CENTER FOR Science IN THE Public Interest
Your Food and Health Watchdog

May 6, 2025

Dockets Management Staff (HFD-600)
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Amending Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (Docket No. FDA-2024-N-4734-0001)

Dear Dockets Management Staff:

The undersigned individuals write in strong support of the Food and Drug Administration's (FDA's) November 8, 2024, proposed order to remove the oral decongestant phenylephrine (PE) as a nasal decongestant active ingredient from OTC Monograph M012. Data provided to the agency and summarized in the FDA's Briefing Document for the Nonprescription Drug Advisory Committee meeting on September 11-12, 2023, confirm that oral PE is barely absorbed into the bloodstream and that the best conducted clinical trials provide no evidence of efficacy on relevant clinical outcomes.

Dr. Leslie Hendeles is a Professor Emeritus in the College of Pharmacy and the Department of Pediatrics at the University of Florida. Dr. Randy Hatton is a Clinical Professor in the Department of Pharmaceutical Outcomes & Policy at the University of Florida. Together, they have submitted two Citizen Petitions to the FDA on oral PE efficacy. Their work has been pivotal in prompting the FDA's review of clinical and pharmacological evidence on oral PE. The Center for Science in the Public Interest (CSPI) is a non-profit consumer education and advocacy organization. Since 1971, CSPI has advocated for evidence-based policies to improve health, nutrition, and food safety.

The proposed order draws on a comprehensive review of clinical and pharmacological evidence to make clear that orally administered PE hydrochloride and PE bitartrate are not generally recognized as safe and effective (GRASE).[1] The Briefing Document concludes, "[O]ral PE at monographed dosages is not effective as a decongestant."[2] Moreover, a 2023 Nonprescription Drug Advisory Committee panel concluded 16-0 that "the current scientific data do not support that the monograph dosage of orally administered phenylephrine is effective as a nasal decongestant."[3] According to the FDA, retailers sold 242 million packages of oral products containing PE in the United States in 2022, for a total value of $1.76 billion.[2] This proposed order, if finalized, would remove these ineffective medications from retailers' shelves nationwide and reduce spending on PE-containing products. While consumers would need to seek out alternate decongestants, as the only effective oral nasal decongestant is currently kept behind the counter, relative ease in accessing an effective substitute does not warrant exposing Americans to the cost burden and side effect risks of using an ineffective decongestant.

The Citizen Petitions

Drs. Hendeles and Hatton's work has sparked the national conversation on re-evaluating the efficacy of oral PE. Their interest in oral PE started when nasal decongestants containing pseudoephedrine (PSE) were moved behind the counter through the Combat Methamphetamine Epidemic Act of 2005 in an

effort to curb illicit methamphetamine synthesis.[4,5] Companies, in their desire to maintain a readily available over-the-counter decongestant, reformulated many decongestant products to use PE instead.[4] The sudden availability and increased use of PE raised questions about its effectiveness as a decongestant.

In their 2007 Citizen Petition to FDA, Drs. Hendeles and Hatton reviewed the scientific evidence used to inform the FDA OTC Decongestant Monograph, first proposed in 1976 and finalized in 1994.[6] They revealed that one study site (Elizabeth Biochemical Labs) drove the reported positive efficacy outcomes for PE, and that this site's results could not be replicated by the other study sites.[7] Although the monograph established that a 10 mg oral dose of PE hydrochloride every 4 hours is considered GRASE, Drs. Hendeles and Hatton challenged that conclusion, citing evidence from their analysis which did not support the FDA's conclusion that a 10 mg dose of PE effectively relieved nasal congestion.[6]

Following the petition, the FDA convened the Nonprescription Drugs Advisory Committee (NDAC) in December 2007 to discuss the effectiveness of oral PE as a nasal decongestant.[8] While 11 of 12 committee members agreed that "given the available data that exist, the evidence is supportive that the 10 mg immediate release formulation *may* [emphasis added] be effective," the committee also noted that the efficacy data were not consistent across studies.[8] Nine of 12 committee members acknowledged that the 10 mg dose of oral PE was at the lower end of the dose-response range and recommended additional clinical studies of oral PE to evaluate the safety and efficacy of higher doses.[8]

In the years following the NDAC meeting, evidence challenging the claimed efficacy of oral PE continued to accumulate. Clinical studies evaluating the efficacy of oral PE since then, reviewed in more detail below, have shown that oral administration of PE is not more effective than placebo.[9-11]

Consequently, in 2015, Drs. Hendeles and Hatton filed a new Citizen Petition that called for the removal of oral PE from the OTC monograph.[12] Publication of additional studies in subsequent years further challenging the efficacy of oral PE led to Drs. Hendeles and Hatton filing a 2022 supplement to the 2015 Citizen Petition.[13]

In September 2023, the FDA convened an NDAC meeting to discuss oral PE efficacy data and to determine whether oral PE should be reclassified as not GRASE. The briefing materials prepared for the NDAC meeting conclude that "the new data appear compelling that the monographed dosage of oral PE results in no meaningful systemic exposure or evidence of efficacy."[2] As mentioned above, the advisory committee voted unanimously that "current scientific data do not support that the monograph dosage of orally administered phenylephrine is effective as a nasal decongestant."[3] It was this FDA scientific review and the NDAC recommendation that formed the basis for FDA's proposed order to amend OTC Monograph M012 to remove oral PE as an active ingredient because it is not GRASE.[1] In the following sections, we review the underlying evidence in more detail.

Clinical trial efficacy evidence

The FDA review of the original studies submitted prior to 1976 highlighted methodological limitations and called into question the quality of the data.

Sterling-Winthrop, a manufacturer of oral PE, submitted 11 studies for the 1976 Panel's consideration. These studies were conducted across three sites and represented six of the seven studies the 1976 Panel concluded demonstrated the efficacy of oral PE. The seventh study was provided by Whitehall Labs. According to the Briefing Document, methodological and statistical issues in the conduct of these

studies undermine the claims made about statistical differences and clinical benefits.[2]

These studies all used nasal airway resistance (NAR) as a primary endpoint, but this is no longer considered the agency's gold standard for developing allergic rhinitis drugs, which often treat nasal decongestion similar to oral PE.[14] NAR is an indirect, variable measure of congestion, which is subjective and is subject to between- and within-day fluctuations in congestion, procedural variation, equipment inaccuracy, and evaluator experience.[15] The FDA no longer uses NAR as a primary endpoint for evaluating congestion in clinical studies and has recommended that industry use nasal symptom scores in assessing the efficacy of allergic rhinitis drugs.[2,14]

In addition, all but one of the original studies reviewed by the 1976 Panel evaluated the efficacy of oral PE in patients with the common cold.[2] But the common cold resolves spontaneously while patients with allergic rhinitis experience congestion symptoms over a longer period, which offers a more stable platform for clinical studies on nasal congestion.[2]

The original studies reviewed by the Panel also contained statistical issues, including small sample sizes and lack of clearly presented statistical endpoints and methodology. The Briefing Document noted "bias and/or data integrity issues [found in] at least one study center, Elizabeth Biochemical Labs, where five of the seven positive oral PE studies were conducted."[2] The results reported at the Elizabeth site were not replicated at the other study sites sponsored by Sterling-Winthrop nor by other researchers.[7] Furthermore, these claimed favorable results did not align with what is expected based on oral PE bioavailability and pharmacodynamic effects, as the positive NAR outcomes reported were not accompanied by clinically relevant changes to blood pressure or heart rate as would be expected with an alpha adrenergic drug. Drs. Hendeles and Hatton and their colleagues also analyzed the variability of results at the Elizabeth site and found a disproportionately high occurrence of the digit "5" as the final digit in results, suggesting data integrity concerns.[16] Taken together, the study design and statistical issues in the original Panel studies cast doubt upon the conclusion that oral PE is effective. Overall, the FDA Briefing Document concluded, "the multiple methodological and statistical issues inherent in the studies reviewed by the Panel make the original studies evaluated for efficacy unacceptable as continued support for the efficacy of monographed doses of oral PE".[2]

At the 2023 NDAC meeting, new evidence derived since the 2007 NDAC meeting was also reviewed. These include two trials conducted by Schering-Plough and a Phase 2 study conducted by Johnson & Johnson.[9-11]

The first Schering-Plough study was a multicenter, randomized, placebo-controlled, parallel-group dose-ranging trial, evaluating fixed dosages of 10, 20, 30, and 40 mg of immediate-release oral PE or placebo in healthy adults with seasonal allergic rhinitis caused by spring allergens.[9] The primary endpoint was reflective nasal congestion scores, and there was no statistically significant change in these scores from baseline between any of the active treatment groups and the placebo group (Figure 1).[9]

The second Schering-Plough study was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial comparing 30 mg of extended-release oral PE hydrochloride and placebo in the treatment of healthy adults with seasonal allergic rhinitis caused by fall pollen.[10] Again, there was no statistically significant difference in the change in daily reflective nasal congestion scores between the active treatment and placebo groups (Figure 2).[10]

Finally, the FDA reviewed an unpublished Johnson & Johnson Phase 2, randomized, double-blind,

placebo-controlled, parallel-group trial.[11] This study sought to evaluate the efficacy of an extended-release 30 mg PE oral tablet and an immediate release 12 mg PE capsule in subjects with nasal congestion due to the common cold.[11] The study was terminated early because the investigators could not enroll enough participants during the cold season.[11] At study termination, there was no significant difference between either PE treatments compared to placebo in the reflective nasal congestion severity score.[11]

These recent studies avoided the statistical issues in the original Panel studies by reporting sample size calculations and using these calculations to inform patient recruitment. To overcome the methodological limitations of prior studies, the Schering-Plough studies recruited subjects with seasonal allergic rhinitis and all three trials evaluated efficacy using nasal congestion score as an endpoint.[9-11] This led the Briefing Document to conclude that "new clinical pharmacology and clinical data are consistent, substantial, and believable, and they confirm that orally administered PE is not effective at any dose that can be developed and still provide a reasonable margin of safety."[2]

Pharmacological evidence

At the time of the 1976 Panel review, the FDA was aware of the high degree of effectiveness of intranasally administered PE, and this may have influenced its decisions regarding oral PE.[2] At the time, oral PE bioavailability was estimated to be 38%, a figure that includes both the concentration of the active, parent PE and its *inactive* metabolites, which were indistinguishable using the best laboratory methods available at the time.[17,18] However, more recent clinical pharmacology studies using more advanced technology that can now distinguish between PE and its metabolites make clear that true oral bioavailability of PE is <1%, primarily due to extensive first-pass metabolism in the liver. At the 2007 NDAC meeting, Schering-Plough presented pharmacokinetic (PK) data from 14 subjects establishing the true bioavailability of oral PE to be <1%, and data from a 2010 New Drug Application for Advil Sinus Congestion & Pain (ibuprofen 200 mg and phenylephrine HCl 20 mg), reported the same result (Figure 3).[2,18] The lack of effectiveness observed in clinical studies of oral PE, therefore, has a clear explanation: unlike its nasal counterpart, oral PE is simply not well-absorbed.

The lack of a significant physiological response to oral PE compared to intravenous (IV) administration further supports the conclusion that oral PE has poor bioavailability. A 2015 Phase 2 study by McNeil Consumer Healthcare examined the pharmacokinetic and cardiovascular effects of single-dose oral PE at various doses, compared to a placebo. At the monograph dose of 10 mg, the active PE concentration reached a peak of just 1.35 ng/ml—substantially lower than the concentration observed with IV PE, which reached around 10 ng/ml at lower-than-oral doses (total dose of a 0.42 mg infusion over 6 minutes for a 70 kg subject).[2,19]

The investigators also examined whether oral PE produced the predictable effects associated with alpha adrenergic drugs. In the McNeil study, the maximum increase in mean systolic blood pressure (BP), after adjustment for placebo effects, within two hours of taking single oral doses of 10, 20, and 30 mg of PE was minimal with no apparent dose-response relationship: 4.1, 3.3, and 4.4 mmHg, respectively.[2 19] Additionally, FDA's clinical pharmacology team confirmed that meaningful increases in systolic and diastolic BP do not occur until oral PE doses reach 80-100 mg. One study cited BP elevations of 5-10 mmHg in oral PE doses begin at 50 mg, still well in excess of the maximum labeled dose.[20] In contrast, a 1986 in vitro study showed that PE administered as a continuous IV infusion at lower-than-oral doses resulted in an approximately 10 mmHg increase in both systolic and diastolic blood pressures.[2]

The minimal increase in systolic BP following oral PE administration is supported by the low blood

concentration achieved at the monograph dose. The high doses required to affect BP underscore the poor bioavailability. The stark difference in physiological effects between oral and IV PE further supports the notion that the monograph doses of oral PE have low bioavailability, and therefore, little physiological effect.

Regulatory standards

According to 21 CFR § 330.10(a)(4)(ii), an over-the-counter drug must demonstrate "a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed." The available clinical and pharmacological evidence clearly indicates that oral PE, at the doses currently allowed in the final monograph, is unlikely to provide meaningful relief. It is, therefore, FDA's obligation to remove this ineffective drug from the market.

The best available clinical studies demonstrated that at doses ranging from the monograph dose of 10 mg to doses as high as 40 mg, oral PE was not effective for nasal decongestion compared to placebo.[9] On the safety side, increases in BP can be seen in doses as low as 50 mg.[20] Taken together, these data suggest that oral PE doses that might be high enough to demonstrate efficacy for nasal decongestion would also impose safety risks due to meaningful increases in BP. Further, as there are no studies to support the safety and efficacy of oral PE doses higher than 40 mg, we support the Briefing Document's assertion that "orally administered PE is not effective at any dose that can be developed and still provide a reasonable margin of safety," and we discourage the agency from allowing higher doses of oral PE as an alternative course of action as these doses have not been studied in appropriately designed investigations.[2]

Alternatives to oral phenylephrine

After the removal of oral PE from the market, consumers will still be left with a number of effective treatment options for nasal congestion. First, intranasally administered PE acts locally in the nasal mucosa (reducing the risk of adverse effects) and is an effective nasal decongestant. This product will remain on the market for use in patients with the common cold. Other intranasal products such as corticosteroids and antihistamines will also remain available over-the-counter to consumers with allergic rhinitis. Second, an effective orally administered nasal decongestant will remain on the market in the form of pseudoephedrine (PSE). Though PSE, due to its abuse potential, is required by law to be kept behind the counter of pharmacies, the additional steps consumers would need to take to gain access to this effective product are not insurmountable.[5] In any event, relative ease in obtaining an effective decongestant is no justification for keeping an ineffective decongestant on the market.

Ability of manufacturers to reformulate

A potential argument against the FDA's proposed order is the downstream impact on the pharmaceutical industry, which includes addressing combination products containing PE currently on the market. From 2012 to 2021, 711 out of 732 unique PE products were combination products.[21] But the experience with PSE indicates that manufacturers are able to adapt quickly to policy changes. In the year following the implementation of the 2005 Combat Methamphetamine Epidemic Act, manufacturers' sales of cough, cold, or allergy medications containing PSE dropped drastically while oral PE products saw a sharp increase in sales in the same time period (Figure 4).[2] The speed of adaptation in the 2000s suggests that manufacturers will be able to quickly adapt to remove phenylephrine from their products.

Conclusion

The proposed order to remove oral PE from OTC Monograph M012 is critical to protect consumer health. The FDA's review of available clinical and pharmacological evidence clearly shows that oral PE is not effective at the monographed dosages. We support the FDA's proposed action to remove oral PE and protect consumers from ineffective ingredients, reduce healthcare costs, and mitigate risks related to potential allergic reactions, side effects, and delayed care as patients first try this ineffective medication. With effective decongestants already available to consumers, there is no scientific justification for keeping oral PE on the market. The FDA should expeditiously finalize the proposed order. We appreciate your work on this proposed order and thank you for taking our comment into consideration.

Sincerely,

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Figure 1. Schering-Plough Protocol #CL2010-06. Reflective Nasal Congestion Scores by Treatment and Study Day (ITT Population)

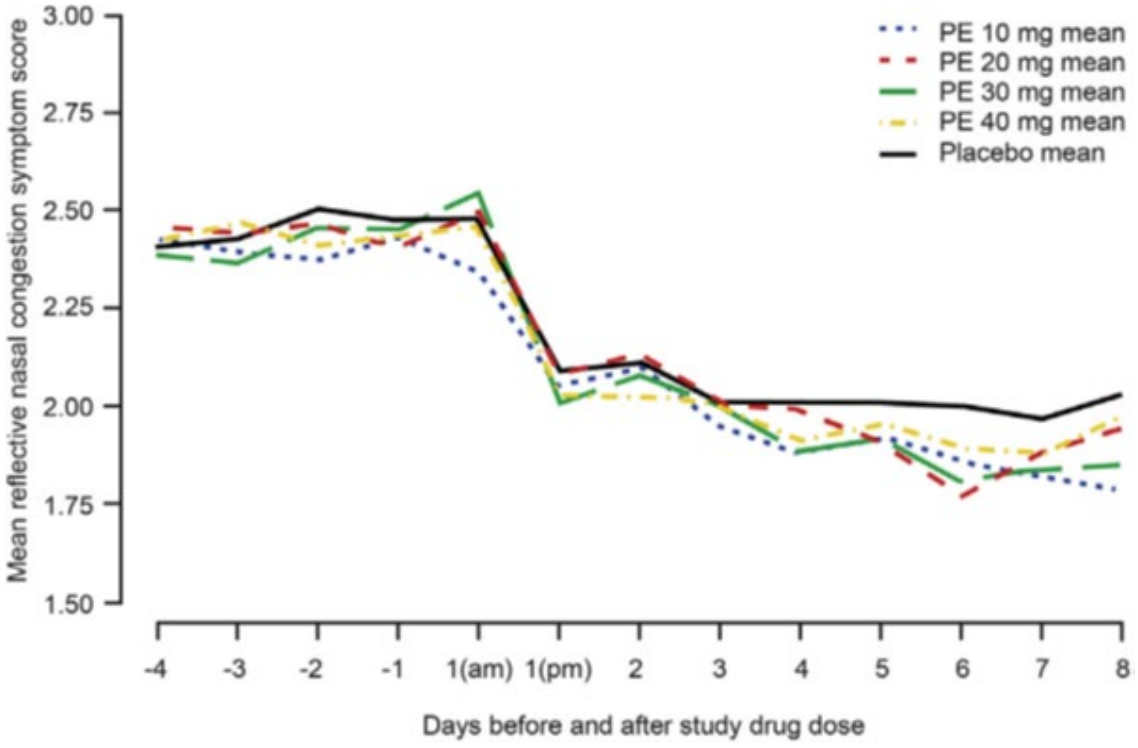

Figure: Meltzer et al. 2015 - Oral Phenylephrine HCl for Nasal Congestion in Seasonal Allergic Rhinitis: A Randomized, Open-label, Placebo-controlled Study.

Figure 2. Schering-Plough Protocol #CL2011-06. Mean Change From Baseline in Reflective Nasal Congestion Score Over the Entire Treatment Period (ITT Population)

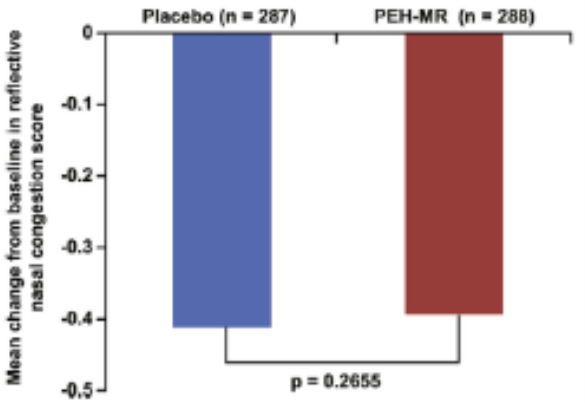

Figure: Meltzer et al. 2016 - Phenylephrine hydrochloride modified-release tablets for nasal congestion: a randomized, placebo-controlled trial in allergic rhinitis patients.

Figure 3. Geometric Mean Parent and Total Phenylephrine (PE) Pharmacokinetic Profile (N=42) Following 10 mg Single Oral Dose of Sudafed PE

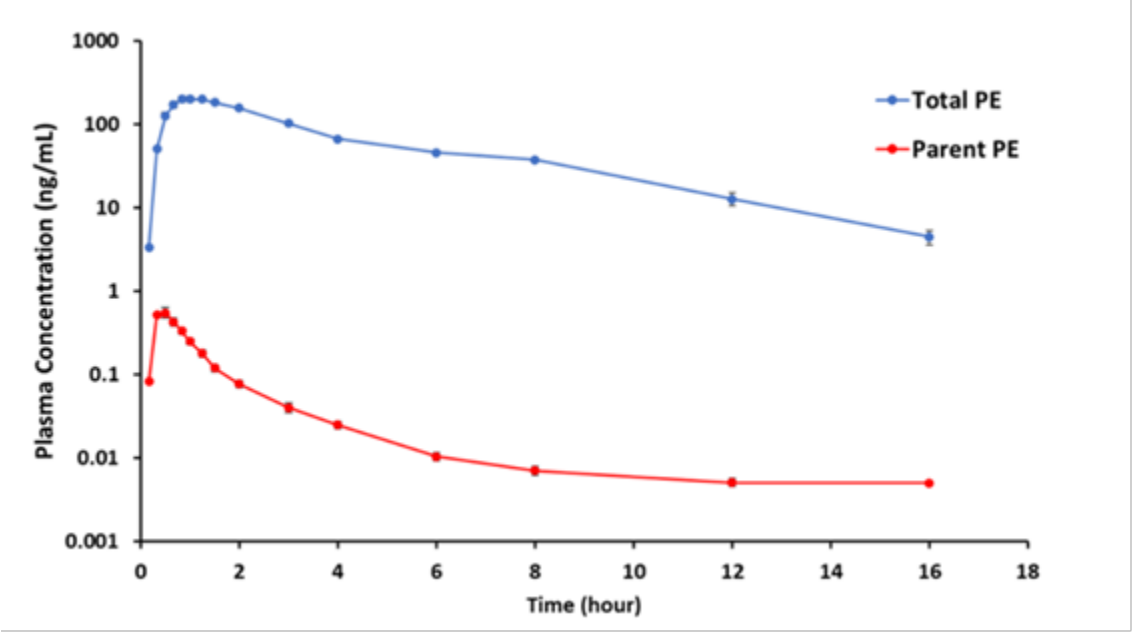

Figure: FDA Briefing Document – NDA 022565, Study 0813

Figure 4. National Annual Estimates of Bottles/Packages of Over-the-Counter Cough/Cold/Allergy Oral Products Containing Phenylephrine or Pseudoephedrine Sold from Manufacturers, 2000-2022

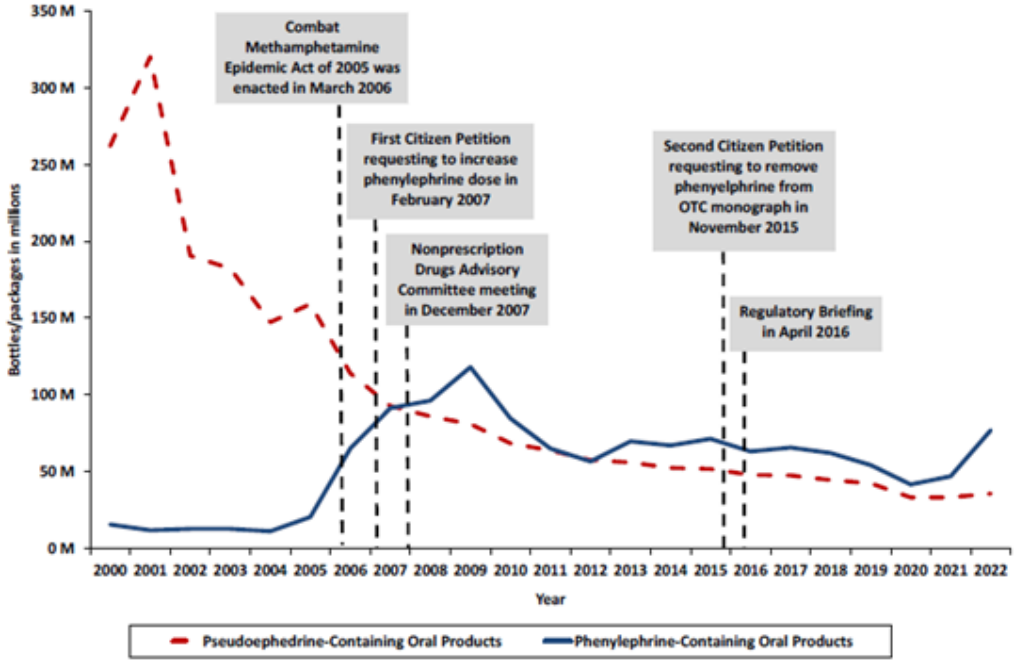

Figure: FDA Briefing Document - National Sales Perspectives™, 2000-2022

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