THE REASON FOR THE SNEEZING: ORAL PHENYLEPHRINE AND THE FDA'S FOCUS ON SAFETY AT THE EXPENSE OF EFFECTIVENESS

Note

THE REASON FOR THE SNEEZING: ORAL PHENYLEPHRINE AND THE FDA'S FOCUS ON SAFETY AT THE EXPENSE OF EFFECTIVENESS

Note

INTRODUCTION

On September 12, 2023, an FDA advisory committee declared the popular over-the-counter (OTC) drug phenylephrine ineffective as a nasal decongestant when taken orally[1] (such as by pill or capsule).[2] To most, this announcement came as a shock. Phenylephrine has been on shelves for more than eighty years, and the FDA vouched for its effectiveness by approving it as one of only two types of oral-delivery nasal decongestants that can be used in OTC drugs.[3] These findings present two major questions for consumers: 1) How could the FDA allow an ineffective drug to be sold over the counter for so long and 2) What should the FDA do to ensure that this is not a widespread issue?

This Note seeks to address those two questions. To answer the first, it is essential to understand the history of how the FDA has regulated OTC drugs and, more specifically, how the FDA struggled through the herculean task of assessing the effectiveness of every OTC drug on the market starting in 1972. While the FDA largely succeeded in ensuring that OTC drugs were safe and effective, the magnitude of this undertaking made perfection impossible. This Note will discuss the many flaws of the OTC Drug Review process and show how the FDA's focus on safety at the expense of effectiveness led, unsurprisingly, to the approval of safe but ineffective drugs.

The answer to the second question is far less clear. It is yet to be seen how the FDA will address the immediate issue of oral phenylephrine, much less the more widespread problem of ineffective OTC drugs. Regardless of how the FDA sorts out the phenylephrine problem, it needs a more proactive mechanism to identify and remove ineffective drugs. Identification is currently the most significant hurdle in this process because there has long been no incentive to perform the studies necessary to prove these drugs' ineffectiveness. This Note will propose a regulatory framework to remedy this problem by incentivizing pharmaceutical companies to provide the findings needed for the FDA to take action against ineffective OTC drugs while placing minimal burden on the FDA's time and budget.

---

1. Phenylephrine products are still effective when taken nasally, such as through nasal sprays.

2. *See* U.S. FOOD & DRUG ADMIN., NDAC BRIEFING DOCUMENT: ORAL PHENYLEPHRINE IN THE CCABA MONOGRAPH (2023) [hereinafter PHENYLEPHRINE BRIEFING].

3. 21 C.F.R. § 341.20 (2024).

I. A BRIEF(ISH) HISTORY OF THE FDA'S OVER-THE-COUNTER DRUG REVIEW PROCESS

To understand how the FDA could allow an entirely ineffective drug to be sold over the counter for decades, it is helpful to first look at the history of OTC drug regulation. This brief history will show how daunting a task it was for the FDA to ensure the effectiveness of OTC drugs and why, largely due to forces outside the FDA's control, this system ultimately failed. With this context, it will be much easier to understand the modern problems that this massive, ambitious undertaking produced—namely, safe but ineffective OTC drugs.

A. The Food, Drug, and Cosmetics Act of 1938 and Durham-Humphrey Amendment of 1951

While the FDA was initially created to enforce the Pure Food and Drug Act of 1906,[4] it was not until the passage of the Food, Drug, and Cosmetics Act of 1938 (FDCA) that the agency gained serious power to regulate the sale of drugs.[5] The FDCA established the foundation upon which modern drug review is built and remains the principal statute that authorizes the FDA to regulate drugs.[6] Perhaps the most important dictate of the FDCA was that a drug had to be "generally recognized . . . as safe" before it could be sold to consumers.[7] However, it would be another few decades before the FDA applied a similar premarket approval standard to a drug's effectiveness.[8]

How a drug became generally recognized as safe varied based on whether it was considered a "new drug." A "new drug" was "[a]ny drug . . . not generally recognized, among experts . . . as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof."[9] Before a new drug could enter the market, its sponsor would have to provide the FDA evidence that it was safe for its intended use in the form of a new drug application (NDA).[10] The FDCA also contained a grandfather clause that excluded drugs already generally recognized as safe at the time of the FDCA's passage from the definition of "new drugs."[11] This exception meant that a large number of

4. *FDA History*, FDA, https://www.fda.gov/about-fda/fda-history [https://perma.cc/LQ6W-6KX6] (June 29, 2018).

5. JENNIFER A. STAMAN, CONG. RSCH. SERV., R43609, ENFORCEMENT OF THE FOOD, DRUG, AND COSMETIC ACT: SELECT LEGAL ISSUES 4–5 (2018).

6. 21 U.S.C. §§ 371, 393.

7. Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-757, § 201(p)(1), 52 Stat. 1040, 1041 (current version at 21 U.S.C. §§ 301–99).

8. Elizabeth Guo et al., *An Unofficial Legislative History of Over-the-Counter Monograph Reform*, 76 FOOD & DRUG L.J. 36, 38 (2021).

9. Federal Food, Drug, and Cosmetic Act, § 201(p)(1), 52 Stat. at 1041.

10. *Id.* § 505(a), 52 Stat. at 1052.

11. *Id.* § 201(p)(2), 52 Stat. at 1042.

drugs—many of which were nonprescription—were allowed to stay on the market without receiving the enhanced safety testing required of new drugs under the FDCA.

The FDCA was also the first statute to distinguish between prescription and nonprescription drugs, albeit indirectly.[12] The FDCA did not explain what these two terms actually meant, but it did exempt prescription drugs from certain labeling requirements so long as other disclosures were provided.[13] This distinction was clarified somewhat by the 1951 Durham-Humphrey Amendment which defined prescription drugs as those which "because of [their] toxicity or other potentiality for harmful effect . . . [are] not safe for use except under . . . supervision."[14] However, beyond this definitional distinction and some labeling requirements, there was no real difference in how the FDA regulated prescription and nonprescription drugs.

B. The Kefauver-Harris Amendments and the Beginning of the OTC Drug Review

It was not until after the 1962 enactment of the Kefauver-Harris Amendments to the FDCA that the FDA developed a distinct regime to regulate the sale and manufacture of OTC drugs. The most significant change implemented by these Amendments was the requirement that both prescription and OTC drugs be generally recognized as safe *and* effective (GRASE) before the FDA would approve them for sale.[15] Like the FDCA itself, these Amendments also included a grandfather clause that allowed OTC drugs sold at the time of enactment to stay on the market without further testing.[16]

After the enactment of the Kefauver-Harris Amendments, the FDA commenced the Drug Efficacy Study Implementation (DESI) program to assess the effectiveness of drugs put to market under an NDA between 1938 and 1962, meaning that drugs grandfathered in by the FDCA were exempt from testing.[17] Under the DESI program, the FDA would assess the effectiveness of these drugs on a case-by-case basis by requiring the holder of a drug's NDA to submit a report containing relevant literature and studies evaluating that drug's effectiveness.[18] The FDA would then review this report to determine whether there was sufficient evidence of effectiveness to allow that drug to remain on the market.[19] Despite numerous legal challenges, the DESI program was relatively successful in assessing the effectiveness of prescription drugs

12. *Id.* § 503(b), 52 Stat. at 1052.
13. *Id.*
14. Act of Oct. 26, 1951, Pub. L. No. 215-578, § 503(b), 65 Stat. 648, 648–49.
15. Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 781, 781.
16. *Id.* § 107(c)(4), 76 Stat. at 789.
17. Reports of Information for Drug Effectiveness, 31 Fed. Reg. 9426, 9426 (July 9, 1966).
18. *Id.*
19. *Id.*

developed before 1962.[20] However, this approach quickly proved unworkable when applied to OTC drugs. The case-by-case approach of the DESI program was simply too slow to ensure the timely and efficient review of the hundreds of thousands of OTC drugs on the market.[21] Before the FDA moved on from the DESI program in 1972, four hundred and twenty OTC drugs were subject to DESI evaluations.[22] Of that relatively small (but representative) handful, only about one in every four was found sufficiently effective.[23]

This shockingly low efficacy rate among OTC drugs drove the FDA to action, which came in the form of the OTC Drug Review process.[24] The FDA implemented this system in 1972 after it finalized its rule detailing the process of OTC review.[25] This process aimed to sort through the droves of OTC drugs and drug formulations on the market and determine which were considered GRASE.[26] The FDA would then compile and publish this data as an OTC monograph.[27] An OTC monograph is a form that describes what active ingredients are GRASE and the dosage, dosage form, route of administration, labeling, warnings, and use instructions required to sell a drug containing those ingredients.[28] So long as a company markets a drug in accordance with its applicable monograph and the general requirements for the sale of OTC drugs, it is recognized as safe, effective, and not misbranded.[29]

Under this system, the FDA divided the OTC-drug landscape into specific therapeutic classes (e.g., antacids, nighttime sleep aids, topical antifungals, etc.).[30] The FDA then assembled advisory panels composed of pharmaceutical experts and charged each panel to research the active ingredients within its assigned therapeutic class.[31] Each panel had access to a bibliography prepared by the FDA containing the available data on that panel's category of drugs.[32] The panel was permitted to gather further information from sources outside this bibliography and from "[a]ny interested person" who requested to speak to

---

20. *See, e.g.*, Weinberger v. Hynson, Wescott & Dunning, Inc., 412 U.S. 609 (1973); Weinberger v. Bentex Pharm. Inc., 412 U.S. 645 (1973); CIBA Corp. v. Weinberger, 412 U.S. 640 (1973).

21. Proposal Establishing Rule Making Procedures for Classification, 37 Fed. Reg. 85, 85 (Jan. 5, 1972) (to be codified at 21 C.F.R. pt. 130).

22. *Id.*

23. *Id.*

24. *Id.*

25. *See* Procedures for Classification of Over-the-Counter Drugs, 37 Fed. Reg. 9464, 9464–75 (May 11, 1972) (to be codified at 21 C.F.R. pt. 130).

26. *Id.*

27. *Id.*

28. 21 C.F.R. § 330.10(a)(5) (2024).

29. *Id.* § 330.1 ("An over-the-counter (OTC) drug listed in this subchapter is generally recognized as safe and effective and is not misbranded if it meets each of the conditions contained in this part and each of the conditions contained in any applicable monograph.").

30. Procedures for Classification of Over-the-Counter Drugs, 37 Fed. Reg. at 9475.

31. 21 C.F.R. § 330.10(a)(1) (2024).

32. *Id.* § 330.10(a)(2).

the panel.[33] The panel then reviewed this data, deliberated, and reached its final conclusions as to the safety and effectiveness of the active ingredients within the therapeutic class. In this final report, reviewed ingredients were assigned to one of three categories: Category I) "generally recognized as safe and effective"; Category II) "not . . . generally recognized as safe and effective"; and Category III) "further testing is . . . required."[34]

The FDA then reviewed this final report and published a proposed monograph, separating ingredients into the same categories used in the panel's report.[35] After public comment, this proposed monograph became a tentative final monograph (TFM), which again retained the category system (although the FDA could change the category that an ingredient was in based on the comments it received).[36] After a final round of comments, this TFM would become a final monograph, definitively announcing which drugs were GRASE (i.e., Category I) and excluding all Category II and III drugs as not sufficiently safe or effective to be sold over the counter.[37]

While this system of review was effective as a sifting mechanism to limit the pool of viable ingredients, it was not without issue. The OTC Drug Review quickly proved unworkable as it slowed to a crawl due to legal challenges, statutory changes to administrative procedures, and budgetary constraints.

C. Issues with the OTC Drug Review Process

Constant legal challenges to this new regulatory scheme seriously inhibited the FDA's ability to quickly and efficiently publish finalized monographs. The most immediate issue that faced the FDA after commencing the OTC Drug Review was deciding what to do with the hundreds of thousands of drugs already on the market while their initial monographs slowly progressed through notice-and-comment rulemaking. The FDA's initial solution was to declare a moratorium on enforcement against OTC products without a monograph unless there were extenuating circumstances.[38] Once a proposed monograph was published, Category II products were taken off the market while the enforcement moratorium remained for Category III products (those which needed further testing to make a final determination as to their safety and effectiveness).[39]

33. *Id.* § 330.10(a)(3).
34. *Id.* § 330.10(a)(5)(i)–(iii).
35. *Id.* § 330.10(a)(6).
36. *Id.* § 330.10(a)(7).
37. *Id.* § 330.10(a)(9).
38. Guo et al., *supra* note 8, at 47.
39. *See id.*

This intentional nonenforcement against Category III drugs prompted a challenge from consumer groups in *Cutler v. Kennedy*.[40] In that case, the U.S. District Court for the District of Columbia held that the FDA's "regulations [were] unlawful to the extent they affirmatively sanction[ed] continued marketing of Category III drugs."[41] The reasoning behind this decision was simple: the FDCA allows only for the sale of GRASE drugs, Category III drugs are definitionally not GRASE, so by affirmatively allowing Category III drugs to be sold, the FDA exceeded its administrative authority.[42] In response, the FDA shifted from affirmative nonenforcement to a regime of "discretionary enforcement," a tactic that the *Cutler v. Kennedy* court very clearly suggested in dicta.[43] Under this approach, while the FDA could choose to utilize its enforcement powers against Category III drugs at any time, it assured firms that it would do so only when products "present a potential health hazard or a significant and substantial effectiveness question."[44] This policy was subject to further legal challenge by consumer groups, but the FDA was able to overcome these claims.[45]

Discretionary enforcement was initially implemented as a stop-gap to ensure that consumers were guaranteed continued access to a competitive, largely safe OTC drug market while firms could provide stronger data to establish the GRASE status of their Category III drugs.[46] Theoretically, once all monographs were finalized, there would be no need for discretionary enforcement because Category III drugs would no longer exist.[47] Unfortunately, discretionary enforcement became the rule rather than the exception due to the snail's pace at which the FDA completed these monographs.[48] This regulatory stagnation left several classes of drugs governed by unfinished monographs for decades, meaning that many OTC drugs on the market were Category III and, thus, not actually GRASE.[49]

In addition to regular legal challenges, there were two primary reasons for this painfully slow progress: changes to administrative procedures and a lack of

40. Cutler v. Kennedy, 475 F. Supp. 838 (D.D.C. 1979).

41. *Id.* at 855.

42. *See id.* at 853.

43. *Id.* at 856 ("Informally, of course, the FDA will be free to exercise its discretion to seek enforcement actions or not to seek enforcement actions. It may thus be argued that the Court's ruling simply permits the agency to accomplish informally and indirectly what it cannot accomplish in a formal order.").

44. Over-the-Counter (OTC) Category III Policy, 45 Fed. Reg. 31422, 31425 (proposed May 13, 1980) (to be codified at 21 C.F.R. pt. 330).

45. *See* Cutler v. Hayes, 818 F.2d 879 (D.C. Cir. 1987).

46. *Modernizing FDA's Regulation of Over-the-Counter Drugs: Hearing Before the Subcomm. on Health of the Comm. on Energy and Commerce*, 115th Cong. 144 (2017) [hereinafter *OTC Reform Hearing*] (statement of Scott Melville, President and CEO, CHPA).

47. This is because previously Category III drugs would either be included in or excluded from the final monograph (in which all drugs had to be Category I) based on whether there was enough data to prove that drug's GRASE status. 21 C.F.R. § 330.10(a)(9) (2024).

48. Guo et al., *supra* note 8, at 50.

49. *OTC Reform Hearing*, *supra* note 46, at 14 (statement of Janet Woodcock, CDER Director, FDA).

funding. As to the former, the FDA designed the OTC monograph system to be a relatively slow, comment-heavy process both to ensure that manufacturers had a voice in deliberation and so that final monographs would be resistant to legal challenges.[50] Unfortunately, in the years after the OTC Drug Review's creation, a series of laws and executive orders heaped requirements on agencies seeking to utilize notice-and-comment rulemaking, further hindering this already slow process.[51]

The FDA's inability to adequately fund the OTC Drug Review process exacerbated the slowing effects of these legal changes. While funding was not a major issue in the early years, as more legal challenges were levied and more bureaucratic requirements were implemented, the FDA struggled to provide its OTC division with sufficient funding to keep a reasonable pace.[52] The passage of the Prescription Drug User Fee Act (PDUFA) of 1992 worsened this struggle. Before the passage of this Act, the FDA was funded by appropriations (money set aside for its budget from the national treasury).[53] After the enactment of the PDUFA, the FDA steadily became more reliant on user fees for funding.[54] User fees are payments collected from industry sources as preconditions for being allowed to take certain actions.[55] While this practice massively increased the FDA's overall funding, these funds could be used only to support the program for which they were created.[56] Because no user fees were collected on OTC drugs, the OTC Drug Review continued to be funded only by allocations and saw no increase in funding from this innovation.

The budget distribution between the OTC and prescription divisions of the FDA in 2016 illustrates just how underfunded the OTC division was. During the 2016 fiscal year, appropriations for OTC products totaled $7.9 million, while appropriations for prescription drugs totaled nearly $321 million.[57] User fees for prescription drugs provided an additional $837 million, meaning that upwards of $1 billion were allocated towards prescription drugs that year.[58] OTC products, on the other hand, generated no additional funding from user fees, meaning the OTC division's budget remained at merely $8 million.[59] With the OTC division's budget often being devoted mainly to nonmonograph

50. Guo et al., *supra* note 8, at 51.

51. *Id.*

52. *Id.* at 52–53.

53. AMANDA K. SARATA, CONG. RSCH. SERV., R44576, THE FOOD AND DRUG ADMINISTRATION (FDA) BUDGET: FACT SHEET 1 (2020).

54. *Id.* at 3.

55. *See* 21 U.S.C. § 379h (assessing fees to file a new drug application and annual fees for any company selling qualifying prescription drugs).

56. *OTC Reform Hearing*, *supra* note 46, at 10 (statement of Janet Woodcock, CDER Director, FDA).

57. *Id.*

58. *Id.*

59. *Id.*

issues, the problems presented by these limited resources were acutely harmful to the OTC Drug Review process.[60]

These issues ultimately led the OTC Drug Review to be considered a failure compared to its original goals and timeline. When the FDA first implemented this system, it predicted that every monograph would be complete by 1983.[61] However, as 1983 approached, only 9% of monographs had been finalized.[62] The FDA pushed its goalposts back to 1990 in response but was similarly unable to meet this deadline.[63] Even into the 2010s, significant portions of the OTC market were still governed by unfinalized monographs, leaving consumers with many products that were not guaranteed to be GRASE.[64]

D. The 2020 CARES Act

In recognition of these failings, the OTC monograph system was overhauled as part of the 2020 Coronavirus Aid, Relief, and Economic Security (CARES) Act. The most important innovation of this Act was that monographs could be finalized through administrative orders rather than notice-and-comment rulemaking.[65] This change allowed the FDA to dramatically speed up the process by which it could finalize monographs. This statute also created a user-fee program for OTC products, which extracts a fee from facilities used to manufacture OTC drugs and from certain OTC-related application processes.[66] Other changes increased the FDA's flexibility in altering OTC monographs, provided firms with an exclusivity incentive for proving a new dosage of a drug to be GRASE, and overall made the OTC monograph system more streamlined and adaptable.[67]

Because of how recently the CARES Act was passed, it is difficult to assess how successful these changes will be at improving the OTC-drug landscape. Additionally, these changes include no mechanism to address the issue that consumers should be most concerned with: the presence of ineffective drugs in finalized monographs.[68]

---

60. *Id.* at 25 (noting that in 2015, 2016, and 2017 the FDA's OTC budget was almost entirely devoted to dealing with the statutory requirements of sunscreen legislation, issues with antiseptic drug products, and "[u]rgent safety activities").

61. Cutler v. Hayes, 818 F.2d 879, 885 (2d Cir. 1987).

62. *Id.* at 855 n.38.

63. *See id.* at 855 n.39.

64. *OTC Reform Hearing*, *supra* note 46, at 10 (statement of Janet Woodcock, CDER Director, FDA).

65. 21 U.S.C. § 355h(b).

66. *Id.* § 379j-72.

67. *See id.* § 355h(c).

68. *See* discussion *infra* Part II.

II. THE FDA'S FOCUS ON SAFETY AT THE EXPENSE OF EFFECTIVENESS

The FDA's willingness to approve safe but questionably effective drugs is a symptom of its chronic focus on safety at the expense of effectiveness. While there has been no official announcement from the FDA stating that it takes safety more seriously than effectiveness, it is clear from FDA enforcement and regulation that safety is its favorite child.

The approval of oral phenylephrine is a clear example of this favoritism. Evidence calling oral phenylephrine's effectiveness into question is not a modern revelation. The expert panels recognized the drug's uncertain effectiveness during its review but, because it presented no safety concerns, decided that it should stay on the market.[69] The FDA listed oral phenylephrine as a Category I ingredient in the proposed monograph (published in 1976)[70] and TFM (1985)[71] before approving it as one of three active ingredients in the final monograph for oral-delivery nasal decongestants in 1994.[72] But how could this happen? A Category I classification is reserved for drugs generally recognized as safe *and effective*. The placement of oral phenylephrine in Category I despite explicit acknowledgement of its questionable efficacy shows that the FDA is willing to turn a blind eye to effectiveness when safety is assured.

This disparate treatment is apparent from the different evidentiary standards required to establish safety and effectiveness during the OTC Drug Review. For a drug to be considered safe, the expert panel had to review the "results of significant human experience during marketing" in addition to data collected from "adequate tests by methods reasonably applicable to show the drug is safe."[73] These "adequate tests" had to consist of at least some published, controlled studies which the panel could then corroborate with studies that may be unpublished, partially controlled, or otherwise less veracious than published, controlled studies.[74] The standards for establishing effectiveness, on the other hand, were notably lower.[75] The requirement for controlled clinical investigations could actually be waived by the expert panel if they felt such a

69. PHENYLEPHRINE BRIEFING, *supra* note 2, at 22 ("While the Panel specifically noted that the data were 'not strongly indicative of efficacy', in the absence of a safety concern, they recommended that the Agency categorize oral PE . . . as safe and effective for use as an orally administered nasal decongestant.").

70. Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products, 41 Fed. Reg. 38312, 38312 (Sept. 9, 1976) (to be codified at 21 C.F.R. pt. 341).

71. Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Over-the-Counter Nasal Decongestant Drug Products, 50 Fed. Reg. 2220, 2220 (Jan. 15, 1985) (to be codified at 21 C.F.R. pt. 341).

72. Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Nasal Decongestant Drug Products, 59 Fed. Reg. 43386, 43386 (Aug. 23, 1994) (to be codified at 21 C.F.R. pts. 310, 341, 369).

73. 21 C.F.R. § 330.10(a)(4)(i) (2024).

74. *See id.* § 330.10(a)(4)(ii).

75. *Id.*

study was not "essential to the validity of the investigation."[76] These investigations could be supported by "partially controlled or uncontrolled studies, documented clinical studies, . . . and reports of significant human experience" even when controlled studies were not available.[77] So long as some "scientifically valid data [was] available," the panel could corroborate this data with much weaker evidence like "long use by the professional and the consumer," "common medical knowledge," or "subjective clinical studies."[78]

A likely reason for the disparity in proof necessary to establish safety versus effectiveness was the lower quality of effectiveness data available during the OTC Drug Review. Before the Kefauver-Harris Amendments, the FDA did not require manufacturers to prove their drug's effectiveness.[79] As such, the effectiveness data that was available for the OTC Drug Review was rarely from high-quality, well-controlled studies.[80] That many OTC drugs were exempt from effectiveness studies under the Kefauver-Harris Amendments' grandfather provision meant that companies often had no incentive to invest in further testing.[81] The regular inadequacy of efficacy data left the FDA and expert panels with little choice but to accept lower standards when assessing a drug's effectiveness.

Further evidence of the FDA's safety bias can be found in its standard for discretionary enforcement. When proceeding under this standard, the FDA announced that it would allow Category III drugs to remain on the market unless they presented "a *potential* health hazard or a *significant and substantial* effectiveness question."[82] While it is unclear what data was sufficient to show a "significant and substantial" effectiveness issue, it is obvious from the wording of this standard alone that the FDA was much more sensitive to safety issues than effectiveness questions.

The FDA's mechanisms for postmarket regulation further reveal its unbalanced approach to safety and effectiveness. The FDA has two main methods of continued quality assurance once it approves a drug for sale: postmarketing studies and adverse-event reporting.[83] Postmarketing studies are performed pursuant to an agreement between the drug's sponsor and the FDA when that drug's safety and effectiveness cannot be fully assessed in premarket

76. *Id.*

77. *Id.*

78. Procedures for Classification of Over-the-Counter Drugs, 37 Fed. Reg. 9464, 9469 (May 11, 1972) (to be codified at 21 C.F.R. pt. 130).

79. Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, FDA CONSUMER MAG., Jan.–Feb. 2006.

80. Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185, 210 (1971).

81. Over-The-Counter Drug Monograph System—Past, Present, and Future; Public Hearing, 79 Fed. Reg. 10168, 10170 (Feb. 24, 2014).

82. Over-the-Counter (OTC) Category III Policy, Proposed Revised Rule, 45 Fed. Reg. 31422, 31425 (proposed May 13, 1980) (to be codified at 21 C.F.R. pt. 330) (emphasis added).

83. *See* 21 U.S.C. § 356b(a); *see also* 21 C.F.R. § 310.305(a) (2024).

trials.[84] However, because these studies attach only to new drugs, this mechanism does little to ensure the continued safety and effectiveness of longstanding OTC drugs.[85] The second of these two mechanisms, adverse-event reporting, requires manufacturers to record and report any adverse reactions to a drug that they become aware of.[86] But, again, this requirement does nothing to ensure effectiveness because an individual's reaction to a drug is "adverse" only if it results in a negative (i.e., unsafe) health outcome.[87]

The reason for pointing out this enforcement disparity is not to suggest that the FDA has committed some grave disservice in ensuring the quality of medication provided to the American public by prioritizing safety over effectiveness. The unfortunate reality is that the FDA's limited resources make OTC regulation a zero-sum game. Devoting OTC budget towards ensuring safety necessarily reduces the time and money available for reviewing effectiveness. As discussed earlier, one reason the OTC monograph process slowed so significantly was because the FDA devoted much of its budget for OTC drugs to addressing pressing safety concerns.[88] The FDA even recognized these budgetary limitations when it announced the decidedly safety-skewed discretionary enforcement standard by explaining: "[T]hese priorities constitute the agency's current views about how best to use available resources consistent with its obligation to protect the public health. That FDA is attempting to allocate its resources as efficiently as possible does not mean that it will neglect any matter that significantly affects the consumer."[89]

Forced to prioritize one over the other, the FDA was right to choose safety. After all, the vast majority of people would rather treat their sniffles with a drug that turned out to be ineffective than with one that had a chance of giving them a stroke. Even so, while safe but ineffective OTC drugs pose less of a threat to consumers than effective but unsafe ones, that does not make the former a nonissue.

In some ways, an ineffective drug cannot actually be safe, especially if it is sold over the counter. The most apparent safety risk is that consumers will continue being sick. Prolonged sickness, while harmful in and of itself, can have knock-on effects that could impact consumers' health (e.g., not going to the doctor under the belief that OTC drugs would provide sufficient treatment or operating heavy machinery while distracted by lingering symptoms). Furthermore, seemingly all drugs have the potential for adverse side effects. If

84. *See* 21 U.S.C. § 356b(a).

85. Linda R. Horton, *Over-the-Counter Drug Authority Issues: Selected Topics*, 48 FOOD & DRUG L.J. 545, 552 (1993).

86. 21 C.F.R. § 310.305(a) (2024).

87. *Id.* § 310.305(b).

88. *OTC Reform Hearing*, *supra* note 46, at 14 (statement of Janet Woodcock, CDER Director, FDA).

89. Over-the-Counter (OTC) Category III Policy, Proposed Revised Rule, 45 Fed Reg. 31422, 31425 (proposed May 13, 1980) (to be codified at 21 C.F.R. pt. 330).

a drug is ineffective, the consumer experiences those side effects without having them offset by relief from their original symptoms. This lack of relief may even lead consumers to take more than the intended dose, increasing the risk of overdose.[90] Because consumers can take OTC drugs without the supervision of a medical professional, these negative outcomes—and the risk of adverse drug interactions—are difficult to mitigate.[91] Finally, many OTC drugs treat multiple symptoms with different active ingredients, meaning consumers may be building up a tolerance to those effective ingredients while only seeking the relief promised by the ineffective ingredient.[92]

Granted, some of these risks are similarly present with effective OTC drugs, but when a drug is effective, the potential risk is balanced by a realized benefit. With ineffective drugs, consumers bear nothing but risk with no offsetting benefit other than the mistaken belief that their symptoms will soon be relieved. This false belief is at the core of the most obvious harm to consumers posed by ineffective OTC drugs: fraud.

Since approval, oral phenylephrine products have seen massive commercial success, drawing in more than $1.7 billion in 2022 alone.[93] The popularity and longevity of these drugs prove that consumers cannot assess for themselves whether an OTC drug is actually effective. Additionally, with the risk of injury posed by ineffective drugs being so difficult to quantify beyond the cost of the drug itself, damages in a potential lawsuit will likely be far lower than in cases over drug safety issues. Because damages may not be particularly substantial, the profits generated by these ineffective drugs could outweigh the losses posed by litigation. Indeed, the fact that firms have continued to sell oral phenylephrine for years after the studies conclusively showing its ineffectiveness were published suggests that they may have already made these calculations.[94] Regardless of how effective a deterrent civil liability will be, the viability of such cases will rely on FDA recognition of ineffectiveness.[95] However, the FDA currently has no reliable mechanism to identify ineffective

90. *See Phenylephrine 10 Mg Tablet Oral Decongestants – Uses, Side Effects, and More*, WEBMD, https://www.webmd.com/drugs/2/drug-21821/phenylephrine-oral/details [https://perma.cc/GT8J-ESCQ] (discussing potential side effects and overdose symptoms of phenylephrine).

91. REX LOTT & KRISTEN N. GARDNER, MONOAMINE OXIDASE INHIBITORS: A TOOLKIT FOR CLINICAL USE 21–23 (June 21, 2024) (discussing the particularly adverse interactions between phenylephrine and certain antidepressants).

92. *See* Shalini S. Lynch, *Tolerance and Resistance to Drugs*, MERCK MANUAL (Sept. 2022), https://www.merckmanuals.com/home/drugs/factors-affecting-response-to-drugs/tolerance-and-resistance-to-drugs [https://perma.cc/2HQ6-SUST].

93. PHENYLEPHRINE BRIEFING, *supra* note 2, at 68.

94. *See id.* at 44 (these studies became public in 2015).

95. *See generally* Alexander Tin, *FDA to Pull Common but Ineffective Cold Medicine from Market*, CBS (Nov. 7, 2024), https://www.cbsnews.com/news/fda-cold-medicine-phenylephrine-ineffective/ [https://perma.cc/4TXP-MF7F].

ingredients because it does not have the budget or research infrastructure to conclusively prove the ineffectiveness of suspect drugs.[96]

The purpose of highlighting the FDA's approach to balancing safety and effectiveness is not to question its institutional competence but, instead, to show how the modern dilemma of ineffective but safe OTC drugs is not merely a coincidence. Rather, it is a natural result of the inevitable shortcomings of the OTC Drug Review and the FDA's long focus on safety at the expense of effectiveness. Regardless of this problem's source, it needs a solution. So, what should the FDA do?

III. A POTENTIAL SOLUTION

Ineffective OTC medication is the product of long-lasting, systemic issues with how the FDA conducted the OTC Drug Review and regulated OTC drugs in general. Unfortunately, the breadth of these shortcomings means that oral phenylephrine is just the tip of the ineffectiveness iceberg. Experts have already identified several other active ingredients on finalized monographs with dubious effectiveness data. Examples include guaifenesin as an expectorant,[97] antihistamines for cold symptoms,[98] and dextromethorphan for coughs caused by viral infections.[99] Because of how widespread this issue may be, the FDA needs a mechanism to identify, review, and remove these ingredients going forward.

Perhaps the greatest challenge in developing such a mechanism is how difficult it has been to identify and sufficiently prove an OTC drug's ineffectiveness. Many OTC drugs were evaluated using weak effectiveness data that relied on outdated, suspect testing methods.[100] Even after the OTC monograph process began, manufacturers had little reason to perform further testing.[101] Throughout the OTC Drug Review, expert panels and the FDA showed they were willing to authorize ingredients with weak efficacy data so long as those drugs were safe.[102] Manufacturers recognized this acquiescence and felt there was no reason to provide stronger efficacy data because it was just as possible that they would end up proving their ingredient ineffective.[103]

---

96. *See* discussion *infra* Part III.

97. *See* Miles Weinberger & Leslie Hendeles, *Nonprescription Medications for Respiratory Symptoms: Facts and Marketing Fictions*, 39 ALLERGY & ASTHMA PROC. 169, 173–74 (2018).

98. *See* Avadhesh Saraswat et al., *Antihistamines for the Common Cold*, COCHRANE DATABASE OF SYSTEMATIC REVS., Nov. 2015, at CD009345.

99. *See* Susan Smith et al., *Over-the-Counter Medications for Acute Cough in Children and Adults in Community Settings*, COCHRANE DATABASE OF SYSTEMATIC REVS., Nov. 2014, at CD001831.

100. *See* discussion *supra* Part II.

101. *See* discussion *supra* Part II; *see also* Over-The-Counter Drug Monograph System—Past, Present, and Future; Public Hearing, 79 Fed. Reg. 10168, 10170 (Feb. 24, 2014).

102. *See* discussion *supra* Part II.

103. Over-The-Counter Drug Monograph System—Past, Present, and Future; Public Hearing, 79 Fed. Reg. at 10170.

While aspects of the CARES Act added a few incentives for further OTC drug testing, these incentives are weak, overly specific, and will do little to supplement the dearth of industry-performed effectiveness studies.[104] The reason this lack of involvement from pharmaceutical companies is so harmful is that the FDA places a higher value on the large scale, well-controlled clinical studies that these firms can perform than on the data that independent researchers can gather.

The process by which oral phenylephrine was finally declared ineffective illustrates the FDA's bias toward industry testing. Suspicion of oral phenylephrine's ineffectiveness was an open secret within pharmaceutical circles for years.[105] Taken aback by rumors that such a widely sold drug was no better than a sugar pill, Dr. Randy C. Hatton and Dr. Leslie Hendeles from the University of Florida petitioned the FDA to reconsider oral phenylephrine's inclusion in the cold, cough, allergy, bronchodilator, and antiasthmatic (CCABA) monograph.[106] This petition led to a review in 2007 where "several meta-analyses of the original studies" as well as data from bioavailability and environmental exposure unit studies were presented, all showing that oral phenylephrine was "not more effective than placebo."[107] Despite this data, the review board decided that it needed more clinical data to make a final decision.[108] What changed since the 2007 review was that three large clinical trials on oral phenylephrine's effectiveness were conducted, two by Schering-Plough (since acquired by Merck) and one by Johnson & Johnson.[109]

It was the results of these studies that ultimately persuaded the FDA's expert panel to declare oral phenylephrine ineffective.[110]

It is clear from this process that the FDA requires affirmative proof of ineffectiveness before it is willing to take action, rather than data that only calls the original studies used by OTC Drug Review panels into question. The FDA currently has no mechanism to obtain this data proactively. Instead, it waits passively until someone takes it upon themselves to conduct and publish the conclusive studies needed to prove a drug's ineffectiveness. Pharmaceutical companies are some of the few entities with the infrastructure and funding to perform such studies, but there is no real incentive for firms to provide this data. Because of how profitable the sale of ineffective drugs can be,[111] it is

104. *See generally* 21 U.S.C. § 355h(c).

105. Randy C. Hatton & Leslie Hendeles, *We've Known for 20 Years This Cold Medicine Doesn't Work*, N.Y. TIMES (Sept. 29, 2023), https://www.nytimes.com/2023/09/29/opinion/cold-medicine-fda.html [https://perma.cc/TTX6-NTEX].

106. *Id.*

107. PHENYLEPHRINE BRIEFING, *supra* note 2, at 8.

108. *Id.*

109. *Id.*

110. *Id.* at 9.

111. *See id.* at 68; *see also* Alvin Powell, *Why Are Ineffective Oral Decongestants Still on Store Shelves?*, HARV. GAZETTE (Sept. 20, 2023), https://news.harvard.edu/gazette/story/2023/09/why-are-ineffective-oral-

usually in these companies' best interest to turn a blind eye. To combat this inaction, the FDA should implement a regulatory scheme that incentivizes pharmaceutical companies to devote their vast research capabilities toward removing ineffective OTC drugs.

A. The Basic Framework

Under this system, once a prima facie case of ineffectiveness is presented, the FDA will randomly select a pharmaceutical company to perform testing on the drug. This selection will prioritize companies with lower market share in that drug to minimize their potential biases in testing. The selected company will have the option to decline this testing responsibility, in which case a new company with comparably low market share will be randomly selected. To ensure participation, the firm that agrees to testing will receive one (or multiple) attractive incentives they may use, keep, or sell to another company. Once testing is complete, the FDA will convene an expert panel to review this data and make a final determination on the suspect drug's effectiveness.

The inspiration for this framework came from the story of how oral phenylephrine was declared ineffective. That process made clear that obtaining sufficiently conclusive proof is the largest obstacle to establishing ineffectiveness. While pharmaceutical companies are best suited to perform the studies necessary to produce this proof due to their vast funding and research infrastructure, there is currently no incentive for these firms to get involved. This scheme seeks to entice these companies with valuable incentives so they are willing—if not eager—to conduct such studies.

This system seeks to address three major issues faced by the FDA when dealing with ineffective OTC drugs: 1) budgetary constraints, 2) a lack of industry support and buy-in, and 3) the unavailability of conclusive effectiveness data. Besides implementation and oversight, this scheme will minimally burden the FDA's OTC budget because it offloads testing onto participating pharmaceutical companies. Ideally, companies will be willing to shoulder these costs to obtain one (or multiple) of several alluring incentives. If not, then tax breaks or benefits could also be included to ensure industry cooperation, although this would require congressional action.[112] This buy-in from firms will produce the essential data needed to properly assess suspect drugs: large-scale, well-controlled clinical trials.

decongestants-still-on-store-shelves/ [https://perma.cc/8959-QJ8B] (discussing prominence of ineffective drugs on the market).

112. *See generally* 26 U.S.C. § 45C (providing for tax credits already offered to encourage companies to develop drugs to treat rare conditions).

1. Establishing a Prima Facie Case for Ineffectiveness

The first step in this system will be identifying drugs with suspect effectiveness. While the OTC Drug Review was flawed in many ways, it served as a relatively effective initial filter by sifting out the vast majority of unsafe or ineffective drugs on the market. As such, reviewing all OTC drugs is unnecessary and the FDA should instead take a more case-by-case approach.

When there is suspicion about a drug's effectiveness, a challenger will file a petition to the FDA requesting review. This petition will include the data that the challenger is basing their opinion on. Challenges should be accepted only against drugs on a finalized monograph. Petitions could be sent through the existing citizen-petition mechanism[113] or the FDA could create a new form of petition to ensure that effectiveness challenges are dealt with quickly and efficiently. However, the former is more favorable because it minimizes the administrative change necessary for this system's implementation. The use of citizen petitions to question effectiveness has also proven viable, as this was the administrative mechanism used to initially bring oral phenylephrine's effectiveness to the FDA's attention.[114]

The FDA should then convene a panel of experts to review the petition and determine whether the evidence presented is sufficient to prove the ingredient's ineffectiveness. The panel could conclude that the evidence is insufficient to call the drug's effectiveness into question, that more testing and information is needed, or that the data presented is enough to prove the drug's ineffectiveness on its own. The panel's findings will then be sent to the FDA for public comment before a making a final decision. The FDA would then decide to follow or deviate from the panel's recommendation based on the comments received. A conclusion that additional data is needed will trigger the next stages of this process.

The main issue with this phase is the potential for abuse. Pharmaceutical companies may constantly petition the FDA with questionable data just for the chance of getting the incentives offered for performing testing. This framework has several natural deterrents to combat this form of abuse and a few more contrived measures which could be implemented. The FDA and panel review ensure that each petition must pass multiple levels of expert scrutiny, hopefully defeating most frivolous petitions. The mostly random selection of which company gets to test the ingredient further dissuades frivolous petitions because it is only clear *after* a prima facie case is made what company will receive the desired incentive. These two features are likely enough to ensure that petitions are filed mostly by consumer groups and independent researchers who are sincerely concerned about a drug's efficacy. If not, a cause of action for

113. *See* 21 C.F.R. § 10.30 (2024).

114. PHENYLEPHRINE BRIEFING, *supra* note 2, at 8.

frivolous petitions or a restriction on what parties could file petitions could be included.

2. Tester Roulette

Once a prima facie case for ineffectiveness is established and the FDA decides that further data is needed, a pharmaceutical company will be selected to perform testing. Firms will first be sorted into groups based on their market share in the ingredient at issue. Selection will occur randomly, starting with the group of firms with no market share. The selected firm may decline to perform testing, in which case the opportunity will pass to the next firm chosen within that group. Once all firms in a group are exhausted, randomization and selection will move to the next lowest market share group and continue until a firm accepts testing responsibilities.

This approach certainly has some risk because it requires a firm to voluntarily participate in testing. Offering first choice to low-market-share firms is a strong incentive for these firms to agree to testing as it allows them to weaken their competitors by proving that a drug the competitor sells is ineffective. If these low-market-share firms decline testing responsibilities, they run the risk of a higher-market-share firm that may be biased against a finding of ineffectiveness performing these studies. For this selection process to work, this natural incentive (in tandem with the incentives described in the next Section) must be valuable enough to outweigh the cost of testing.

The attractiveness of this incentive can be inferred from Schering-Plough's publication of its studies proving oral phenylephrine's ineffectiveness.[115] This willingness to publish results that ostensibly work against this company's best interest may seem altruistic at first blush. However, a quick review of the drugs sold by Schering-Plough (and later by Merck) paints a much different—and more cynical—picture. Neither Schering-Plough nor Merck sold any phenylephrine-based drugs, but they did manufacture a formulation of Claritin that contained pseudoephedrine.[116] Pseudoephedrine happens to be the only active ingredient approved for use as an oral-delivery nasal decongestant other than phenylephrine.[117] There is no direct evidence that Schering-Plough's goal in publishing these studies was to improve its product's market share, but it is hard to believe that this confluence of facts is merely a coincidence.

If incentives alone are not enough to ensure firm participation, then either tax breaks or user-fee reductions could be offered to defray the cost of testing. The FDA currently uses both of these incentives to encourage companies to

115. *See id.* at 23.

116. *See Claritin Reditabs- Loratadine Tablet, Orally Disintegrating*, NAT'L LIBR. OF MED. (Dec. 6, 2024) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b681ea25-d00b-4c8a-8054-cc6f983ce337&audience=consumer [https://perma.cc/X852-CB2M].

117. 21 C.F.R. § 341.20 (2024).

invest in drugs for rare diseases.[118] User-fee reductions would be easier to implement because it is already within the FDA's authority to reduce user fees in certain situations,[119] but this approach would be somewhat self-defeating as it reduces the FDA's budget.[120] On the other hand, tax breaks would avoid limiting the FDA's budget any further, but would require more significant legislative support to pass (although passing tax breaks for wealthy companies does not seem to be particularly difficult).

3. Incentives

One of the main reasons that OTC Drug Review panels had to rely on dated effectiveness studies was that drug companies had no incentive to do further research.[121] It was often in these companies' best interest to avoid producing additional data because it was possible they would end up proving their drug to be ineffective. Any solution that seeks to remedy this problem must reverse these negative incentives and offer attractive benefits that will make firms willing, if not eager, to conduct the necessary studies. While this proposed regulatory framework has several intrinsic incentives (e.g., the opportunity to reduce a competitor's market share), firms will likely need something more substantial before they are willing to participate.

Once a firm has been selected and agrees to conduct the necessary studies, it will receive an exclusivity extension, an exclusivity waiver, or priority review status.[122] An exclusivity extension allows a company to maintain exclusivity for a drug they developed for longer than the statutory period.[123] An exclusivity waiver allows a company to begin developing generic drugs during another firm's exclusivity period.[124] Priority review status allows a company to speed up the approval of a new drug by putting it through the priority review process.[125] Tuning the specifics of each of these incentives will require input from both the FDA and firms to determine what is sufficiently attractive while remaining fair. For example, the number of years of additional exclusivity could be fixed at five years or vary based on the initial exclusivity period. Similarly, the exclusivity waiver could be limited to only the last year of another company's exclusivity period to maintain the value of exclusivity.

---

118. *See* 21 U.S.C. §§ 360cc, 379h(a)(1)(F).

119. *See id.* § 379h(a)(1)(D).

120. *See generally id.* § 379h.

121. *See* discussion *supra* Part II.

122. Exclusivity is a privilege granted by the FDA that allows the company that developed a new drug or medical device to be the only one selling it for a set period of time. *See generally* 21 U.S.C. § 355(j)(5)(B)(iv).

123. *See generally id.* § 355f (referencing the different periods of exclusivity available under the FDCA).

124. A generic drug is one with the same chemical composition as a new drug that other companies are allowed to sell once a company's exclusivity period ends. *See generally* 21 U.S.C. § 355(t)(3).

125. *See generally id.* §§ 360ff, 360bbb-4a, 360n (providing priority review for various designated categories of drugs).

Companies should be able to transfer these incentives or hold them indefinitely to ensure they are equally attractive to all firms. Allowing firms to trade or sell these benefits guarantees they will be valuable regardless of whether that firm has a drug with an active exclusivity window, the manufacturing capabilities to make a generic drug and intrude on another's exclusivity window, or an active drug application that could benefit from fast-tracking. Similarly, allowing firms to hold these incentives indefinitely provides valuable flexibility in deciding how and when to use them. However, limits should be placed on how long exclusivity for a drug can be extended to ensure that consumers receive the benefits of generic drugs within a reasonable time.

If access to just one of these incentives is not enough to get firms to agree to testing, then multiple could be offered. The FDA could also negotiate with firms on a case-by-case basis to increase the number of incentives proportionally to the expected cost of the study. However, this approach is likely unwise because larger firms would have more leverage when negotiating and could use the incentives to greater effect than smaller firms.

4. Room for Improvement

This proposal only provides the bare-bones framework for how this regulatory scheme could function. A complete cost-benefit analysis would be necessary to determine the viability of this idea, but I have neither the numbers nor the mathematical competence to even attempt one. Further, negotiations and discussions between the FDA and pharmaceutical companies will be essential to fine-tune what incentives would be sufficient to cement industry support without throwing the broader regulatory goals of the FDA into disarray.

While this scheme is far from perfect and may not even be the best option, the FDA needs to do something to encourage testing of suspect OTC drugs. The FDA's current approach to dealing with ineffective active ingredients is to wait passively, hoping for some organization to conduct conclusive effectiveness studies while consumers are defrauded of more than a billion dollars a year buying medicine that does not work.[126] This problem will never be solved without a plan of action that involves a proactive approach to obtaining this data. Otherwise, the necessary studies may never happen and consumers will bear the consequences.

B. Alternative Solutions

Because this proposed regulatory framework attempts to consider and balance the various forces that have historically confounded effective OTC

126. *See* PHENYLEPHRINE BRIEFING, *supra* note 2, at 68.

drug regulation (FDA budgetary constraints, industry resistance, etc.), proper enactment will be relatively complex. While the end result aims to minimally burden FDA resources, refining and implementing this system will require time and investment. Recognizing this difficulty, it is worth discussing some cheaper, simpler solutions that the FDA may consider to combat the continued sale of ineffective OTC drugs.

One such change could be the present and retroactive expansion of drug companies' reporting requirements. Currently, companies are only required to disclose the results of studies into biologics (e.g., stem cell therapies) and drugs under an NDA.[127] Because these reporting requirements apply only to new drugs, they often necessarily exclude studies on OTC monograph drugs which are definitionally not "new."[128] Requiring companies to disclose all studies into OTC ingredients, past and future, would provide a much more complete, robust evidentiary basis for determining these drugs' effectiveness. The main issue with this approach is that it does not proactively address the lack of well-controlled clinical studies on effectiveness. Because research into prescription drugs is far more lucrative[129] and drug companies have long been incentivized to not conduct studies on OTC drugs,[130] many of the disclosed studies may be outdated, unreliable, and provide negligible value in establishing suspect drugs' ineffectiveness. Furthermore, such a regulation would be difficult to pass due to the heavy industry pushback it would likely receive.

Alternatively (or additionally), the FDA could change the standard of proof necessary to establish a drug's efficacy. Implementing a more exacting standard of proof would have two major beneficial effects: increasing the quality of evidence necessary before an OTC drug could be put to market and lowering the burden on petitioners seeking to call an existing drug's effectiveness into question. While this solution may seem simple and elegant in the abstract, in reality it is a formidable challenge. The current standard of proof for a drug to be generally considered effective is that there be "substantial evidence" backing this finding.[131] The FDA has promulgated regulations detailing what kinds of evidence may be used to meet this standard but has not attempted to definitively establish where the proverbial efficacy goalpost stands.[132] Instead, the FDA has

127. 42 U.S.C. § 282(j)(1)(A)(iii)(I) (defining "applicable drug clinical trial" for the purposes of reporting as studies of drugs considered new drugs).

128. *See* discussion *supra* Part I; *see generally* 42 U.S.C. § 282(j)(3)(E)(v).

129. *Compare* Matej Mikulic, *Prescription Drug Expenditure in the United States from 1960 to 2022*, STATISTA (Jan. 18, 2024), https://www.statista.com/statistics/184914/prescription-drug-expenditures-in-the-us-since-1960/ [https://perma.cc/74VM-6HGD], *with* Matej Mikulic, *Total OTC Drug Retail Sales in the U.S. from 1965 to 2022*, STATISTA (Apr. 18, 2023), https://www.statista.com/statistics/307237/otc-sales-in-theus/ [https://perma.cc/ALS8-NTBP].

130. *See* discussion *supra* Part II.

131. 21 U.S.C. § 355(d).

132. *See* 21 C.F.R. § 330.10(a)(4)(i) (2024).

heavily relied upon expert discretion, resulting in some natural variance in what counts as "effective" depending on who conducted the review.[133]

With the current standard of proof being so discretionary, it is difficult to pinpoint exactly how it can be specified. There is also the broader concern of how such a change would impact the current OTC-drug landscape.[134] Regardless of the exact change, effectively all drugs may be subject to potential review because they were initially approved under a laxer standard of proof. Such a change may necessitate a second drug review similar to the one brought on by the Kefauver-Harris Amendments, which would be wasteful and unwise considering the generally satisfactory state of modern medicine. To prevent broader issues, this stricter standard of proof could be applied only when a petitioner challenges an OTC drug as potentially ineffective. This limited application may encourage firms to take testing responsibilities upon themselves to ensure that sufficiently well-conducted studies support their drug's efficacy.

In addition to these smaller tweaks, there are a few existing larger-scale proposals for expanding FDA postmarket regulation that could be adapted to deal with ineffective OTC drugs.[135] For example, testing responsibility for OTC drugs could shift from manufacturers to the government.[136] This approach would require massive funding but would ensure that there was a minimally biased entity capable of conducting the well-controlled studies needed to assess suspect drugs' effectiveness. The FDA could also look into developing a database to collect and monitor patient-level treatment outcomes to allow for continued assessment of drug efficacy.[137] Doing so would also be incredibly expensive and time-consuming but would give the FDA a powerful tool for monitoring the continued safety and effectiveness of drugs once they are put to market. Finally, Congress could give the FDA the explicit power to require firms to engage in postmarket studies when a potential effectiveness concern arises.[138] However, it is difficult to imagine such a measure passing over pressure from industry lobbyists.

---

133. *See Drug Efficacy and the 1962 Drug Amendments*, *supra* note 80, at 208–09.

134. *Cf.* Lee Kennedy-Shaffer, *When the Alpha Is the Omega: P-Values, "Substantial Evidence," and the 0.05 Standard at FDA*, 72 FOOD & DRUG L.J. 595, 633 (2017) (discussing concerns associated with adopting new statistical methods to assess efficacy).

135. These ideas have been adapted from existing proposals for improving postmarket regulation of prescription drugs. Because the proven existence of ineffective OTC drugs is so new, there are no existing proposals for how to potentially address the threat they pose (to my knowledge).

136. *See* SUSAN THAUL, CONG. RSCH. SERV., RL 32797, DRUG SAFETY AND EFFECTIVENESS: ISSUES AND ACTION OPTIONS AFTER FDA APPROVAL 31–32 tbl.1 (2007).

137. *See id.* at 26–27.

138. *Id.* at 27.

CONCLUSION

While the announcement of oral phenylephrine's ineffectiveness was the first of its kind, it likely will not be the last. The shortcomings of the OTC Drug Review and the FDA's long focus on safety at the expense of effectiveness have allowed an unknown number of safe but ineffective drugs to be sold over the counter. However, without conclusive effectiveness data, there is no reliable way to identify and remove these drugs. The best way to obtain this data is through large-scale clinical studies, but the FDA currently has no mechanism to conduct this research itself or incentivize others to do it for them. The FDA's inability to proactively address this problem costs consumers billions while leaving their symptoms untreated. Creating a strong incentive program to encourage pharmaceutical companies to devote their vast research and development infrastructure toward rooting out ineffective OTC drugs may solve this problem at little cost to the FDA. Even if this framework proves unworkable, the FDA needs to develop a solution to guarantee consumers access to safe *and* effective OTC drugs.

*Daniel Hall**

* Third-year J.D. candidate at the University of Alabama School of Law. This Note is dedicated to my family and Olivia, who always make me want to try my hardest. Without their support, I wouldn't have cared enough to put the effort into writing this. I would also like to thank Professor Luke Herrine for his excellent consumer protection seminar which formed the basis for my knowledge on this topic and for the in-depth notes that he provided on my drafts which guided this Note to the state it is in today.