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May 7, 2025

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U.S. Food and Drug Administration
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Re: Amending Over-the Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Notice of Availability; 89 *Fed. Reg.* 88787 (November 8, 2024); Docket No. FDA-2024-N-4734[1]

Dear Dr. Brum:

On November 8, 2024, the United States (U.S.) Food and Drug Administration (FDA or the Agency) announced that it was taking regulatory action after reviewing all relevant information related to the efficacy of oral phenylephrine (PE) as an over-the-counter (OTC) nasal decongestant.[1] The *Federal Register* noted that the Agency's proposed administrative order (Proposed Order; Proposed Order OTC000036), if finalized as written, would amend Final Administrative Order OTC000026 to remove orally administered phenylephrine hydrochloride and phenylephrine bitartrate in effervescent dosage forms as nasal decongestant active ingredients due to lack of effectiveness.[2,3] In September 2023, FDA convened a meeting[4] of the Nonprescription Drugs Advisory Committee (NDAC or Committee) to discuss new data regarding the Generally Recognized As Safe and Effective (GRAS/E) status of oral phenylephrine as a

[1] FDA Amending Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human; 89 *Federal Register* 88787 (November 8, 2024). Accessed from https://www.govinfo.gov/content/pkg/FR-2024-11-08/pdf/2024-25910.pdf on November 11, 2024.

[2] Proposed Order (Order Number OTC000036). Order Title: Amending Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the Counter Human Use. Accessed from https://dps-admin.fda.gov/omuf/sites/omuf/files/primary-documents/2024-11/Proposed%20Administrative%20Order%20OTC%20000036%20-%20Amending%20OTC%20M012.pdf on January 25, 2025.

[3] FDA Proposed Order (Order Number OTC000036). Scientific Review for Proposed Administrative Order OTC000036 – Amending OTCM012 (Supporting Documents). Accessed from https://dps-admin.fda.gov/omuf/sites/omuf/files/supporting-documents/2024-11/Scientific%20Review%20for%20Proposed%20Administrative%20Order%20OTC000036%20-%20Amending%20OTC%20M012_0.pdf on January 25, 2025.

[4] September 11-12, 2023: Meeting of the Nonprescription Drugs Advisory Committee Meeting Announcement. Accessed from https://www.fda.gov/advisory-committees/advisory-committee-calendar/september-11-12-2023-meeting-nonprescription-drugs-advisory-committee-meeting-announcement-09112023 on November 11, 2024.

nasal decongestant that have become available since the Agency last examined this issue.[5,6]

The Consumer Healthcare Products Association[7] (CHPA) disagrees with the Agency's stated position that phenylephrine should no longer be recognized as GRAS/E as an oral OTC nasal decongestant within Final Administrative Order OTC000026. We also want to highlight that FDA stated in its NDAC briefing book prepared for the September meeting, that "…the Agency has not identified any safety issues with orally administered PE products."[8] Furthermore, we are providing rebuttals to the FDA stated positions concerning the largest cold study referenced in the Scientific Review supporting the Proposed Order OTC000036. CHPA respectfully requests the FDA withdraw its proposal to remove oral phenylephrine from the Final Administrative Order OTC000026 for the following reasons.

Scientific Evidence Supports Oral Phenylephrine as an Effective OTC Nasal Decongestant

CHPA maintains its position that scientific evidence, when taken in totality, supports oral PE as an effective nasal decongestant. We note the studies FDA highlights that appear to show a lack of efficacy were done exclusively in allergy. Our stated position and rationale have been outlined in previous submissions to the regulatory docket. We refer FDA to these filings to reiterate our disagreement with the Agency's proposal to remove phenylephrine from M012 as a permitted orally administered nasal decongestant:

1. CHPA Briefing Book from December 2007 Meeting of the Nonprescription Drugs Advisory Committee. Available at https://wayback.archive-it.org/7993/20170405052525/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-03-CHPA.pdf. Accessed November 11, 2024.
2. CHPA Briefing Book from September 2023 Meeting of the Nonprescription Drugs Advisory Committee. Available at https://www.fda.gov/advisory-

[5] Unless otherwise noted, any reference to phenylephrine in this briefing book pertains to oral dosage forms of the ingredient.

[6] Prior to the September 11-12, 2023, Nonprescription Drugs Advisory Committee (NDAC) meeting, the last FDA public discussion regarding the safety and efficacy of phenylephrine was a December 14 ,2007, meeting of the NDAC. NDAC members voted 11-1 that based on the available data that existed, there was evidence to support that 10 mg immediate release formulation [of PE] may be effective. See Question 2b (modified by the NDAC) in the FDA meeting minutes accessed from https://wayback.archive-it.org/7993/20170404050459/https://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4335m1-Final.pdf on November 11, 2024.

[7] CHPA is committed to empowering self-care by ensuring that Americans have access to products they can count on to be reliable, affordable, and convenient, while also delivering new and better ways to get and stay healthy. Visit www.chpa.org.

[8] FDA Briefing Document Efficacy of Oral Phenylephrine as a Nasal Decongestant Nonprescription Drugs Advisory Committee Meeting September 11 and 12, 2023 (see page 9). Accessed from https://www.fda.gov/media/171915/download on May 7, 2025.

committees/advisory-committee-calendar/updated-september-11-12-2023-meeting-nonprescription-drugs-advisory-committee-meeting-announcement#event-information. Accessed November 11, 2024.
3. CHPA Letter to the Docket on phenylephrine (and supporting documents) from the September 2023 Meeting of the Nonprescription Drugs Advisory Committee. Available at https://www.regulations.gov/comment/FDA-2023-N-2653-0008 under Docket No. FDA-2023-N-2653 (ID: FDA-2023-N-2653-0008). Accessed May 6, 2025.
4. Kenvue Inc. (previously the Consumer Healthcare division of Johnson and Johnson and now doing business in the U.S. under the subsidiary Kenvue Brands LLC) September 8, 2023, Letter to the Docket on phenylephrine for the September 2023 Meeting of the Nonprescription Drugs Advisory Committee. Available at https://www.regulations.gov/comment/FDA-2023-N-2653-0005 under Docket No. FDA-2023-N-2653 (ID: FDA-2023-N-2653-0005). Accessed May 6, 2025.

Additional Considerations to Support Continued Access to Oral Phenylephrine

Consumer-reported Data

Phenylephrine has played an important role in consumers' temporary self-treatment of nasal congestion and is the only available oral nonprescription medicine for nasal congestion that can be purchased without having to complete a logbook or show an official form of identification. When the FDA announced in 2023 that it would convene the NDAC to discuss the efficacy of oral PE as a nasal decongestant, CHPA members reviewed consumer data that could support the efficacy of this ingredient to augment efficacy data from clinical studies. In preparation for the September 2023 advisory committee meeting, CHPA members reviewed household panel data from April 2022 through April 2023 and found that half of the U.S. households rely on phenylephrine. Of these households, over two-thirds chose to repurchase medicines containing phenylephrine which suggests the purchaser found its effect sufficient to warrant another purchase.[9]

Furthermore, in a national consumer survey of 1200 adults age 21 and older, conducted by CHPA in July 2023, findings showed that American adults repeatedly rely on oral phenylephrine because they find it efficacious as a nasal decongestant and they see the physical and personal benefits of oral PE when they use it.[10] Over 80% of respondents indicated that PE helps relieve their "nasal or sinus congestion or pressure." Seventy-eight percent indicated the need for mild or moderate symptoms

[9] Circana (formerly IRI); all outlets, all doses; 52-week data April 2022 to April 2023.
[10] Bullfinch Group National Consumer Survey on Phenylephrine conducted for CHPA July 24-28, 2023. Accessed from https://www.chpa.org/sites/default/files/media/docs/2023-08/2023-PE-Survey.pdf on February 10, 2025.

relief.[10] And more than half of those 1200 surveyed indicated they "really need to have a pill or medicine" without a prescription or showing ID.[10] These survey respondents, and the overall healthcare system, would be significantly burdened if oral phenylephrine were not available OTC. This is especially true among older adults and people living in rural communities. Although the household panel study results collected from consumers do not technically meet the Agency's current definition of real-world data/real-world evidence (RWD/RWE)[11], CHPA believes this type of consumer data is, in fact, a form of RWD that should be considered within the totality of available evidence supporting the efficacy of oral phenylephrine as an OTC nasal decongestant.

Self-reported patient (*i.e.,* consumer) data and outcomes should not be ignored in the case of oral phenylephrine. In fact, via issuance of the proposed order, individual consumers (along with other interested stakeholders) were invited to provide their feedback on whether oral phenylephrine is an effective nasal decongestant using the current monograph dose to the official regulatory docket for the Agency's consideration. CHPA reviewed the comments posted to the regulatory docket prior to the closing of the open public comment period.[12] Individuals who chose to respond to the Agency's call for input on the proposed administrative order, which included consumers and healthcare professionals, predominantly disagreed with the Agency's decision to remove oral phenylephrine from the OTC monograph as an effective nasal decongestant.[13] This feedback should not be ignored simply because it was not collected from a randomized, double-blinded, placebo-controlled study.

Cohen 1975 Phenylephrine Efficacy Study (Largest Cold Study)

The Cohen (1975) study (BEI 1025 and 1025a; Ref #26 in: FDA OTC Volume 040288B) was a randomized, double-blind, placebo-controlled, multiple-dose parallel group study of 200 subjects with nasal congestion due to the common cold.[14] PE 10 mg was administered orally every 4 hours for 4 doses. Nasal airway resistance was determined using electronic posterior rhinometry in 50 subjects after the first dose, from 15 to 120 minutes, and the severity of nasal congestion and other cold symptoms were assessed by the subjects at designated times over the 12-hour observation period.

In the PE 10 mg group, subjects (n=100; 35 men/65 women) had a mean age of 50.8 years [range 16-83 years]. In the placebo group, subjects (n=100; 49 men/51 women)

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[11] See FDA Real World Evidence website. Accessed from https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence on February 6, 2025.
[12] Comments made publicly available through April 24, 2025, were reviewed.
[13] CHPA conducted a review of comments posted to www.regulations.gov before the regulatory docket closed. As of April 24, 2025, three hundred eighty-nine (389) comments were filed.
[14] Cohen BM. June 1975. Objective and subjective evaluation of phenylephrine HCl (5 mg) versus placebo tablets. In: FDA OTC Volume 040288B.

had a mean age of 52.8 years [range 13-78 years]. PE 10 mg produced significant reductions in nasal airway resistance compared to placebo from 15 to 120 minutes (11 to 28%; p≤0.05). Changes in subjective symptom scores for PE were significantly better than placebo for stuffy nose (p< 0.05).

FDA and Expert Panel Opportunity to Review the Cohen 1975 Study Protocols

In the 2023 Briefing Document[15] as well as in a more recent Scientific Review[16], FDA reviewed the largest phenylephrine efficacy study performed in subjects with the common cold (Cohen 1975). In the absence of locating specific FDA records at the time, the FDA raised several concerns related to study conduct and data analysis including controlling for bias, subjective scoring and whether clinically meaningful results were obtained.

FDA also noted that "*…the study protocol was not submitted to FDA for the FDA or the Panel to review*"[17] and that "*…the study protocols were first submitted to FDA by Consumer Health*[care] *Product*[s] *Association to the 2023 meeting docket.*"[18] Below we address each of the FDA's concerns noted above and provide evidence to demonstrate that the Expert Panel did in fact review the study protocols for Cohen 1975 when making a determination of the safety and efficacy of phenylephrine.

1976 Advanced Notice of Proposed Rulemaking (ANPR)

The 1976 ANPR, reflecting the view of the Expert Panel, describes the Cohen 1975 study in detail.[19] Two separate studies were performed – one with 50 subjects and another with 150 subjects. FDA noted that "*…it is likely that this particular study pushed the panel in favor of a positive recommendation for oral PE.*"[20]

March 14, 2012, Freedom of Information Act (FOIA) Request

A Freedom of Information Act request (sent by a CHPA member) was fulfilled by FDA on March 14, 2012.[21] This letter notes the following:

> Enclosed are the records you requested: (1) CD concerning memo

[15] FDA Briefing Document Efficacy of Oral Phenylephrine as a Nasal Decongestant Nonprescription Drugs Advisory Committee Meeting September 11 and 12, 2023.
[16] FDA, Scientific Review Supporting Proposed Administrative Order (OTC000036); November 4, 2024.
[17] Scientific Review Supporting Proposed Administrative Order; November 4, 2024; page 14.
[18] FDA, Scientific Review Supporting Proposed Administrative Order (OTC000036); November 4, 2024. Footnote 31, Page 14.
[19] This study (Reference 26 in the ANPR) was cited as" OTC Volume 040288B."
[20] September 11, 2023 FDA Briefing Document.
[21] This is the document that the Consumer Healthcare Products Association submitted to the phenylephrine docket in September 2023.

> from OTC volume 040288B, June 1975: Cohen BM, Objective and subjective evaluation of phenylephrine HCI (5 mg) versus placebo tablets.

This document (≈430 pages) includes separate protocols for both the 50 and 150 subject studies described in Cohen 1975 (OTC Volume 040288B). Although we cannot say with 100% certainty that this is the document reviewed by the Expert Panel and the FDA included these protocols, it does seem very likely that this information would have been available to both sets of reviewers.

Below, we address points initially raised by FDA in their September 2023 Briefing Document and reiterated in the November 2024 Scientific Review accompanying the Proposed Administrative Order regarding the rigor of the Cohen 1975 study.

> **FDA:** "… there were methodological and statistical issues with the study. The methodology to reduce bias and the scoring methodology were not specified, and no adjustments were made for multiplicity."

CHPA response: The study protocol, in addition to randomized allocation of patients to the treatments, describes techniques for bias control in the Methods section.[22] Point 4 describes a key aspect undertaken to reduce bias – "Neither the investigator or the patient or other personnel having contact with the patients will know the identity of the contents of the envelopes." The scoring methodology is described in the protocol. Multiplicity, though not performed, would not matter when p-values are so significant for all timepoints past 15 min (p-value≤ 0.001).

> **FDA:** "Since FDA was unable to review the protocol, an assessment of how symptoms were rated cannot be made. Baseline symptoms appear to be evaluated by both the subjects and the investigators and rated on a five-point scale, from mild to very severe, with improvement rated on a two-point scale with 0 being no change and 2 being much improved. However, FDA does not know the frequency of the scoring, whether it was instantaneous or reflective, and how much weight was placed on investigator judgement. While the study report notes that subjects who

[22] Protocol for a subjective placebo controlled study involving phenylephrine HCl tablets (5 mg.); Protocol BEI 1025b, page 3.

> experienced the largest magnitude of changes in NAR also experienced the largest magnitude of changes in symptom scores, it is unknown how much the investigator reporting of symptoms influenced those results."

CHPA response: In this specific paragraph, the Scientific Review accompanying proposed Administrative Order OTC000036 presents speculation concerning all of the items mentioned above. The protocol clearly describes the rating scale[23] and how frequently subjects were asked to record the effect of treatment on their initial cold symptoms.[24] Description in the FDA Briefing Document of both subjects and investigators scoring subjective is misleading.[25] Subjects rated their subjective symptoms at individual timepoints; the investigator did provide an initial and final symptom assessment but did not assess individual timepoints as noted in the Briefing Document.

> **FDA:** "The study did not specify what difference in absolute change might be clinically meaningful."

CHPA response: Study investigators did provide a description of clinically meaningful changes in the study report - "*…patients are most likely to notice desirable medical or biological changes in their own condition when the tests improve by a minimum of 20%.*"[26] Several references were cited in support of this statement. In the Cohen 1975 (BEI 1025) study, the reduction in nasal airway resistance (NAR) at 30, 60, and 120 minutes were within this range. Assessment of 'clinically meaningful' effects using a variety of metrics (anchor-based or distribution-based) was recently computed based on the Cohen 1975 subjective data. We observed clear evidence that not only are all timepoints past 15 minutes highly significant, but also clinically meaningful.

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[23] At baseline subjects scored symptoms to the following scale - 0=none; 1=mild; 2=moderate; 3=severe; 4 very severe. After treatment, subjects were asked to write down the number which most accurately described the effect that treatment had on their cold symptoms according to the following scale – 4 = not present; 3 = much better; 2 = moderately better; 1 = slightly better; 0 = no change; -1 = slightly worse; -2 = moderately worse; -3 = much worse; -4 = very severe.

[24] 0 min, 15 min, 30 min, 1 hour, 2 hours, 4 hours, 4.5 hours, 5.5 hours, 8 hours, 8.5 hours, 12 hours, 12.5 hours.

[25] In the Briefing Document, FDA notes that "Baseline symptoms appear to have been rated on a scale of 5 from mild to very severe, with improvement rated on a 0-2 scale with 0 being no change and 2 being much improved, and this evaluation appears to have been performed by both the subjects and investigators."

[26] See page 3 of the Final Report for BEI 1025 - "Evaluation of the effectiveness of phenylephrine HCl tablets (5 mg) in the relief of upper respiratory congestion and symptoms associated with the common cold in a 200 patient study conducted for Whitehall Laboratories."

Rebuttals to Additional Points Raised by FDA in the Scientific Review Supporting Administrative Order OTC000036

p.4 Section 2a FDA: "Data are lacking to support a correlation between improvement in NAR and clinical improvement in nasal congestion symptoms."

> **CHPA response**: Data supports the relationship in question. The Cohen 1975 (BEI 1025) final study report states that the reduction in nasal airway resistance was correlated with an increase in symptom relief. Furthermore, the Cohen 1972 publication reveals similar patterns for nasal airway resistance and subjective efficacy. Additionally, among 14 monograph studies, 7 demonstrated statistical significance regarding nasal airway resistance, with 5 of those also showing significance in subjective measures.

p.4 Section 2b FDA: "The common cold platform for studying nasal congestion is known to be highly variable, thereby introducing additional difficulty in obtaining consistent results in and across studies."

> **CHPA Response:** Despite the increased variability associated with cold studies, half of the monograph studies demonstrated significant findings in nasal airway resistance, with 5 out of the 7 significant NAR studies showing significance in subjective endpoints as well.

p.8 Section 3aii FDA: "The results from studies at the Elizabeth site could not be duplicated by studies at the two other Sterling-Winthrop sites (Cintest and Huntingdon), with the exception of Cintest 1. Additionally, the results from studies at the Elizabeth site could also not be duplicated by other investigators..."

> **CHPA Response:** Please note that Cohen conducted the largest cold study at Whitehall Laboratories (BEI-1025), which also demonstrated efficacy for phenylephrine at a dosage of 10 mg.

p.9 Section 3aii FDA: "Three of the positive studies, Elizabeth 2, Elizabeth 5, and Cintest 1 (see Table 2), all appear to have been outliers because their results do not match the results obtained in the other studies."

> **CHPA Response:** Labeling these three studies as outliers is an inappropriate use of statistical terminology. Half of the monograph cold studies demonstrated significance; further, conclusions about the efficacy of an active ingredient are based on the totality and quality of the data.

p. 48 Section V. FDA: "Furthermore, there are no clinical data demonstrating that oral PE is effective as a nasal decongestant at any dosage."

CHPA Response: Previously, both an Expert Panel (1976) and the FDA have confirmed the effectiveness of phenylephrine following a thorough review of the available studies. Considering that multiple cold monograph studies support the efficacy of phenylephrine, the assertion that there is no clinical data demonstrating the effectiveness of oral phenylephrine is not accurate.

Correction to §M012.80 Labeling of nasal decongestant drug products between proposed order and final administrative order needed.[27]

While comparing Proposed Order OTC000036 and Final Administrative Order OTC000026 (Monograph M012), CHPA noted a typographical error that would need to be corrected if FDA determines that phenylephrine should no longer be GRAS/E as an OTC monograph active ingredient.

Current text: §M012.80(b)(1) Labeling of nasal decongestant drug products in Final Administrative Order OTC000026 (Monograph M012)

> (1) (Select one of the following: "For the temporary relief of nasal congestion" or "Temporarily relieves nasal congestion") (which may be followed by any of the following in §§ M012.80(b)(1) (i) and (ii)):

Current text: §M012.80(b)(1) Labeling of nasal decongestant drug products in Proposed Order OTC000036

> (1) (Select one of the following: "For the temporary relief of nasal congestion" or "Temporarily relieves nasal congestion") (which may be followed by any of the following in §§ M012.80(b)(1)(i), (ii), and (iii)):

Technical correction to §M012.80(b)(1) Labeling of nasal decongestant drug products in Proposed Order OTC000036

> (1) (Select one of the following: "For the temporary relief of nasal congestion" or "Temporarily relieves nasal congestion") (which may be followed by any of the following in §§ M012.80(b)(1)(i)~~,~~ *and* (ii)~~, and (iii)~~):[28]

[27] FDA Over-the-Counter (OTC) Monograph M012: Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (Posted October 14, 2022). Accessed from https://dps-admin.fda.gov/omuf/sites/omuf/files/monograph-documents/2022-10/OTC%20Monograph_M012-Cough%20Cold%20Allergy%20Bronchodilator%20and%20Antiasthmatic%20Drug%20Products%20for%20OTC%20Human%20Use%2010.14.2022.pdf on May 7, 2025.

[28] Italicized text in blue (*e.g., sample text*) reflects revisions recommended by CHPA. Text with double strikethrough (*e.g.,* ~~sample text~~) reflects text recommended for deletion.

Factors to Consider When Establishing a Compliance Date Should FDA Issue a Final Order that Removes Phenylephrine from OTC Monograph M012

CHPA and its member companies are mindful of the potential market disruption that may occur should FDA issue a final order removing the GRAS/E status of PE as an oral decongestant. As noted above and as reflected in submitted comments, many consumers rely on PE to relieve their nasal congestion, whether it be as a single ingredient product or in combination with ingredients to relieve cough and cold symptoms. Should FDA's final order remove the GRAS/E status of PE, the order will include a date by which manufacturers must comply. CHPA expects the Agency to adhere to its proposed timing of one year (365 calendar days) from the date the final order is issued for the effective date.[2] The compliance date in final rules has historically prohibited the introduction of a misbranded or unapproved product into interstate commerce on or after the specified date. CHPA requests that any final administrative order that removes oral phenylephrine (as a permitted OTC oral nasal decongestant) explicitly states that products that are introduced into interstate commerce prior to the compliance date are not adulterated or misbranded. This will provide an opportunity for consumers who have had positive prior experience relieving their congestion with oral phenylephrine to make an orderly and informed decision about their self-care.

In considering a timeline for compliance with a final order that removes the GRAS/E status of PE, it is important to note that medicine supply chains are complex, and that reformulation and relabeling of combination products takes considerable time, typically at least 12-18 months. More time may be needed to conduct final stability testing.

In a typical year, major retailers will begin planning for the cough and cold season (defined as November through March, varying based on location) in June, July, and August. Planning for the 2025-2026 cough and cold season will begin no later than June 2025. At that time retailers will make major decisions about the products they will purchase and stock to ensure consumers have access to medicines to treat their symptoms during the colder months. Products will start to ship from the manufacturer to retail distribution centers shortly after the purchase orders are placed, thus setting in motion a complex supply chain.

Should a final order removing the GRAS/E status be issued during cough and cold season or contain a compliance date that falls within the season, it could potentially result in major disruptions in the market, which would be felt by the consumer at the retail level. Consumers who do find relief from oral PE should be afforded sufficient time to transition to alternative products. CHPA and its member companies that manufacture PE-containing products respectfully request FDA to consider these points as it develops a compliance timeline for a final order that removes the GRAS/E

status of PE, should one be issued, and allow for more time should a final order be issued with a compliance date that falls between November and March.

Summary

CHPA reiterates its position that the totality of the scientific evidence supports oral phenylephrine as an effective OTC nasal decongestant. Oral phenylephrine has been marketed in the United States for over 75 years and is also available globally. In the January 15, 1985, *Federal Register* notice, the Agency stated it had reviewed the information cited by the comment [Comment 10, page 2226 of the *Federal Register*[29]]:

> [Comment] 10. One comment questioned the studies used by the Panel to substantiate the effectiveness of phenylephrine hydrochloride as an oral nasal decongestant. The comment stated that numerous unpublished studies, which split evenly between mild successes and total failures, were quoted by the Panel, and in the one study (Ref. 1) published in an academically acceptable journal, no efficacy was seen even with doses higher than usually recommended. In addition, the comment cited two references which questioned the oral bioavailability of phenylephrine hydrochloride (Refs. 2 and 3). The comment recommended that phenylephrine hydrochloride not be used as an oral nasal decongestant.
>
> The Panel concluded that phenylephrine hydrochloride was effective as an oral nasal decongestant after a thorough review of published and unpublished studies, oral and written submissions by manufacturers, and evaluations of clinical and marketing experience. The published study referred to by the comment (Ref. 1) is discussed in comment 11 below. The Panel was aware of one of the references that the comment cited as questioning the oral bioavailability of phenylephrine hydrochloride (Ref. 3), and cited this reference is discussing the safety of phenylephrine hydrochloride (41 FR 38399). This study is not relevant to the effectiveness of phenylephrine hydrochloride, but does confirm the potentiation of the effect of oral phenylephrine by a monoamine oxidase inhibitor.
>
> The agency has reviewed the information cited by the comment, the Panel's recommendations, and all of the supporting data and concludes that, based on the studies cited by the Panel, information on clinical use and marketing

[29] FDA 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; Notice of Proposed Rulemaking (January 15, 1985). 50 *Federal Register* 2220-2241. Accessed from https://archives.federalregister.gov/issue_slice/1985/1/15/2198-2241.pdf on May 4, 2025. See page 2226 of the *Federal Register* notice.

> experience, and the Panel's expertise in evaluating the clinical-and marketing experience of this ingredient, there is sufficient basis to determine the phenylephrine hydrochloride is generally recognized as effective for OTC use as an oral nasal decongestant. The comment's recommendation is therefore not accepted.[29]

FDA affirmed the GRAS/E (*i.e.*, generally recognized as safe and effective) status of oral phenylephrine when it issued the final rule for the cough cold monograph.[30] Furthermore, in announcing the 2024 proposed order to amend the final monograph, the Agency acknowledged that there were no concerns with safety identified with the use of oral phenylephrine as an OTC nasal decongestant. For these reasons, CHPA does not support FDA's proposal to remove phenylephrine as an oral nasal decongestant from OTC Monograph M012.

We strongly urge FDA to reconsider its position of removing oral PE from the OTC Monograph M012 and withdraw the proposed order so those consumers who do find the ingredient to be effective for their symptoms and experience temporary relief of bothersome nasal congestion can purchase these products when needed. Consumers for whom phenylephrine is effective should have continued access to those products as they have for decades. This is no different from any other FDA-regulated drug product. Not every drug is effective for every patient or consumer who uses it. It bears repeating that there are no safety concerns at monograph dosages of phenylephrine. Additionally, as shown by consumer comments to the docket, many consumers do find phenylephrine to be efficacious for their congestion. Removal of oral phenylephrine from the OTC monograph would have negative unintended consequences for consumers who rely on it and diminish their choice of OTC nasal decongestant treatments.

Sincerely,

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[30] FDA Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Nasal Decongestant Drug Products, Final Rule (August 23, 1994; 59 *Federal Register*; Docket No. 04-20456). Accessed from https://www.govinfo.gov/content/pkg/FR-1994-08-23/html/94-20456.htm on April 7, 2025.