Comments of the American College of Clinical Pharmacy to the Food and Drug Administration related to Proposed Administrative Order (OTC000036) "Amending Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use."

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The American College of Clinical Pharmacy (ACCP) appreciates the opportunity to provide the following statement to the Food and Drug Administration (FDA) related to the proposed administrative order (proposed order) (OTC000036) entitled "Amending Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use."

ACCP fully supports this proposed order that will, if finalized, amend Final Administrative Order OTC000026, to remove orally administered phenylephrine hydrochloride and phenylephrine bitartrate in an effervescent dosage as nasal decongestant active ingredients because they are not effective.

The American College of Clinical Pharmacy is a professional society representing more than 16,000 clinical pharmacy practitioners, scientists, educators, administrators, students, residents and fellows committed to excellence in clinical pharmacy. The College's mission is to improve human health. This mission relies on the foundation of clinical pharmacy – namely, the science and practice of rational medication use.

Since its passage in 1962, the Kefauver-Harris Drug Amendments to the Federal Food Drug and Cosmetic (FD&C) Act have required that both prescription and nonprescription drugs must be safe and effective for their labeled indication.[1] For over-the-counter (OTC) nonprescription drugs, the monograph system was established in 1972 to evaluate drugs on the market before the FD&C Act was passed.[2] However, ineffective nonprescription drugs remain on the market 50 years after establishing the OTC monograph system.[3]

Oral phenylephrine (PE), phenylpropanolamine (PPO), and pseudoephedrine (PSE) were determined to be safe and effective for nonprescription therapy of nasal congestion by a 1976 Food and Drug Administration panel (FDA).[4]

Although both are sympathomimetic amines, their efficacy varies. In particular, phenylephrine is subject to first-pass metabolism and therefore is not bioavailable in currently recommended doses.[5]

In 2005, Congress passed the Combat Methamphetamine Epidemic Act in response to growing concern that PSE was used to illegally manufacture methamphetamine that required all retail

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[1] Goodrich WW. A look into the nooks and corners of the Kefauver-Harris Drug Amendments of 1962. Bus Law. 1963;18:187-192

[2] Over-The-Counter (OTC) Drug Monograph Process. United States Food and Drug Administration. Current as of September 3, 2020. Accessed September 5, 2023. /

[3] Weinberger M, Hendeles L. Nonprescription medications for respiratory symptoms: facts and marketing fictions. Allergy Asthma Proc. 2018;39:169-176. doi:10.2500/aap.2018.39.4117

[4] Department of Health, Education, and Welfare. Food and Drug Administration. Establishment of a monograph for over-the-counter (OTC) cold, cough, allergy, bronchodilator, and anti-asthmatic products. Fed Regist 1976;41:38399- 400. https://www.federalregister.gov/documents/2005/07/13/05-13708/cold-cough-allergy-bronchodilator-and-antiasthmatic-drug-products-for-over-the-counter-human-use

[5] Hendeles L. Selecting a decongestant. Pharmacotherapy. 1993 Nov-Dec;13(6 Pt 2):129S-134S; discussion 143S-146S. PMID: 7507590

stores nationwide to keep products containing PSE "behind the counter."[6] Consequently, since PE cannot be converted to methamphetamine and can be sold without restrictions, the manufacturers of OTC oral cough, cold and allergy products have substituted PE for pseudoephedrine in their over-the-counter products.

Phenylephrine is now a major ingredient in oral OTC products marketed for treatment of upper respiratory congestion. Although it is found in 261 such products,[7] published peer-reviewed research has demonstrated no clinically significant decongestant effect in patients with nasal congestion from seasonal allergic rhinitis, even in doses up to 40 mg, four times the FDA-approved OTC dose.[8]

The Coronavirus Aid, Relief, and Economic Security (CARES) Act of 2020 included the first major overhaul to the original OTC monograph process since it was established.[9] These changes facilitate the review of existing nonprescription drugs to assess their safety and effectiveness.

As articulated in a 2015 citizens' petition[10] and demonstrated by numerous studies and analyses,[8,11, 12]oral phenylephrine is ineffective at the doses employed in current over-the-counter (OTC) products available in the United States. As noted, phenylephrine is the most common ingredient in oral OTC products marketed for treatment of nasal congestion and sinus symptoms. However, due to its poor bioavailability, sufficient phenylephrine concentrations never reach the patient's systemic circulation. Hence, consumers are regularly purchasing FDA-approved products that clearly don't work.

Despite evidence that oral phenylephrine is ineffective as a decongestant, the US Food and Drug Administration (FDA) has failed to remove it from the OTC nasal decongestant monograph. The OTC monograph system must assure consumers that all drugs on the market are effective. ACCP therefore calls on the FDA to remove oral OTC products containing phenylephrine from the market.

Removal of oral phenylephrine will not deprive patients of effective treatment; there are several effective OTC products available. For patients who have nasal congestion from the common

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[6] Combat Methamphetamine Epidemic Act of 2005 (H.R.3889,TitleVII). https://www.congress.gov/bill/109th-congress/house-bill/3889

[7] McCoul ED. Assessment of pharmacologic ingredients in common over-the-counter sinonasal medications. Otolaryngol Head Neck Surg. 2020;146(9):810-815. doi:10.1177/0194599820969177

[8] Meltzer EO. Ratner PH, McGraw T. Oral phenylephrine HCl for nasal congestion in seasonal allergic rhinitis: a randomized, open-label, placebo controlled study. J Allergy Clin Immunol Pract. 2015; 3:702–708

[9] Over-The-Counter (OTC) Drug Review—OTC Monograph Reform in the Cares Act. US Food and Drug Administration. Current as of November 23, 2021. Accessed September 5, 2023

[10] Hendeles L, Hatton RC. Citizens' Petition-2015-P-4131-0001, Requesting a Final Rule Removing Oral Phenylephrine from the Final Rule Removing Oral Phenylephrine from the Final Monograph for OTC Nasal Decongestant Products.

[11] Horak F, Zieglmayer P, Zieglmayer R, et al. A placebo-controlled study of the nasal decongestant effect of phenylephrine and pseudoephedrine in the Vienna challenge chamber. Ann Allergy Asthma Immunol 2009;102:116-20

[12] Day JH, Briscoe MP, Ratz JD, Danzig M, Yao R. Efficacy of loratadine-montelukast on nasal congestion in patients with seasonal allergic rhinitis in an environmental exposure unit. Ann Allergy Asthma Immunol 2009;102:328-338

cold, phenylephrine nasal spray[13] or the longer acting oxymetazoline provide near instant relief. For patients who have nasal congestion from allergies, maintenance therapy with nasal corticosteroids[14] or nasal azelastine,[15] an antihistamine/mast cell stabilizer, are highly effective and oral pseudoephedrine is readily available behind the counter for both types of patients ≥ 18 yr.

Summary

We thank you for the opportunity to provide input on the proposed order proposed order (OTC000036) entitled "Amending Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use." We hope you will act with urgency to remove oral OTC products containing phenylephrine from the market.

[13] Dressler WE, Myers T, Rankell AS, London SJ, Poetsch CE. A system of rhinomanometry in the clinical evaluation of nasal decongestants. Ann Otol Rhinol Laryngol. 1977 May-Jun;86(3 Pt 1):310-7. doi: 10.1177/000348947708600306. PMID: 68703.

[14] Di Lorenzo G, Pacor ML, Pellitteri ME, Morici G, Di Gregoli A, Lo Bianco C, Ditta V, Martinelli N, Candore G, Mansueto P, Rini GB, Corrocher R, Caruso C. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. Clin Exp Allergy. 2004 Feb;34(2):259-67. doi: 10.1111/j.1365-2222.2004.01877.x. Erratum in: Clin Exp Allergy. 2004 Aug;34(8):1329. PMID: 14987306.

[15] Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, Munzel U, Bousquet J. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012 May;129(5):1282-1289.e10. doi: 10.1016/j.jaci.2012.01.077. Epub 2012 Mar 13. PMID: 22418065.