trap like the FDA’s leaves citizens feeling disenfranchised and encourages them

274. *Washington*, 2023 WL 2825861, at *6. Thankfully, the ACOG petition falls within the 29% of petitions the FDA responds to within 180 days.

275. See *All. for Hippocratic Med. v. FDA*, No. 2:22-CV-223-Z, 2023 WL 2825871, at *15 (N.D. Tex. Apr. 7, 2023); *supra* Section II.A.

276. See *Washington*, 2023 WL 2825861, at *5–6.

277. *Ass’n of Am. Physicians & Surgeons v. FDA*, 539 F. Supp. 2d 4, 21–22 (D.D.C. 2008).

278. *Ctr. for Food Safety v. Hamburg*, 142 F. Supp. 3d 898, 909 (N.D. Cal. 2015). Additionally, the *Washington* court arguably broke with Ninth Circuit practice in waiving exhaustion after the Court of Appeals held in an unpublished opinion that “the facts of [Center for Food Safety’s] case” required that the FDA “be afforded an opportunity to apply its expertise to assess [Center for Food Safety’s] claims in the first instance ‘prior to possible judicial intervention.’” *Ctr. for Food Safety v. Hamburg*, 696 F. App’x 302, 303 (9th Cir. 2017). Of course, this unreported court of appeals opinion has only persuasive authority.

279. Plaintiff’s Opposition to Intervenor-Defendant’s Motion to Dismiss at 12, *Ctr. for Food Safety*, 142 F. Supp. 3d 898 (No. 4:14-cv-4932), 2015 WL 7774387 (asserting that the FDA delayed for years in responding to two citizen petitions submitted by the plaintiffs, one of which concerned the same drug as this case).

to reject the Agency's protocols.²⁸⁰ Leaving petitioners languishing without recourse, or any sign that their concerns are being considered by the government, harms due process, democratic accountability and participation, and even agency legitimacy. Instead, the FDA's exhaustion regime must be reworked to ensure petitioners can expect a reasonably timed answer when they play by the rules.

III. SOLUTIONS: UNLOCKING THE FDA'S EXHAUSTION TRAP

This Note proposes and evaluates three potential escape routes from the FDA's exhaustion trap. The first potential solution is to return to a proper interpretation of § 704 and *Darby*. *Darby*'s "inoperativeness" holding requires that if an agency wishes to require exhaustion based on its own administrative rule, it must provide that the agency's original decision be rendered inoperative while the administrative appeal is still pending.²⁸¹ If the agency prefers not to render its original decision inoperative, then exhaustion cannot be required based on administrative rule alone. Applying this to REMS petitions, parties wishing to get a second look at the FDA's REMS decisions should be free to file in court. As a second option, this Note advocates for a statutory amendment to the FD&C Act that will automatically waive the Agency's exhaustion requirement once it has delayed beyond a specified point.²⁸² As a last resort, courts should more readily waive exhaustion for FDA petitioners.²⁸³

A. Requiring Inoperativeness Is the Best Reading of Section 704 and Darby

Courts should apply the inoperativeness requirement of § 704 and *Darby* when analyzing exhaustion issues regarding REMS. This is the best solution because it simply follows existing law and it only requires courts to look more closely at the statute and the leading precedent (i.e., *Darby*).²⁸⁴ In fact, several prominent voices support this approach, including the U.S. Department of Justice ("DOJ").²⁸⁵

280. See *Washington*, 2023 WL 2825861, at *5–6. Perhaps the Plaintiff States in *Washington* never filed a citizen petition because they knew how hard it would be to get a timely response.

281. See *infra* Section III.A; see also *Darby v. Cisneros*, 509 U.S. 137, 154 (1993).

282. See *infra* Section III.B.

283. See *infra* Section III.C; *Ctr. for Food Safety*, 142 F. Supp. 3d at 907–08 (finding only one case under the APA since *Darby* in which a court had waived an exhaustion requirement and calling that case "unfortunately" wrong).

284. 5 U.S.C. § 704; *Darby*, 509 U.S. at 154.

285. U.S. Dep't of Just., Civ. Res. Manual § 34 (2018).

Specifically, the DOJ's online Civil Resource Manual describes *Darby* as holding the following:

[A] person aggrieved by an agency action can seek judicial review of the action *without exhausting* an available administrative appeal, *unless* the agency's regulations provide *both* (1) that the administrative appeal must be taken, *and* (2) that during the pendency of the administrative appeal the agency action shall be inoperative.²⁸⁶

Administrative law scholars like William Funk agree with the DOJ; Funk asserts that to apply § 704 “faithfully with the Supreme Court’s guidance in *Darby*,” exhaustion cannot be required “as a precondition of judicial review of [agency action] unless either a statute requires it . . . or an agency has required it by rule and provided that the [agency action] would be inoperative pending its reconsideration.”²⁸⁷

An inherent logic appears in the difference between § 704’s two stated methods of requiring exhaustion.²⁸⁸ In our culture that values giving people their “day in court,”²⁸⁹ it is “fundamental[ly] inconsisten[t]” to subject parties to a currently operational administrative action while forcing them to exhaust administrative remedies.²⁹⁰ Of course, § 704 implicitly concedes that there are times when it is necessary for a party to abide the government’s operative action while appealing that action, so it allows that a statute can mandate exhaustion while not rendering the disputed agency action inoperative.²⁹¹ But, perhaps seeing the risk of abuse by government, § 704 reserves this authority to Congress alone, the elected representatives of the people. Agency officials, on the other hand, are not elected, giving the people significantly less power over their actions. Thus, Congress restrained agencies’ power to require parties to exhaust

286. *Id.* (emphasis added).

287. Funk, *supra* note 120, at 18; *see also* Case Comment, *Partial Repeal of the Doctrine of Exhaustion of Administrative Remedies*: United States v. Consol. Mines & Smelting Co., 1972 DUKE L.J. 292, 294 (analyzing a pre-*Darby* case applying the inoperativeness requirement and remarking that § 704’s “statutory language appears to significantly alter the exhaustion doctrine”); Admin. Conf. of the U.S., *supra* note 136:

Section 704 makes clear that, unless expressly required by statute, a party seeking review of otherwise final agency action pursuant to the APA need not pursue (1) any process for agency reconsideration of its decision or (2) any intra-agency appeals (except where the agency has, by rule, required exhaustion of the appeal and provided that the agency action is inoperative during the time of the appeal).

288. 5 U.S.C. § 704.

289. Arthur R. Miller, *It Just Got a Lot Harder for Americans to Have Their Day in Court*, NATION (Sept. 24, 2015), <https://www.thenation.com/article/archive/it-just-got-a-lot-harder-for-americans-to-have-their-day-in-court/> [<https://perma.cc/SRE9-W43D>] (“Most Americans believe they have the right to take their grievances to court.”).

290. *Darby v. Cisneros*, 509 U.S. 137, 148 (1993) (quoting S. REP. NO. 79-752, at 213 (1945)).

291. 5 U.S.C. § 704; *see, e.g.*, 15 U.S.C. § 717r(a) (requiring aggrieved parties to file an administrative appeal of the Federal Energy Regulatory Commission’s orders on natural gas regulation before filing suit).

administrative remedies by rule to only those occasions when the agencies have rendered their challenged actions inoperative.²⁹² This “inconsistency” is especially strident in the REMS context, in which petitioners wait an average of two-and-a-half years in the FDA’s exhaustion trap, all while the Agency’s action remains effective.²⁹³

Further, contrary to the court’s assertion in *Center for Food Safety* that the inoperativeness requirement only applies to optional administrative remedies, an optional remedy cannot simultaneously be mandatory.²⁹⁴ First, optional and mandatory are mutually exclusive. The court essentially asserted that an agency need only make its original decision inoperative if it wishes to require plaintiffs to exhaust available optional remedies.²⁹⁵ This logic means an optional remedy becomes mandatory when the agency calls it mandatory. But if the agency calls the remedy mandatory, then it was never optional in the first place. This understanding cannot mesh with *Darby*’s description of § 704’s requirement: “[W]here the APA applies, an appeal to ‘superior agency authority’ is a prerequisite to judicial review *only* when expressly required by statute or when an agency rule requires appeal before review *and the administrative action is made inoperative pending that review.*”²⁹⁶ Second, this understanding frustrates *Darby*’s exhortation that § 704 not become “a trap for unwary litigants.”²⁹⁷ As Marcia Gelpe remarked decades ago, the current state of exhaustion case law remains “confusing and poorly reasoned,”²⁹⁸ but grounding the doctrine in a faithful reading of § 704 and *Darby* would bring clarity.

Fortunately, some courts in other agency contexts have properly interpreted § 704, allowing for agency-mandated exhaustion only when the challenged agency decision was rendered inoperative.²⁹⁹ In *Idaho Watersheds Project v. Hahn*, for example, the Court of Appeals for the Ninth Circuit held that the Bureau of Land Management’s (“BLM’s”) exhaustion regulations did not “effectively render inoperative” its

292. 5 U.S.C. § 704.

293. *See supra* Section II.A.

294. *Ctr. for Food Safety v. Hamburg*, 142 F. Supp. 3d 898, 906 (N.D. Cal. 2015).

295. *See id.*

296. *Darby v. Cisneros*, 509 U.S. 137, 154 (1993) (second emphasis added) (quoting 5 U.S.C. § 704).

297. *Id.* at 147; *see also* AM. IMMIGR. COUNCIL, FAILURE TO APPEAL TO THE AAO: DOES IT BAR ALL FEDERAL COURT REVIEW OF THE CASE? 7 (2016), https://www.americanimmigrationcouncil.org/sites/default/files/practice_advisory/failure_to_appeal_to_aao_practice_advisory.pdf [<https://perma.cc/D7VB-H8LW>] (telling immigration lawyers that “[e]ven were there a regulation mandating exhaustion of an appeal . . . exhaustion still would not be required under *Darby* unless that regulation also required a stay of the agency decision pending the administrative appeal.”).

298. Gelpe, *supra* note 121, at 1.

299. *Idaho Watersheds Project v. Hahn*, 307 F.3d 815 (9th Cir. 2002), *abrogated on unrelated grounds by Monsanto Co. v. Geertson Seed Farms*, 561 U.S. 139, 157–58 (2010).

decision to grant sixty-eight grazing permits on public land after environmental groups had challenged the permits.³⁰⁰ Therefore, the Plaintiffs were free to sue in federal court despite not having exhausted BLM's mandatory appeal procedure.³⁰¹

How would such a requirement play out in the REMS context? We must first determine to which agency determination the inoperativeness requirement would apply. Section 704 makes clear that it applies to "action."³⁰² Although it is tempting to characterize the FDA's decision not to require a REMS as inaction,³⁰³ that decision is better understood as part of the Agency's overall action of approving the drug in question. As an analogy, think of the FDA's approval of a drug without a REMS like an ice cream shop employee providing a customer with an ice cream cone without sprinkles, despite the customer having requested sprinkles. Preparing the ice cream cone is not a separate action from the inaction of not applying sprinkles.³⁰⁴ Instead, they are parts of the same whole: the employee prepared ice cream that did not come with sprinkles. Likewise, the FDA may approve a drug without a REMS as a single action. Thus, a petitioner who seeks to challenge that drug's lack of a REMS really challenges the drug's risky approval in whole. As a REMS program is meaningless without its accompanying drug, so too are sprinkles without ice cream. Therefore, as the customer is challenging the action of providing a sprinkle-less ice cream cone, so too is the petitioner challenging the REMS-less drug approval.

300. *Id.* at 825–28. Under BLM's regulations, a party challenging a grazing permit decision first has a hearing before an ALJ, and if they disagree with the ALJ's decision, they are required to file an appeal. *Id.* at 825. BLM would only render its initial permit decision inoperative if the challenger filed a petition for a stay and BLM granted the stay. *Id.* If BLM denied the stay, then the challenger was free to sue. *Id.* But even when BLM granted the stay, the regulations essentially left the grazing permits operational until the administrative appeal was resolved if either (1) grazing was *illegal* the previous year or (2) grazing was *permitted* the previous year. *Id.* at 826. The court caught this sleight of hand which left the grazing permits operational in one hundred percent of scenarios and held that exhaustion could not be required. *Id.* at 826–28.

301. *Id.*; *see also* *United States v. Consol. Mines & Smelting Co.*, 455 F.2d 432, 438–40 (9th Cir. 1971) (interpreting § 704 pre-*Darby* and rejecting BLM's argument that the plaintiff was required to exhaust an administrative appeals process in a mining permit dispute because BLM's decisions remained operative while pending appeal); *DSE, Inc. v. United States*, 169 F.3d 21, 26–27 (D.C. Cir. 1999) (refusing to require that a disappointed bidder for a government contract appeal the Small Business Administration's decision to classify its competitor as a small business when the regulations provided the initial decision "becomes effective immediately and remains in full force and effect unless and until reversed" on administrative appeal).

302. 5 U.S.C. § 704.

303. This would create a conundrum: How does one render inaction inoperative?

304. This framework does not fit as neatly with the Agency's later decision to not require a REMS when significant time has passed since the drug's initial approval. In that case, the approval appears to be a separate action followed by later inaction. Still, § 704's inoperativeness requirement would most likely apply to the initial approval because that is the nearest action to the plaintiff's grievance.

Similarly, the FDA's decision to require a REMS on a drug is likewise best understood as part of the drug's overall approval for two reasons. First, such an approach is logically consistent with the above scenario. Returning to the ice cream analogy, the Agency is making one decision here: an ice cream cone with sprinkles. Second, putting the inoperativeness requirement on the drug's entire approval would prevent a potentially risky drug from going to the market without a REMS just because a petitioner who favored the drug filed a petition. When the petitioner files the petition, the entire approval would be rendered inoperative, thus ensuring only petitioners motivated by a long-term goal of vindicating their drug—rather than a short-term win of temporarily dropping the drug's REMS—will petition the FDA. While this approach has its downsides, it is better than unmitigated risk reaching American consumers.

This Note provides two hypotheticals simulating the inoperativeness requirement in action. If the FDA has a practice of leaving its REMS determinations operational after a citizen petition is filed, then plaintiffs would be free to sue without first exhausting this process.³⁰⁵ Thus, if the Agency prefers to answer petitioners directly instead of litigating against them, the Agency would be incentivized to render its determinations inoperative while their petitions are pending.

Hypothetical 1: The FDA determines a REMS is necessary and approves a drug conditioned on compliance with the program. A party who believes the REMS program is unnecessarily burdensome, such as a concerned healthcare provider,³⁰⁶ research group, or the drug's sponsor, then files a citizen petition. This would render the drug's entire approval inoperative until the Agency provides the final decision on the citizen petition, thus freezing the distribution of the potentially risky drug to the public. Critics will quickly find a problem with this scenario: if this drug is set to fill an unmet need, then patients suffering without it would have to wait longer. This Note responds that this very real pressure from patients in need of the drug would incentivize the FDA to respond quickly to these petitions.

Hypothetical 2: A drug is already approved with relatively few precautions, and a concerned citizen believes a heightened REMS is necessary. Upon filing a citizen petition, the drug's approval would be

305. While some may contend this inoperativeness requirement would open the litigation floodgates, this Note predicts not a change in volume of REMS litigation but rather a change in its timing. This is because the FDA already opens itself up to suit every time it approves or denies a petition and allows the petitioner to exhaust its remedies. If the Agency decides it values the operativeness of its REMS determinations over requiring exhaustion, plaintiffs merely get to sue earlier. And as this Note has shown, that would mean *years* earlier.

306. Such as Dr. Behar or ACOG. See *supra* Section II.A.

rendered inoperative until the FDA provided its final decision on the petition. This would lead to the same problem of potential patients being unable to access the drug, but it could also generate a reliance cost, as some patients may have already become dependent on it. Once again, this would incentivize the FDA to act quickly. Also, the FDA would have to establish a verification system to ensure these were good-faith citizen petitions; otherwise, activists, trolls, or bad actors could potentially pause the sale of any drug by filing a petition against it.³⁰⁷

Clearly, there are several potential obstacles to this solution. First, the exhaustion-is-required-if-the-agency-says-so rule is pervasive.³⁰⁸ Convincing courts to reinterpret this rule could therefore upend precedents like the cases analyzed above. Second, the if-the-agency-says-so camp has a colorable textual argument against applying the inoperativeness exception to REMS determinations. The phrase in question in § 704 mentions “appeal to superior agency authority,” and defenders of the status quo may argue this terminology implies the necessity of some kind of administrative adjudication that has already occurred. “[A]ppeal,” they may argue, means, in our legal context, an adjudicatory decision reviewing another decision that has already taken place, and “superior” implies a decision made by an inferior agency authority. Finally, the if-the-agency-says-so camp may cite administrative and medical chaos if the inoperativeness requirement were to go into effect. If anyone can take a drug off the market by simply filing a citizen petition, our healthcare system might start and stall like a stick shift with a first-time driver behind the wheel.

These are fair arguments, but they do not necessarily win the day. First, incorrect statutory interpretations need not be maintained just because they are widely accepted.³⁰⁹ Second, a wide variety of agency actions—including REMS determinations—fall within the category of informal adjudication, thus belying any presumptions that

307. See Alexander Gaffney, *Human Rights Group to FDA: Reglan Needs New Restrictions, REMS to Prevent Use at Guantanamo Bay*, REGUL. FOCUS (Sept. 5, 2013), <https://www.raps.org/news-and-articles/news-articles/2013/9/human-rights-group-to-fda-reglan-needs-new-restri> [<https://perma.cc/3NT2-23AL>] (stating a human rights activist group had submitted a citizen petition to require the FDA to restrict the prescription of Reglan to prisoners at Guantanamo Bay).

308. PETER L. STRAUSS, TODD D. RAKOFF, GILLIAN E. METZGER, DAVID J. BARRON & ANNE JOSEPH O’CONNELL, GELLHORN & BYSE’S ADMINISTRATIVE LAW, CASES & COMMENTS 1413–18 (12th ed. 2018) (stating that exhaustion of administrative remedies is mandatory under the APA when required by statute or regulatory rule); see also COLE, *supra* note 99, at 8 (stating courts cannot require exhaustion under the APA when it is not already required by statute or an agency rule).

309. See *Milner v. Dep’t. of Navy*, 562 U.S. 562, 576 (2011) (noting that “we [the Supreme Court] have no warrant to ignore clear statutory language on the ground that other courts have done so”).

court-like hearings are required prior to an appeal.³¹⁰ Further, since “appeal” can also mean a “call to a recognized authority for . . . decision in one’s favour”³¹¹ it should apply to the first administrative remedy (i.e., the citizen petition). Finally, the chaos scenario is concerning, but the judiciary’s job is to interpret the directives the legislature has provided, while the legislature and executive, as the elected representatives of the people, weigh the policy outcomes.³¹² In fact, with proper regulatory guardrails in place, no chaos need ensue.³¹³ If Congress indeed decides the inoperativeness requirement is not desirable, it has the power to legislate a new exhaustion regime that balances the availability of drugs with administrative accountability to good-faith petitioners.³¹⁴ Of course, legislative gridlock is a concern. Given the stakes of a hypothetical medical chaos scenario, however, Congress would likely be able to quickly overcome its gridlock.³¹⁵ But one thing is certain: the status quo of simultaneously misinterpreting § 704 and trapping petitioners cannot remain.

310. BEN HARRINGTON & DANIEL J. SHEFFNER, CONG. RSCH. SERV., R46930, INFORMAL ADMINISTRATIVE ADJUDICATION: AN OVERVIEW 24–27 (2021), <https://crsreports.congress.gov/product/pdf/R/R46930> [<https://perma.cc/F8TN-65M2>].

311. *Appeal*, OXFORD ENG. DICTIONARY, https://www.oed.com/dictionary/appeal_n?tab=meaning_and_use&tl=true (last visited Apr. 17, 2024) [<https://perma.cc/6G82-YFTN>] (showing this definition—4.a.—existed in 1945).

312. *Arizona v. Navajo Nation*, 599 U.S. 555, 566 (2023) (“Under the Constitution’s separation of powers, Congress and the President may update the law to meet modern policy priorities and needs But it is not the Judiciary’s role to update the law.”).

313. One idea for making the inoperativeness requirement more palatable in the REMS context would be creating an exception for patients who are already reliant on the drug in question when its approval is rendered inoperative. The FDA could pass a rule (or Congress a statute) maintaining the drug’s availability to those patients who are already using it and wish to continue, but the drug’s approval for new patients would be rendered inoperative until the FDA resolves the petitioner’s claims. Because many of the riskiest drugs are for people with the most serious and rare conditions, *see supra* note 55 and accompanying text, this mechanism could resemble the accelerated approval process.

314. *See* 5 U.S.C. § 704 (providing that exhaustion can be required by statute); Food & Drug Administration Amendments Act of 2007, Pub. L. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.) (codifying the FDA’s power to require REMS); *see also* 21 U.S.C. § 355(q)(2) (waiving the FDA’s exhaustion requirement for 505(q) petitions if the Agency has not responded within 150 days).

315. *See, e.g.*, Coronavirus Aid, Relief, and Economic Security Act, Pub. L. No. 116-136, 134 Stat. 281 (2020) (passed by both houses of Congress and signed by the President shortly after the start of the pandemic).

B. Statutory Waiver

As a second option, Congress should pass legislation to provide a period for the FDA to respond, after which the FDA will have waived the exhaustion requirement. A potential provision could read as follows:

The Secretary shall be considered to have taken final agency action on a petition if:

- (i) during the 180-day period referred to in section 10.30(e)(2) of title 21, Code of Federal Regulations (or any successor regulation), the Secretary makes a final decision within the meaning of that section; or
- (ii) such period expires without the Secretary having made such a final decision, and an additional thirty calendar days expire without the Secretary having made such decision.

This provision creates a firm deadline after which a petitioner may seek judicial review while maintaining some of the Agency's flexibility. Since the FDA is already required to respond to all citizen petitions within 180 days,³¹⁶ the amended statute allows courts to begin hearing a petitioner's lawsuit 210 days after the original filing. This would increase accountability for the administrative decision and encourage the Agency to act quickly, knowing judicial review is possible even if it withholds a decision. On the other hand, it also considers the Agency's scarce time and resources and provides a thirty-day grace period after the expiration of the 180-day response window. There is, unfortunately, a major problem with this solution: legislative gridlock. The legislative process is cumbersome at best, but it is especially difficult during times of political polarization.³¹⁷ And although the medical chaos scenario mentioned above would likely spur lawmakers to overcome partisan divides,³¹⁸ remedying a somewhat obscure pitfall in our regulatory scheme is unlikely to build sufficient pressure to bring our legislators together until it is too late. But even while the FDA has a history of being embroiled in political controversy,³¹⁹ sharpening the processes of the administrative system while also protecting the public from risky drugs is a cause that can unite many people.³²⁰ Even more encouraging, Congress has already done this before; this provision

316. 21 C.F.R. § 10.30(e) (2023).

317. Michael Pinkerton, Eric Veiel & Blerina Uruci, *Divided Government Likely to Usher in Legislative Gridlock*, T. ROWE PRICE (Nov. 17, 2022), <https://www.troweprice.com/personal-investing/resources/insights/divided-government-likely-to-usher-legislative-gridlock.html> [<https://perma.cc/N5RQ-V9TE>].

318. See *supra* notes 314–315 and accompanying text.

319. See *supra* notes 47–53 and accompanying text.

320. See Sheri Doyle & Vanessa Baaklini, *President Signs Bipartisan Measure to Improve Addiction Treatment*, PEW CHARITABLE TRS. (Dec. 30, 2022), <https://www.pewtrusts.org/en/research-and-analysis/articles/2022/12/30/president-signs-bipartisan-measure-to-improve-addiction-treatment> [<https://perma.cc/3X5M-56GT>] (detailing the recent passage of the bipartisan Mainstreaming Addiction Treatment Act).

closely models—and is slightly more forgiving than—21 U.S.C. § 355-q(2), through which Congress created the 505(q) petitions regarding generic drug applications.³²¹

C. Judicial Waiver

If these options fail to persuade, then courts should at least be more willing to waive exhaustion, as the district courts did in *Alliance for Hippocratic Medicine*³²² and *Washington*.³²³ As discussed above, *McCarthy* provides two relevant justifications to excuse a party's failure to exhaust its remedies,³²⁴ including assertions of undue prejudice caused by delay and evidence of agency bias.³²⁵ For at least some of these REMS petitioners, the first factor appears met,³²⁶ especially if the FDA's determination will directly impact the petitioners themselves. Healthcare providers, for instance, may face an increased patient load due to the drug having too-few risk-mitigating restrictions. Similarly, state and local governments and public interest groups also have a direct interest in preserving the welfare of their constituents. Finally, even a drug sponsor who believes it has been assigned too heavy of a REMS program may suffer a direct loss of revenue by implementing the REMS while awaiting the Agency's final decision on a petition. Nonetheless, judicial waiver remains the exception. After all, the Plaintiffs' two petitions in *Alliance for Hippocratic Medicine* languished a total of sixteen years.³²⁷ While the petitions covered by this Note have waited far too long, most have not yet met the extreme "delay, dawdle, and dithering" the court noted in that case.³²⁸ And courts taking the same approach as in *Center for Food Safety* may hold that evidence showing how slowly the FDA responds to other petitions does not prove

321. The text of that provision reads as follows:

The Secretary shall be considered to have taken final agency action on a petition if— (i) during the 150-day period referred to in paragraph (1)(F), the Secretary makes a final decision within the meaning of section 10.45(d) of title 21, Code of Federal Regulations (or any successor regulation); or (ii) such period expires without the Secretary having made such a final decision.

21 U.S.C. § 355(q)(2) (emphasis added).

322. See *All. for Hippocratic Med. v. FDA*, No. 2:22-CV-2230Z, 2023 WL 2825871, at *15 (N.D. Tex. Apr. 7, 2023).

323. See *Washington v. FDA*, No. 1:23-CV-3026, 2023 WL 2825861, at *5–6 (E.D. Wash. Apr. 7, 2023).

324. See *supra* Section II.B; *McCarthy v. Madigan*, 503 U.S. 140, 146–49 (1992).

325. *McCarthy*, 503 U.S. at 146–49.

326. See *supra* Subsection II.A.2.

327. *All. for Hippocratic Med.*, 2023 WL 2825871, at *15.

328. *Id.*

the Agency will delay responding to any individual plaintiff's petition.³²⁹ Prudence cautions against holding out hope that a court will take the *Washington* approach, given other courts' widespread rejection of waiver arguments.³³⁰

CONCLUSION

This Note has analyzed the FDA's citizen petition requirement and the current state of the exhaustion doctrine, finding that their convergence on REMS petitions creates an exhaustion trap. Such traps not only undermine the legitimacy of the Agency's remedies regime, but they leave petitioners' claims unanswered while the societal cost of risky drugs grows unmitigated. Not only is the FDA's exhaustion trap unjust for advocacy groups like the Post-Finasteride Syndrome Foundation but it is also unnecessary, as the escape hatch already exists in the APA. Courts should therefore return to the roots of this doctrine as applied in *Darby*; otherwise, legislative action is necessary. Ensuring the FDA is required to consider and respond to REMS petitions brings more voices into the conversation and increases our chances of preventing a future Vioxx.³³¹ If the American people must

329. *See* *Ctr. for Food Safety v. Hamburg*, 142 F. Supp. 3d 898, 908–09 (N.D. Cal. 2015).

330. A similar option to judicial waiver is filing a suit under § 706(1), which provides that a court can compel agency action that is “unlawfully withheld or unreasonably delayed.” While this is a tempting option that may help some petitioners escape the FDA's exhaustion trap, it is not a worthy substitute to properly interpreting § 704 for several reasons. First, such a suit guarantees greater delay for an already languishing plaintiff because the court would need to decide on fully briefed arguments by the plaintiff and the FDA. Second, a successful suit would only compel the FDA to rule on the plaintiff's citizen petition within a timeframe designated by the court, and this could mean even more years of waiting due to the courts' deference to the Agency on complex scientific issues. *See* *Ctr. for Sci. in the Pub. Int. v. FDA*, 74 F. Supp. 3d 295, 301 (D.D.C. 2014) (“Courts, moreover, routinely defer to the judgment of agencies when assessing timelines that involve complex scientific and technical questions.”). Third, the deck is still stacked against plaintiffs. Courts will only find a delay unreasonable if it is “so egregious as to warrant mandamus.” *In re Cal. Power Exch. Corp.*, 245 F.3d 1110, 1124–25 (9th Cir. 2001) (surveying other cases that found delays of eight years and ten years each unreasonable but delays of five years and two years not sufficiently egregious as to warrant mandamus).

331. *See supra* notes 59–61 and accompanying text.

exhaust their administrative remedies before their day in court, they deserve remedies that are actually exhaustible.

*Michael Krupka**

* J.D. Candidate, 2024, Vanderbilt Law School; B.A. Harding University, 2020. I am deeply thankful to Professors Kevin M. Stack and Laura Dolbow, whose insightful edits were invaluable. My heartfelt gratitude also goes to the entire *Vanderbilt Law Review* editorial staff for their adept assistance throughout this process, especially Christian Dunn, Isaak Elkind, Isabel Florentino, Ari Goldfine, Taylor Lawing, and Stefan Pruessmann. I owe a special thanks to my lovely wife, Meredith Rose Krupka, for her enduring patience and support, and my parents and stepmother, Laura, Mike, and Stephanie Krupka, for their love and encouragement. Finally, I am indebted to my grandparents, Elizabeth Jane and Billy Frank Hefley and Joan May and Alex Daniel Krupka, for instilling in us grandkids the values of education and service. All errors are my own.

APPENDIX

Thank you to Parry Ashford, Inc., for providing access to its citizen petition data. Below is a table summarizing the REMS citizen petitions.

TABLE 1A: SUMMARY STATISTICS

| Summary Statistics | |
|--------------------------------------------------------------------------------------------------------------|-------|
| Average | 937.6 |
| Median | 575.5 |
| Minimum | 37 |
| Maximum | 5,049 |
| Responses Before 180 Days (not counting tentative decisions, not counting withdrawn or pending pre-180 days) | 14 |
| Responses After 180 Days (not counting tentative decisions) | 31 |

Next is the full table. Key: Filers marked “PI” are public interest groups, “Ph” pharmaceutical, “L” law firms, “MP” medical professional, “HCP” healthcare provider, “U” university and research institution, and “G” government entity. All petitions after Columbia University’s regard opioids.

The following table presents the FDA’s response time for every REMS petition in FDAPetitions.com’s database. The first time a drug’s brand name appears, its generic name is listed in parentheses, and if the same petitioner filed multiple petitions on the same topic, then they are numbered in parentheses. Excluded petitions are italicized; these petitions were excluded because they had not yet had a reasonable chance to be responded to by the FDA, either due to petitioner withdrawal or being filed too close to the end of the sample period. Because tentative responses do not exhaust a petitioner’s remedy, only final responses are considered. The tentative response dates are still included in the table but are italicized, and the entries for the final responses to those petitions are denoted below the tentative response dates in ordinary roman text .

TABLE 2A: REMS CITIZEN PETITION TABLE

| Topic | Filer | Petition Date | FDA Action | FDA Action Date | Wait Time (Days) |
|-------------------------------------|------------------------------------------------|---------------|--------------------------------|-----------------|------------------|
| 1. Ferriprox (deferiprone) | Cooley's Anemia Found. (PI) | 1/24/20 | Denied | 4/28/21 | 460 |
| 2. Samsca (tolvaptan) | Otsuka (Ph) | 8/22/19 | Pending | 12/31/23 | 1592 |
| 3. Prolia (denosumab) | Public Citizen (PI) | 4/16/19 | Denied | 4/23/20 | 373 |
| 4. Mifeprex (mifepristone) | Am. Assoc. Pro-life OBGYNs (PI) | 3/29/19 | Denied | 12/16/21 | 993 |
| 5. Mifeprex | Am. Coll. of OBGYNs (PI) | 10/6/22 | Denied | 1/4/23 | 90 |
| 6. Zelnorm (tegaserod) | Hyman Phelps (doesn't say on whose behalf) (L) | 11/21/18 | Denied | 3/29/19 | 128 |
| 7. Propecia & Proscar (finasteride) | Post-finasteride Syndrome Found. (PI) | 9/18/17 | Pending | 12/31/23 | 2295 |
| 8. Kuvan (sapropterin) | K&L Gates (On behalf of generic mfr.) (Ph/L) | 7/10/13 | Denied | 11/17/14 | 495 |
| 9. Lotronex (alosetron) | Prometheus (Ph) | 5/10/13 | Denied In Substance | 10/7/13 | 150 |
| 10. Qnexa (phentermine) | Joseph Dedvukaj (PI) | 7/9/12 | <i>Withdrawn By Petitioner</i> | 7/12/12 | 4 |
| 11. Qnexa | Joseph Dedvukaj (PI) | 7/17/12 | Denied | 12/14/12 | 150 |

| Topic | Filer | Petition Date | FDA Action | FDA Action Date | Wait Time (Days) |
|---------------------------------------|--------------------------------------------------------------------------|---------------|---------------------|-----------------|------------------|
| 12. Xyrem (sodium oxybate) (1) | Jazz Pharm. (Ph) | 5/18/12 | Denied | 11/12/12 | 178 |
| 13. Xyrem (2) | Jazz Pharm. (Ph) | 7/10/12 | Denied | 12/13/12 | 156 |
| 14. Xyrem (3) | Jazz Pharm. (Ph) | 9/2/16 | Granted | 1/17/17 | 137 |
| 15. Clozapine | Dr. David Behar (MD) | 4/9/12 | FDA Withdrew | 4/7/16 | 1459 |
| 16. Clozapine | Genesee Health Sys. (HCP) | 9/3/14 | Withdrawn | 10/1/15 | 393 |
| 17. Suboxone (buprenorphine/naloxone) | Reckitt Benckiser (Ph) | 9/25/12 | Denied | 2/22/13 | 150 |
| 18. Suboxone (1) | Hyman Phelps (likely on behalf of Reckitt Benckiser) (Ph/L) | 12/2/11 | Denied | 9/18/13 | 656 |
| 19. Suboxone (2) | Hyman Phelps (likely on behalf of Reckitt Benckiser) (Ph/L) | 8/12/13 | Denied In Substance | 9/18/13 | 37 |
| 20. REMS | Kaiser Permanente (HCP) | 12/22/09 | Pending | 12/31/23 | 5122 |
| 21. REMS | Roxane (Ph) | 2/3/10 | Withdrawn | 3/18/14 | 1504 |
| 22. REMS | <i>Holland & Knight (on behalf of a mfr. of rsch. materials) (L)</i> | 11/1/11 | <i>Withdrawn</i> | 1/12/12 | 72 |

| Topic | Filer | Petition Date | FDA Action | FDA Action Date | Wait Time (Days) |
|------------------------------|--------------------------------------|---------------|--------------------|-----------------|------------------|
| 23. REMS | Dr. Reddy's Lab (Ph) | 6/10/09 | Granted/ Denied | 8/7/13 | 1519 |
| 24. ACE Inhibitors and ARBs | Dr. Anil Mandal (MD) | 8/22/06 | Denied | 8/3/10 | 1442 |
| 25. ACE Inhibitors and ARBs | Pub. Citizen (PI) | 10/4/12 | Denied | 4/3/15 | 911 |
| 26. Duragesic (fentanyl) (1) | Mylan (Ph) | 3/16/06 | <i>Tentative</i> | 9/11/06 | 179 |
| | | 3/16/06 | Granted/ Denied | 10/29/10 | 1688 |
| 27. Duragesic (2) | Mylan (Ph) | 7/21/06 | Granted/ Denied | 2/19/13 | 2405 |
| 28. Duragesic (3) | Mylan (Ph) | 8/26/09 | Denied | 2/22/10 | 180 |
| 29. Levaquin (levofloxacin) | Illinois AG (G) | 5/18/05 | <i>Tentative</i> | 11/16/05 | 182 |
| | | 5/18/05 | Granted/ Denied | 7/24/08 | 1163 |
| 30. Levaquin | Pub. Citizen (PI) | 8/29/06 | Granted/ Denied | 7/24/08 | 695 |
| 31. Levaquin (1) | S. Network of Adverse Reactions (PI) | 6/18/14 | Denied | 5/12/16 | 694 |
| 32. Levaquin (2) | S. Network of Adverse Reactions (PI) | 9/8/14 | Granted/ Denied | 7/10/18 | 1401 |
| 33. Levaquin | Janssen (Ph) | 6/8/16 | Granted | 12/2/16 | 177 |
| 34. Levaquin (3) | S. Network of Adverse Reactions (PI) | 6/21/19 | Denied | 8/28/20 | 434 |

| Topic | Filer | Petition Date | FDA Action | FDA Action Date | Wait Time (Days) |
|---------------------------------------------------|--------------------------------------------------|---------------|--------------------|-----------------|------------------|
| 35. <i>Levaquin & Other Fluoroquinolone-s</i> | <i>Dr. David Melvin, et al. (MD)</i> | 9/28/23 | <i>Pending</i> | 12/31/23 | 94 |
| 36. Opioids | Columbia Univ. (U) | 5/18/09 | <i>Tentative</i> | 11/18/09 | 184 |
| | | 5/18/09 | Denied | 6/17/13 | 1491 |
| 37. Opioids | Tufts Health Care Inst. (U) | 5/18/09 | <i>Tentative</i> | 11/25/09 | 191 |
| | | 5/18/09 | Granted/ Denied | 4/1/15 | 2144 |
| 38. Opioids | Phys. For Responsible Opioid Prescribing (PI) | 7/25/12 | Granted/ Denied | 9/10/13 | 412 |
| 39. Opioids | Ctr. for Lawful Access and Abuse Deterrence (PI) | 6/11/13 | Granted/ Denied | 10/25/13 | 136 |
| 40. Opioids | Nat'l Advocs. for Pregnant Women (PI) | 10/7/13 | Denied | 4/16/14 | 191 |
| 41. Opioids | Purdue Pharm. (Ph) | 2/11/14 | Granted/ Denied | 3/22/16 | 770 |
| 42. Opioids (1) | Pharm. Mfg. Rsch. Servs. (Ph) | 2/19/16 | Denied | 12/20/18 | 1035 |
| 43. Opioids & Benzodiazepines | City of Baltimore (G) | 2/22/16 | Granted | 8/31/16 | 191 |
| 44. Oxycontin & other Opioids | Pharm. Mfg. Rsch. Servs. (Ph) | 3/6/17 | Pending | 12/31/23 | 2491 |

| Topic | Filer | Petition Date | FDA Action | FDA Action Date | Wait Time (Days) |
|-----------------------------|----------------------------------------------------|---------------|-------------------------|-----------------|------------------|
| 45. Roxybond (oxycodone) | Pharm. Mfg. Rsch. Servs. (Ph) | 5/11/17 | Denied | 10/31/17 | 173 |
| 46. Opioids (2) | Ctr. for Lawful Access and Abuse Deterrence (PI) | 7/3/17 | Pending | 12/31/23 | 2372 |
| 47. Opioids (2) | Pharm. Mfg. Rsch. Servs. (PI) | 7/20/17 | Denied | 12/15/17 | 148 |
| 48. Schedule-II Opioids | Dr. Dennis Ryll (MD) | 8/1/17 | Withdrawn By Petitioner | 11/27/18 | 483 |
| 49. Ultra-High-Dose Opioids | Physicians For Responsible Opioid Prescribing (PI) | 9/1/17 | Pending | 12/31/23 | 2212 |
| 50. Opioids (3) | Pharm. Mfg. Rsch. Servs. (Ph) | 11/13/18 | Denied | 4/29/19 | 167 |
| 51. Opioids | Pub. Citizen (PI) | 4/10/19 | Denied | 9/6/19 | 149 |
| 52. Opioids | Dr. Francis O'Donnell (MD) | 6/16/20 | Pending | 12/31/23 | 1293 |

The following list briefly describes each of the above petitions. The indented bullet points provide notes on the petitions, such as whether the petition was broadly in favor of tightening or loosening drug restrictions (e.g., tightening could mean asking the FDA to add a REMS program or deny a new drug application, while loosening could mean asking the FDA to remove a REMS program or approve a drug), whether the petition was pre-REMS (i.e., pre-2007), and whether the petition was filed under § 505(q) of the FD&C Act.

1. **Ferriprox** (deferiprone): Requesting that ANDAs follow same REMS as brand to protect petitioner's patients.
 - Tighten; 505(q)
2. **Samsca** (tolvaptan): Asking the FDA to remove SAMSCA 60 mg as a reference list drug for ANDAs that would create generics for JYNARQUE (a similar drug to SAMSCA that is used to treat different ailments and has a strict REMS program).
 - Tighten; 505(q)
3. **Prolia** (denosumab): Asserting that new studies show Prolia increases risks of vertebral fractures when a patient ceases using it. Asking FDA to require a REMS to alert providers and patients to the risk.
 - Tighten
4. **Mifeprex** (mifepristone): Asking FDA to increase the REMS on Mifeprex back to its original state.
 - Tighten
5. **Mifeprex** (mifepristone): Asking FDA to add “miscarriage management” to the drug's uses and remove some of the REMS for this purpose.
 - Loosen
6. **Zelnorm** (tegaserod): Explaining that Zelnorm was once approved but displayed serious adverse events like suicidal ideation and cardiovascular disease and was thus removed from market. Asking FDA to deny the SNDA to put Zelnorm back on the market unless new data shows sufficient safety and sponsor agrees to add REMS.
 - Tighten
7. **Propecia** and **Proscar** (finasteride): Asking FDA to add serious REMS to these products because studies show evidence these drugs increase suicidality and sexual dysfunction in men.
 - Tighten
8. **Kuvan** (sapropterin): Asking FDA to let sponsor use a reference drug from Israel to make an ANDA; Original drug had a REMS on it.
 - Loosen
9. **Lotronex** (alosectron): Asking for guidance on how to implement a shared REMS program.
 - Neutral
10. **Qnexa** (phentermine): *Asking FDA to deny an NDA because the drug is too dangerous.*
 - Tighten

11. **Qnexa** (phentermine): Asking FDA to deny an NDA because the drug is too dangerous.
 - Tighten
12. **Xyrem** (sodium oxybate) (1): Asking FDA to not approve any ANDA referencing Xyrem until the Agency has confirmed which types of bioequivalence studies are required to establish bioequivalence to Xyrem.
 - Tighten; 505(q)
13. **Xyrem** (sodium oxybate) (2): Asking FDA to repeal its approval of Roxane's ANDA referencing Xyrem for lacking a REMS and also to deny any other ANDAs referencing Xyrem that also lack a REMS, and to delay approving any new such ANDAs until Jazz has had opportunity to initiate patent infringement claim.
 - Tighten; 505(q)
14. **Xyrem** (sodium oxybate) (3): Asking FDA to deny any ANDA if its label does not include REMS drug info regarding Xyrem's interaction with divalproex.
 - Tighten; 505(q)
15. **Clozapine**: Asking FDA to create an exception to the minimum white blood cell count for certain patients with benignly low white blood cell counts.
 - Loosen
16. **Clozapine**: Asking FDA relax the acceptable white blood cell count on which patients can start using this drug.
 - Loosen
17. **Suboxone** (buprenorphine/naloxone): Asking FDA to deny any ANDA for this drug that doesn't have the same REMS program.
 - Tighten; 505(q)
18. **Suboxone** (buprenorphine/naloxone): Asking FDA to deny any NDA for a sublingual film form of Suboxone unless it properly references the original Suboxone NDA and meets the same purity standards.
 - Tighten
19. **Suboxone** (buprenorphine/naloxone): Asking FDA to deny any NDA or ANDA for this type of drug unless it references Suboxone and meets the same purity standards that Suboxone has met.
 - Tighten; 505(q)
20. **REMS**: Asking FDA to follow the FDAAA by allowing physician input on REMS development process and conducting annual reviews of REMS to see if they are still effective.
 - Neutral

21. **REMS:** Asking FDA to ensure REMS system is not abused to harm competition by hindering generic drug companies.
 - Loosen
22. **REMS:** *Asking FDA to clarify whether REMS apply to research materials, and asking FDA to not take any enforcement action regarding these materials against their manufacturers.*
 - *Neutral; Excluded because withdrawn under 180 days.*
23. **REMS:** Asking FDA to (1) clarify procedure for generics to conduct bioequivalence testing and (2) ensure brand companies cannot use REMS to prevent generics from obtaining samples for testing.
 - Loosen
24. **ACE Inhibitors and ARBs:** Asking FDA to remove these products from the market or restrict their use to exclude patients with diabetes.
 - Tighten; Pre-REMS
25. **ACE Inhibitors and ARBs:** Asking FDA to require a REMS on these products.
 - Tighten
26. **Duragesic (fentanyl):** Asking FDA to require all fentanyl patch producers to do more tests with adhesive overlays to ensure overlays don't harm patch effectiveness.
 - Tighten; Pre-REMS; received tentative response before final response
27. **Duragesic (fentanyl):** Asking FDA to create a unified risk management program for all transdermal fentanyl products.
 - Tighten; Pre-REMS
28. **Duragesic (fentanyl):** Asking FDA to stay approval of an NDA by another company for a new high-dose transdermal fentanyl drug.
 - Tighten; 505(q)
29. **Levaquin (levofloxacin):** Asking FDA to require black-box warning labels alerting physicians and patients to risk of tendinopathy and tendon rupture.
 - Tighten; Pre-REMS; Received tentative response before final response
30. **Levaquin (levofloxacin)** Asking FDA to add black-box warnings regarding risk of tendonitis and tendon rupture.
 - Tighten; Pre-REMS; Same as above
31. **Levaquin (levofloxacin):** Asking FDA to add REMS and a black-box warning label regarding mitochondrial toxicity.
 - Tighten; Pre-REMS

32. **Levaquin** (levofloxacin): Asking for black-box warning labels regarding psychiatric side effects.
 - Tighten
33. **Levaquin** (levofloxacin): Asking FDA to add another drug to the approved reference list for generics because the first drug on the list was removed from market.
 - Loosen
34. **Levaquin** (levofloxacin): Asking FDA to require REMS, ETASU, and warning labels regarding the risks of levofloxacin.
 - Tighten
35. **Levaquin and Other Fluoroquinolones**: *Asking FDA to strengthen language on black-box warning labels.*
 - *Tighten; Excluded because still pending and under 180 days.*
36. **Opioids**: Asking FDA to require a REMS for all opioid products.
 - Tighten; Received tentative response before final response
37. **Opioids**: Asking FDA to take extra safety measures on all opioid products and prioritize abuse-deterrent formulations of the drugs.
 - Tighten; Received tentative response before final response
38. **Opioids**: Asking FDA to create limits on prescriptions for all opioids to non-cancer patients.
 - Tighten
39. **Opioids**: Asking FDA to deny all NDAs and ANDAs for opioid products unless they are shown to help reduce abuse.
 - Tighten
40. **Opioids**: Asking FDA not to implement additions to opioid warning labels regarding neonatal opioid withdrawal syndrome.
 - Loosen
41. **Opioids**: Asking FDA to apply the same safety label changes that were imposed on long-acting opioids to immediate-release forms of opioids.
 - Tighten
42. **Opioids**: Asking FDA to require more measures and testing to avoid opioid abuse.
 - Tighten
43. **Opioids and Benzodiazepines**: Asking FDA to add black-box warning alerting patients to increased risk of overdose when these drug types are combined.
 - Tighten

44. **Oxycontin** and other Opioids: Asking FDA to repeal all opioid approvals except for acute, short-term care.
 - Tighten
45. **Roxybond** (oxycodone): Asking FDA not to approve an oxycodone NDA until FDA has resolved petitioner's previous two petitions because the NDA's evidence of safety is insufficient.
 - Tighten
46. **Opioids**: Asking FDA to transition labeling requirements for all opioids to an abuse-deterrent formulation.
 - Tighten
47. **Opioids**: Asking FDA to not approve new opioids for chronic or long-term use.
 - Tighten; 505(q)
48. **Schedule-II Opioids**: Asking FDA to add warnings advising physicians to only prescribe C-II opioids if no C-III option is available and alerting patients to heightened addiction risk of C-II opioids.
 - Tighten
49. **Ultra-High-Dose Opioids**: Asking FDA to remove ultra-high-dose opioids from the market.
 - Tighten
50. **Opioids**: Asking FDA to not approve any opioid with an indication for chronic pain management.
 - Tighten; 505(q)
51. **Opioids**: Asking FDA to stop approving any new opioid products.
 - Tighten
52. **Opioids**: Asking FDA to add black-box warnings on all opioid analgesics and to create protocol for advising patients to titrate down their opioid dosage.
 - Tighten