Briefing Book

Meeting of the Nonprescription Drugs Advisory Committee
September 11-12, 2023
[Docket No. FDA-2023-N-2653]

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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1.0 EXECUTIVE SUMMARY

The United States (U.S.) Food and Drug Administration (FDA or the Agency) is convening a meeting[1] 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 (PE) as a nasal decongestant that have become available since the Agency last examined this issue.[2,3] Phenylephrine is a safe and effective over-the-counter (OTC) ingredient marketed in both single ingredient and combination products.[4] It has been available in the United States more than 75 years and globally (*e.g.*, Canada, Australia, UK). The efficacy and safety of PE has undergone multiple rigorous reviews undertaken by expert scientific bodies and FDA. Each of these deliberations has confirmed the GRAS/E status of oral PE (10 mg) for its labeled indications (*i.e.,* the temporary relief of nasal congestion due to the common cold, hay fever or other respiratory allergies, or allergic rhinitis) under the cough, cold, allergy, bronchodilator, and anti-asthmatic drug products monograph ("final monograph" or "CCABADP").[5]

In response to a citizen petition, the FDA reviewed the GRAS/E status of PE.[6] At a 2007 NDAC meeting, held in response to the 2007 citizen petition, the Committee noted that the available data were supportive of the efficacy of 10 mg PE, but several NDAC members also voted in support of additional studies to assess the safety and efficacy of higher doses. No changes to the marketing status of PE under the monograph were recommended by the NDAC in 2007 and PE's GRAS/E status has remained unchanged since.

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[1] September 11-12, 2023: Meeting of the Nonprescription Drugs Advisory Committee Meeting Announcement posted on June 14, 2023. Accessed from https://www.fda.gov/advisory-committees/advisory-committee-calendar/september-11-12-2023-meeting-nonprescription-drugs-advisory-committee-meeting-announcement-09112023 on June 27, 2023.

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

[3] The last FDA public discussion regarding the safety and efficacy of phenylephrine was a meeting of the Nonprescription Drugs Advisory Committee (NDAC) in December 2007.

[4] The term "phenylephrine" (PE) is used interchangeably for the hydrochloride and bitartrate salts unless otherwise noted.

[5] Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Drug Products for the Over-the-counter Human Use; Amendment of the Monograph for OTC Nasal Decongestant Drug Products. Accessed from https://www.govinfo.gov/content/pkg/FR-2006-08-01/pdf/E6-12265.pdf on June 29, 2023. This final monograph is now recognized as Administrative Order OTC000026 or OTC Monograph ID M012 (published October 14, 2022).

[6] See Appendix 1, Table A1-1 for additional description of the citizen petitions (and supplements to those petitions) submitted to FDA in 2007 and 2015.

Subsequently, in a November 2015 citizen petition,[7] supported by supplemental submissions in 2015[8] and 2022,[9] two authors from the 2007 citizen petition requested that the Agency remove oral PE from the Final Monograph for OTC nasal decongestant drug products. Citing studies examining PE efficacy and pharmacokinetics, the Petitioners made the following claims:

- Results from four efficacy studies in subjects with seasonal allergic rhinitis (SAR)[10,11,12,13] demonstrate that PE is no more effective than placebo in decreasing nasal congestion.
- Additional plasma concentration data from published pharmacokinetic studies[14,15,16] are consistent with a lack of efficacy due to PE having low oral bioavailability.
- Lack of clinically important adverse effects on blood pressure at the doses evaluated in these pharmacokinetic studies are consistent with a lack of efficacy.
- Because *in vitro* data show the nasal vasculature in man and the pig are less sensitive to PE than the extranasal vasculature, there is no pharmacological basis for oral PE to alleviate symptoms of nasal congestion without attendant peripheral side effects.

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[7] Hendeles L, and Hatton RC 2015. Request to remove oral phenylephrine from the Final Monograph for OTC nasal decongestant products. Submitted to Docket; November 4, 2015.

[8] Wilson VG, Abdulrahman A, Yahya S, Beed M, and Mahajan R. Supporting Evidence for Citizen's Petition. Submitted to Docket FDA-2015-P-4131; November 6, 2015.

[9] Leslie Hendeles and Randy C. Hatton, 2022. Supplement to Oral Phenylephrine Citizen's Petition (FDA 2015-P-4131).

[10] Day JH, Briscoe MP, Ratz JD, *et al*. Efficacy of loratadine-montelukast on nasal congestion in patients with seasonal allergic rhinitis in an environmental exposure unit. *Ann Allergy Asthma Immunol*. 2009;102(4):328-38.

[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(2):116-20.

[12] 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(5):702-708.

[13] Meltzer EO, Ratner PH, McGraw T. Phenylephrine hydrochloride modified-release tablets for nasal congestion: a randomized, placebo-controlled trial in allergic rhinitis patients. *Ann Allergy Asthma Immunol*. 2016;116(1):66-71.

[14] Atkinson HC, Stanescu I, Salem II, *et al*. Increased bioavailability of phenylephrine by co-administration of acetaminophen: results of four open-label, crossover pharmacokinetic trials in healthy volunteers. *Eur J Clin Pharmacol*. 2015;71:151–158.

[15] Gelotte CK, Zimmerman BA. Pharmacokinetics, Safety, and Cardiovascular Tolerability of Phenylephrine HCl 10, 20, and 30 mg After a Single Oral Administration in Healthy Volunteers. *Clin Drug Investig*. 2015;35:547–558.

[16] Gelotte CK. An open-label, randomized, four-treatment crossover study evaluating the effects of salt form, acetaminophen, and food on the pharmacokinetics of phenylephrine. *Reg Tox Pharmacol*. 2018;95:333-338.

The Consumer Healthcare Products Association[17] (CHPA) Phenylephrine Task Group[18] ("Task Group") disagrees with the Petitioners' claims that new data demonstrate that PE is not an effective nasal decongestant.[19] The efficacy studies cited by the Petitioners have inherent methodological aspects that render them inappropriate to serve as the basis for changing the GRAS/E classification of PE for the treatment of temporary nasal congestion (See Section 5.3). In fact, the final results from two of these trials, S-P 04579[11] (Horak *et al.*, 2009) and Study S-P 4822[10] (Day *et al.*, 2009), were previously discussed at the 2007 NDAC meeting and did not result in a change of the GRAS/E status for PE. As such, these newer results do not negate the conclusions of previous findings of efficacy.

In Section 4.3, misconceptions of new clinical pharmacology and nonclinical PE data are discussed. The Petitioners' claims that low oral bioavailability and plasma concentrations, and minimal effects on blood pressure indicate a lack of PE efficacy are not accurate. Many approved drugs have low bioavailability and still show efficacy because multiple factors, such as drug concentration at the active site, potency, receptor sensitivity, and intracellular mediators, have significant roles in determining efficacy.

An additional claim, made in a Supplement[8] to the 2015 Petition, that PE's higher *in vitro* potency to contract peripheral vasculature relative to nasal vasculature negates the expectation of oral PE achieving nasal decongestion without attendant peripheral side effects (*i.e.*, blood pressure elevation) is flawed. This claim improperly conflates a drug's potency (based on *in vitro* bioassay data) with efficacy (based on *in vivo* clinical data). Potency studies measure one endpoint in relation to drug dose or concentration, whereas clinical efficacy measures the therapeutic benefit brought about by a whole cascade of complex interactions among various tissues and mediators.[20]

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[17] The Consumer Healthcare Products Association (CHPA), founded in 1881, is the national trade association representing the leading manufacturers and marketers of consumer healthcare products, including over-the-counter (OTC) medicines, dietary supplements, and consumer medical devices. 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.

[18] The information provided in this document reflects the collective views of the following CHPA member companies that currently market products containing phenylephrine: Bayer Consumer Health; Foundation Consumer Healthcare, LLC; Haleon (formerly GlaxoSmithKline Consumer Healthcare); Kenvue (formerly Johnson & Johnson Consumer, Inc.); Lil' Drug Store Products, Inc.; Perrigo Company; Reckitt; Sanofi Consumer Healthcare; and the Procter & Gamble Company.

[19] Hatton RC and Hendeles L. Why Is Oral Phenylephrine on the Market After Compelling Evidence of Its Ineffectiveness as a Decongestant? *Annals Pharmacother*. 2022.

[20] Waldman SA. Does potency predict clinical efficacy? Illustration through an antihistamine model. *Ann Allergy Asthma Immunol* 2002;89:7–12.

Results from multiple randomized, placebo-controlled trials have shown PE 10 mg to be effective in temporarily relieving nasal congestion in adults (See Section 5.5). In addition, to further support GRAS/E marketing status, the safety of PE is established by a long marketing history, multiple analyses of post-marketing adverse event data demonstrating no safety concerns, and additional data from recent clinical and pharmacokinetic studies.

Consistent with previous determinations made by the FDA expert advisory review panel, the Agency, and the 2007 NDAC, the CHPA Task Group maintains its position that no changes to the GRAS/E status of PE for its labeled indications are warranted based on data made available since the previous review in 2007. The totality of the scientific evidence continues to demonstrate that PE 10 mg is a safe and effective OTC oral nasal decongestant and should remain readily available to consumers for the temporary relief of nasal congestion.

2.0 INTRODUCTION

2.1   Pathophysiology of Nasal Congestion

In the common cold and allergic rhinitis, congestion develops secondary to engorgement of the cavernous venous sinusoids in nasal turbinates, which leads to tissue swelling, reduced internal nasal diameter, and increased resistance to air flow.[21] The basic physiology associated with nasal congestion is substantially similar in children and adults.

There is no difference in the localized physiologic response, whether the inciting trigger is an allergen, infectious agent, or irritant. Nasal congestion is the result of the effect of local mediators by direct or reflex action on nasal blood vessels or on sympathetic nerve terminals.[22] During this vascular process, the nasal mucosa swells leading to congestion, impeding the sense of free breathing.

Figure 2-1 Nasal Anatomy and Function of Venous Sinusoids Inside the Turbinates
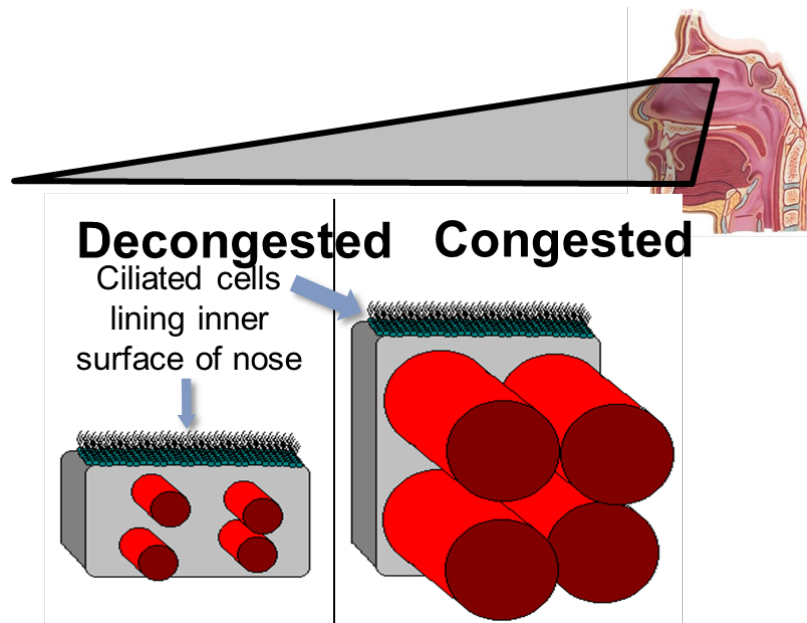
Unpublished image.

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[21] Gentile DA, Friday GA, and Skoner DP. Management of allergic rhinitis. *Immunol Allergy Clin North Amer.* 2000;20:335-368.

[22] Naclerio RW, Bachert C, and Baraniuk JN. Pathophysiology of nasal congestion. *Int J Gen Med.* 2010;3:47-57.

2.2   Importance of Consumer Access to Oral Phenylephrine

Nasal congestion has been found to be the most bothersome and most frequently reported symptom associated with the common cold and allergic rhinitis.[23,24] Nasal congestion also has significant negative impacts on the sufferer and can contribute to negative impact on daily activity, productivity, and absenteeism.[25] It can lead to potential medical complications such as sinusitis, nasal polyps, middle ear infections, and impaired olfaction if left untreated.[26,27] Hence the importance of consumers having direct, on-shelf access to safe, effective nasal decongestants.

OTC topical[28] and oral nasal decongestants provide rapid and effective relief of nasal congestion. While topical decongestants provide a faster and more profound decrease in nasal airway resistance, they have the potential to produce rebound congestion[29] and abuse. The oral dosage form for PE does not have these challenges and is often the preferred route of administration for many consumers.

There are currently only two OTC, oral nasal decongestant active ingredients allowed in the final monograph, phenylephrine, and pseudoephedrine. For pseudoephedrine, federal law does not allow direct access to products before a sale is made; requires registered sellers to maintain records of sales and record identification information on purchasers; and limits the amount of pseudoephedrine that can be sold in a single sale or to a given purchaser in a month.[30] Further, manufacturers of pseudoephedrine-containing medicines must apply for an annual quota for their active pharmaceutical ingredient supplies.[30] These limitations can

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[23] Cleveland Clinic. Nasal Congestion, available at https://my.clevelandclinic.org/health/symptoms/17980-nasal-congestion. Accessed July 22, 2023.

[24] Blaiss MS, Dicpinigaitis PV, Eccles R, Wingertzahn MA. Consumer attitudes on cough and cold: US (ACHOO) survey results. Curr Med Res Opin 2015;1-12.

[25] Dicpinigaitis PV, Eccles R, Blaiss MS, Wingertzahn MA. Impact of cough and common cold on productivity, absenteeism, and daily life in the United States: ACHOO Survey. *Curr Med Res Opin.* 2015;31(8):1519-1525.

[26] Nathan R. The burdens of allergic rhinitis. *Allergy Asthma Proc.* 2007;28:3-9.

[27] Masood A, Moumoulidis I, Panesar J. Acute rhinosinusitis in adults: an update on current management. *Postgrad Med J.* 2007 Jun;83(980):402-8.

[28] Predominantly naphazoline, oxymetazoline, phenylephrine, propylhexedrine, and xylometazoline.

[29] Mortuaire G, de Gabory L, François M, Massé G, Bloch F, Brion N, Jankowski R, Serrano E. Rebound congestion and rhinitis medicamentosa: nasal decongestants in clinical practice. Critical review of the literature by a medical panel. *Eur Ann Otorhinolaryngol Head Neck Dis.* 2013 Jun;130(3):137-44.

[30] 21 U.S.C 830 (2022). See also "General Information Regarding The Combat Methamphetamine Epidemic Act of 2005 [Title VII of Public Law 109-177]" ("Combat Meth Act") for a general discussion of these requirements, accessed from https://www.deadiversion.usdoj.gov/meth/cma2005_general_info.pdf on July 8, 2023.

negatively impact consumers who want easy access to a medication that provides temporary relief of their nasal congestion.

Therefore, it is important that consumers have direct, on-shelf access to phenylephrine as a safe, effective oral nasal decongestant since symptom severity, product availability (both the number of product options and the availability of stores that offer them), and consumer preference may vary. Consumers are aware of these options and have been shown to rely on oral PE products for their temporary relief of nasal congestion. This is supported by findings from a nationally representative household panel collecting information on their purchases through data collected over a 52-week span. Data show that OTC medications containing PE are frequently chosen for the treatment of nasal congestion.[31] Just over 50% of 100,000 U.S. households purchased an OTC medicine containing PE. Of these purchasers, 67.7% were repeat buyers, who purchased PE-containing medicines on approximately four different occasions during that 52-week period.[31]

In conclusion, oral OTC medications containing PE are approved as safe and effective treatments to help temporarily relieve nasal congestion. They have a long history of safe and effective use, both in the US and globally. Further, consumers rely on them for temporary relief of their congestion due to colds, allergic rhinitis, and upper respiratory infections. Therefore, OTC medicines containing PE for the temporary treatment of nasal congestion should remain available to consumers at the store shelf and online.

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[31] Circana, using National Consumer Panel data (collected 52 weeks ending April 9, 2023). The National Consumer Panel is a joint venture of NielsenIQ and Circana. It includes over 100,000 U.S. households who agree to scan purchases or complete diaries on consumer package goods purchases they bring into their households. Participating households are recruited to provide a representative sample of U.S. consumers. Unpublished data obtained by CHPA on April 21, 2023.

3.0 KEY REGULATORY ACTIVITIES RELATED TO OTC ORAL NASAL DECONGESTANTS

3.1 Rulemaking

The OTC Monograph System, also called the OTC Drug Review, was established in 1972 as a scientific process for FDA to use expert advisors to systematically and efficiently review the data and literature of hundreds of established ingredients already used in thousands of medications marketed at that time. OTC monographs establish conditions, including the active ingredients, uses or indications, doses, routes of administration, labeling, and testing requirements, that must be met for a particular therapeutic category.[32]

As part of the OTC Drug Review, when FDA's expert advisors found there were sufficient data to confirm the safety and effectiveness of an ingredient, that ingredient was included in the relevant monograph as Category 1. Ingredients designated as Category 1 are referred to as "generally recognized as safe and effective," or "GRAS/E." Products that adhere to the regulatory requirements of the monograph for being GRAS/E can be legally marketed without seeking prior approval from the Agency. Manufacturers do not need to submit additional clinical data if the product is sold for the permitted indications.

On December 23, 2002, FDA issued a final rule that explained the GRAS/E ingredients that could be used to make combination products for OTC cough and cold products. To establish this combination product rule, FDA reviewed new data and information on these types of products submitted by interested stakeholders.[33]

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[32] The FDA expert advisors also classified other active ingredients under review as Category II (*i.e.,* not GRAS/E) such as mustard oil and oral turpentine oil, and some as Category III (*i.e.,* data are insufficient to permit a final classification), for example oral ephedrine. See 41 *Fed. Reg.*38147 (September 9, 1976). Accessed from https://tile.loc.gov/storage-services/service/ll/fedreg/fr041/fr041176/fr041176.pdf#page=134 on July 30, 2023.

[33] Of note, based on sales data provided to CHPA in preparation for this NDAC meeting, most of the products marketed with oral phenylephrine are combination products used to treat the symptoms caused by the common cold or flu (>95%).

On October 11, 2005, the Agency issued a final rule prohibiting manufacturers from using the sinusitis claim on the product packaging on the basis that:

1. Prospective studies on the role of nasal decongestants in the treatment of sinusitis were lacking and the data on their use as an adjunct in treatment of sinusitis were limited and controversial. The Agency acknowledged that healthcare providers might recommend or prescribe these products as adjunctive therapy for sinusitis, but this should not be construed as evidence that consumers could self-diagnose or self-manage this condition.
2. There was also preclinical evidence that topical nasal decongestants may have a negative effect on the resolution of sinusitis as they may increase the degree of sinus inflammation.

To date, since the removal of the sinusitis claim, no changes to the label directions for phenylephrine as an oral nasal decongestant for the temporary relief of nasal congestion in OTC medicines have been made.

The formality of converting the final monograph to an administrative order was completed on October 14, 2022, as part of implementation of OTC monograph reform under the Coronavirus Aid, Relief, and Economic Security Act (CARES) Act of 2020. This conversion was a technical change only as no changes to any marketing conditions, including GRAS/E status, were made.

Table 3-1 Summary of Key Regulatory Actions Related to Oral Phenylephrine

Date	Regulatory Status	Phenylephrine Salt	GRAS/E Status
September 9, 1976	Advanced Notice of Proposed Rulemaking	Hydrochloride	Proposed Category 1
January 15, 1985	Tentative Final Monograph	Hydrochloride	Proposed Category 1
August 23, 1994	Final Rule (Original Active Ingredients & Labeling)	Hydrochloride	Category 1
December 23, 2002	Final Monograph (Combination Products Rule; CCABACP)	Hydrochloride	Category 1 (Combined with other cough cold ingredients)
November 2, 2004	Proposed Rule	Bitartrate	Proposed Category 1
October 11, 2005	Final Rule	Multiple Ingredients (including PE)	Removed sinusitis claim
August 1, 2006	Final Rule	Bitartrate	Category 1 (Effervescent tablet)
October 14, 2022	Final Order	Multiple Ingredients (including PE)	Converted CCABADP to Administrative Order

Note: Category 1 ingredient = GRAS/E or Generally recognized as safe and effective

3.2 Citizen Petitions and Supplemental Information

Since 2007, there have been two citizen petitions filed by the same group of researchers based at the University of Florida (see Appendix 1). In response to the first citizen petition, FDA held an NDAC meeting in December 2007 to discuss the safety and effectiveness of phenylephrine hydrochloride and phenylephrine bitartrate as OTC oral nasal decongestants. The 2007 NDAC voted 11-1 that the evidence supports PE 10 mg as effective as a nasal decongestant but also felt additional studies were needed to evaluate higher doses.

In November 2015, Drs. Hendeles and Hatton filed a second petition requesting that FDA remove both oral PE from the final monograph for OTC nasal decongestant drug products and phenylephrine bitartrate from the monograph amendment.[7] These petitioners filed additional information in 2022 referencing studies that were published after their revised petition was filed.[9] A letter was filed by Dr. Vince Wilson and colleagues on November 6, 2015,[8] claiming their nonclinical data support the 2015 citizen petition filed by Dr. Hatton and Dr. Hendeles (see Appendix 1).

The CHPA Phenylephrine Task Group Members do not believe the new studies (published since the 2007 NDAC meeting and cited by the Petitioners) were conducted in a study population that represents individuals who generally use oral OTC nasal decongestants to manage their symptoms. Oral OTC phenylephrine products are indicated and labeled for consumers that need _temporary relief_ of nasal congestion for colds, hay fever, and other upper respiratory allergies.

Throughout this briefing book, it will be noted why the body of scientific evidence supporting GRAS/E designation for oral phenylephrine as an OTC nasal decongestant was the correct decision by the FDA and its panel of experts and is still the appropriate position. Furthermore, the studies and data referenced in the 2015 Hendeles and Hatton citizen petition and related submissions are examined and discussed in Sections 4.3 and 5.3. This analysis supports the Task Group's position that the new studies do not justify changing the GRAS/E status of phenylephrine.

4.0 CLINICAL PHARMACOLOGY OF PHENYLEPHRINE

4.1   Indication

Phenylephrine is indicated for the _temporary relief_ of nasal congestion, a prominent symptom of the common cold, hay fever, and other upper respiratory allergies (allergic rhinitis) in the OTC monograph [See 21CFR 341.80(b)(1)].[34]

OTC product labeling may describe the symptoms of nasal congestion as "nasal stuffiness" or "clogged up nose." Additional language may be added to reflect the mechanism of action of decongestants: "reduces swelling of nasal passages," "shrinks swollen membranes," and "promotes nasal and/or sinus drainage."

4.2   Pharmacology and Mechanism of Action

The human nasal mucosa is highly vascularized, and an extensive sinusoidal network of large capacitance vessels reside deep within the submucosa.[35] When this network is engorged with blood, the swollen mucosa reduces the size of the airway lumen, resulting in congestion. The sympathetic nervous system strongly influences nasal vasculature tone.[35] Nasal decongestants are sympathomimetic agents that mimic the action of epinephrine and norepinephrine. They bind to and activate two types of adrenergic receptors, α_1 and α_2.

PE's mechanism of action is the direct selective agonism at α_1-adrenergic receptors.[36] More recently, some evidence for an indirect effect has been reported using an _in vitro_ bioassay where PE stimulates the release of norepinephrine from nerve terminal storage sites.[37] Clinically, PE's selective stimulation of α_1-adrenergic receptors located on pre-capillary arterioles of the nasal mucosa results in vasoconstriction,[38] decreased blood volume, and a decrease in the volume of the nasal mucosa (nasal decongestion).[21] The α_1-mediated decrease in volume of engorged nasal vascular beds ultimately lowers airway resistance[39] and, thus, leads to freer breathing.

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[34] Code of Federal Regulation 21CFR 341.80(b)(1). Accessed from https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-341/subpart-C/section-341.80 on July 23, 2023.

[35] Corboz, MR, Rivelli, MA, Mingo, GG, McLeod, RL, Varty, L, Jia, Y; Hey, JA. Mechanism of decongestant activity of alpha 2-adrenoreceptor agonists. 2008 _Pulm Pharmacol Ther_. 21(3):449-454.

[36] Hoffman BB. Chapter 10: Catecholamines, Sympathomimetic Drugs, and Adrenergic Receptor Antagonists. In: Goodman & Gilman's The Pharmacologic Basics of Therapeutics - 10th Ed. Hardman JG and Limbird LE, eds. McGraw-Hill, Medical Publishing Division, USA, 2001.

[37] Al-Khrasani M, Karadi DA, Galambos AR, _et al_. The Pharmacological Effects of Phenylephrine are Indirect, Mediated by Noradrenaline Release from the Cytoplasm. 2022 _Neurochem Res_ 47:3272-3284.

[38] Johannssen V, Maune S, Werner JA_, et al_. Alpha 1-receptors at pre-capillary resistance vessels of the human nasal mucosa. 1997 _Rhinology_. 35(4):161-165.

[39] Tomassoni AAJ and Weisman RS. Chapter 50. Antihistamines and Decongestants. In: Goldfrank's Toxicologic Emergencies. 8th edition. McGraw-Hill, Medical Publishing Division, USA. 2006.

4.3 Pharmacologic Misconceptions in the Citizen Petition and its Supplements

The 2015 Citizen Petition[7] and its supplements[8,9] infer that clinical pharmacokinetic data and *in vitro* bioassay data from recent studies support the contention that PE 10 mg is not an effective decongestant. Misconceptions drawn from these data include the following:

- New plasma concentration data from published pharmacokinetic studies[14,15,16] are consistent with a lack of efficacy due to PE having low oral bioavailability.
- Lack of clinically important adverse effects on blood pressure at the doses evaluated in these pharmacokinetic studies are consistent with a lack of efficacy.
- Because *in vitro* data show the nasal vasculature in man and the pig are less sensitive to PE than the extranasal vasculature, there is no pharmacological basis for oral PE to alleviate symptoms of nasal congestion without attendant peripheral side effects.[8]

4.3.1 *Low Oral Bioavailability Does Not Mean Lack of Efficacy*

The Petitioners' claims that low oral bioavailability and plasma concentrations of PE indicate a lack efficacy are not accurate.[7] Oral bioavailability of a drug is only one factor associated with clinical efficacy. Pharmacological and clinical effects are determined by multiple factors, including drug concentrations at the site of action, drug potency, density and number of receptors, and intracellular mediators.

Like phenylephrine, many FDA-approved medicines have low-to-moderate bioavailability and have been shown to be clinically effective following oral dosing (several examples are listed in Table 4-1). Some drugs, such as bisphosphonates that treat osteoporosis, are less than 1% bioavailable. In other words, clinical dosing of a drug generally accounts for its bioavailability. For phenylephrine, the 10-mg dose was tested and found to be an effective nasal decongestant in patients experiencing upper respiratory infections (see Section 5.4).

Table 4-1 Examples of Currently Marketed Drugs with Oral Bioavailability ≤ 50%

Drug	% BA	Therapeutic Indication
Pamidronate	0.31-0.48	Osteoporosis
Risedronate	0.6	Osteoporosis
Alendronate	0.76	Osteoporosis
Zanamivir	2-2.5	Acute influenza A and B
Sumatriptan	15	Migraine
Loratadine	40	Allergy symptoms
Phenylephrine	**38**	**Nasal congestion**
Chlorpheniramine	41	Allergy symptoms
Aspirin	50	Minor aches and pain

Source: Package inserts, Drugdex

4.3.2 *Minimal Blood Pressure Effects Do Not Mean Lack of Efficacy*

In the peripheral vasculature, PE's stimulation of α1-adrenergic receptors increases mean arterial pressure (MAP) primarily through an increase in systemic vascular resistance.[40] Elevations in MAP[41] result in reflex bradycardia (reduction in heart rate) and, consequently, a decrease in cardiac output. Typically, changes in systolic and diastolic blood pressures are monitored in clinical studies, including the studies evaluating oral PE doses, where clinically important changes are reported as adverse events.

In the 2022 Supplement[9] to the citizen petition and referencing the pharmacokinetic study by Gelotte *et al*., 2015,[15] the authors state:

> "*The resultant low concentrations of phenylephrine in this study, even after 3 times the maximum FDA approved OTC dose, were associated with no cardiovascular measurements outside normal limits. The plasma concentrations were too low to influence the vasculature, including the nose and sinuses. These data suggest that doses up to three times the labeled OTC* [sic] *for oral phenylephrine are unlikely to be effective as a nasal decongestant.*"[9]

Because most disease is subacute and mild-to-moderate in severity, doses that provide about 50% of the maximum effect (ED50) often are sufficient.[42] The dose–response relationship for

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[40] DeMers D, Wachs D. Physiology, Mean Arterial Pressure. 2023 Apr 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 30855814.

[41] MAP is estimated from measurements of systolic (SP) and diastolic (DP) blood pressure:
$MAP = DP + 1/3(SP - DP)$.

[42] Dimmitt S, Stampfer H, Martin JH. When less is more - efficacy with less toxicity at the ED50. *Br J Clin Pharmacol*. 2017;83(7):1365-1368.

most drugs shows that above the ED50, efficacy increases only marginally, while adverse effects continue to increase, especially with agonist agents.[42] PE appears to follow this relationship. In clinical studies that evaluated reductions in nasal airway resistance, doses higher than 10 mg PE (*e.g.*, 25 mg) did not consistently produce greater decongestant effects (see data in Appendix 6). By contrast, blood pressure elevations for doses between 10 and 30 mg PE were minimal in these latter, and more recent, clinical pharmacokinetic studies,[14,15] whereas higher oral doses from 40 to 120 mg are necessary for consistent, clinically meaningful cardiovascular effects.[43,44]

Given the objective evidence that oral 10 mg PE has demonstrated significant decreases in nasal airway resistance in a number of clinical studies (see Appendix 3 and Appendix 4), minimal blood pressure effects following oral doses from 10 to 30 mg do not mean a lack of nasal decongestant efficacy but reinforce the safety profile of oral PE.

4.3.3   *In Vitro Potency is Just One Contributory Factor of Clinical Efficacy*

Inferences regarding PE's clinical efficacy based on *in vitro* potency data summarized in the 2015 Supplement to the citizen petition by Wilson and colleagues are flawed.[8] The authors assert that PE's higher potency to contract peripheral vasculature relative to nasal vasculature in excised human and pig mucosa negates the expectation of oral PE achieving nasal decongestion without attendant blood pressure elevation. This assertion improperly conflates a drug's potency (derived from an *in vitro* bioassay) with efficacy (determined from *in vivo* clinical assessments).

Potency studies measure one endpoint in relation to drug dose or concentration, whereas clinical efficacy measures the therapeutic benefit brought about by a cascade of complex interactions among various tissues, mediators, and systems.[20] For example, the homeostatic mechanism for preventing increases in blood pressure (*i.e.*, reflex bradycardia) has a role in attenuating PE's pharmacodynamic response (vasoconstriction of the peripheral vasculature) compared with other vascular sites in the body. Further, the authors' assertion does not recognize that PE concentrations at the local effect sites of the nasal and peripheral vasculature may differ.

The authors also incorrectly assert that *"…there is no scientific basis to expect orally administered phenylephrine to achieve a concentration in the nasal vasculature capable of selectively shrinking mucosal volume and acting as an effective decongestant."* [8] They based this assertion on their *in vitro* experiments where PE concentrations of 10 and 100 nM did not affect the magnitude or duration of electrically-evoked contractions of pig nasal arteries. The authors

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[43] Chua SS, Benriomj SI. Non-prescription sympathomimetic agents and hypertension. *Med Toxicol*. 1988;3:387-417.
[44] Keys A, Violante A. The cardio-circulatory effects in man of neosynephrine. *J Clin Invest*. 1942;21:1–12.

speculated that the reported[15] mean maximum concentration (Cmax) of 8 nM following oral ingestion of 10 mg PE is too low to be efficacious, because it is lower than these concentrations.

Clinical efficacious concentrations predicted from *in vitro* potency concentrations may be highly variable and lack biological significance.[45] In an analysis of 164 registered drugs, the ratio of clinically effective plasma concentrations to *in vitro* potency (expressed as the EC50) was estimated for each drug.[45] About 70% of the ratios were at or below unity, with the median ratio of 0.32. The data were also sorted by mechanism of action and target type, where 17 ratios for G protein-coupled receptor agonists (PE's classification) ranged from 0.002 to 4. Given that placebo-controlled, double-blind clinical studies of PE 10 mg show statistically significant reductions in nasal airway resistance, the speculation that orally administered PE cannot achieve efficacious concentrations is without merit (See Section 5.4).

4.4   New Pharmacokinetics Studies

Before the 2007 NDAC meeting, only a limited number of pharmacokinetic studies of PE were available.[46,47] Since then, several new studies have been conducted, and have increased our scientific understanding of the pharmacokinetics and metabolism of PE. Their designs and topline results are highlighted in two tables located in Appendix 2, and an overview with new learnings are summarized below.[14,16]

PE is rapidly absorbed following oral administration, reaching maximum concentrations between 15 and 60 minutes. Its absolute bioavailability has been estimated as 38% using plasma concentration data of racemic ^{3}H-phenylephrine dosed by infusion and oral liquid.[47] Across studies in healthy adults given a 10 mg oral dose after fasting,[14,15,16] mean systemic exposure (area under the curve, AUC∞) ranged from 816 to 1916 pg·h/mL and mean Cmax from 874 to 1354 pg/mL. The intersubject variability for both AUC∞ and Cmax was high across studies, ranging from 25-80%, which is characteristic of drugs, including PE, which undergo high first-pass metabolism and have relatively low-to-moderate bioavailability.

The plasma concentration-time profile for PE following a 10-mg dose is shown in Figure 4-1 on the regular and logarithmic scales, and the pharmacokinetics can be described by a

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[45] Jansson-Löfmark R, Hjorth S, Gabrielsson J. Does In Vitro Potency Predict Clinically Efficacious Concentrations? *Clin Pharmacol Ther*. 2020;108(2):298-305.

[46] Ptacek P, Klima J, Macek J. Development and validation of a liquid chromatography–tandem mass spectrometry method for the determination of phenylephrine in human plasma and its application to a pharmacokinetic study. *J Chromatog B* 2007;858:263–268.

[47] Hengstmann JH and Goronzy J. Pharmacokinetics of ^{3}H-phenylephrine in man. *Eur J Clin Pharmacol* 1982;21:335-341.

two-compartment model. PE rapidly distributes into extravascular tissues, consistent with its estimated steady-state volume of distribution (340 ± 174 L) considerably exceeding body weight.[47] The terminal elimination half-life is about 2 hours, with individual values ranging between 1 and 5 hours.

When a 10 mg dose is taken after a high-fat meal compared with fasting, absorption is delayed (longer time to reach a lower maximum concentration, Cmax), but the total amount of PE absorbed (AUC∞) is bioequivalent.[16] When PE is combined with acetaminophen from 500 to 1000 mg in a tablet, both Cmax and AUC∞ for PE are increased.[14] Regarding safety, single doses of PE from 10 to 30 mg across studies were well-tolerated and further support a favorable safety profile in healthy adults.[15] No clinically significant changes in blood pressure or heart rate were observed.

Figure 4-1 Pharmacokinetic profiles[15] for 10 mg dose of PE on the regular (top) and logarithmic (bottom) scales
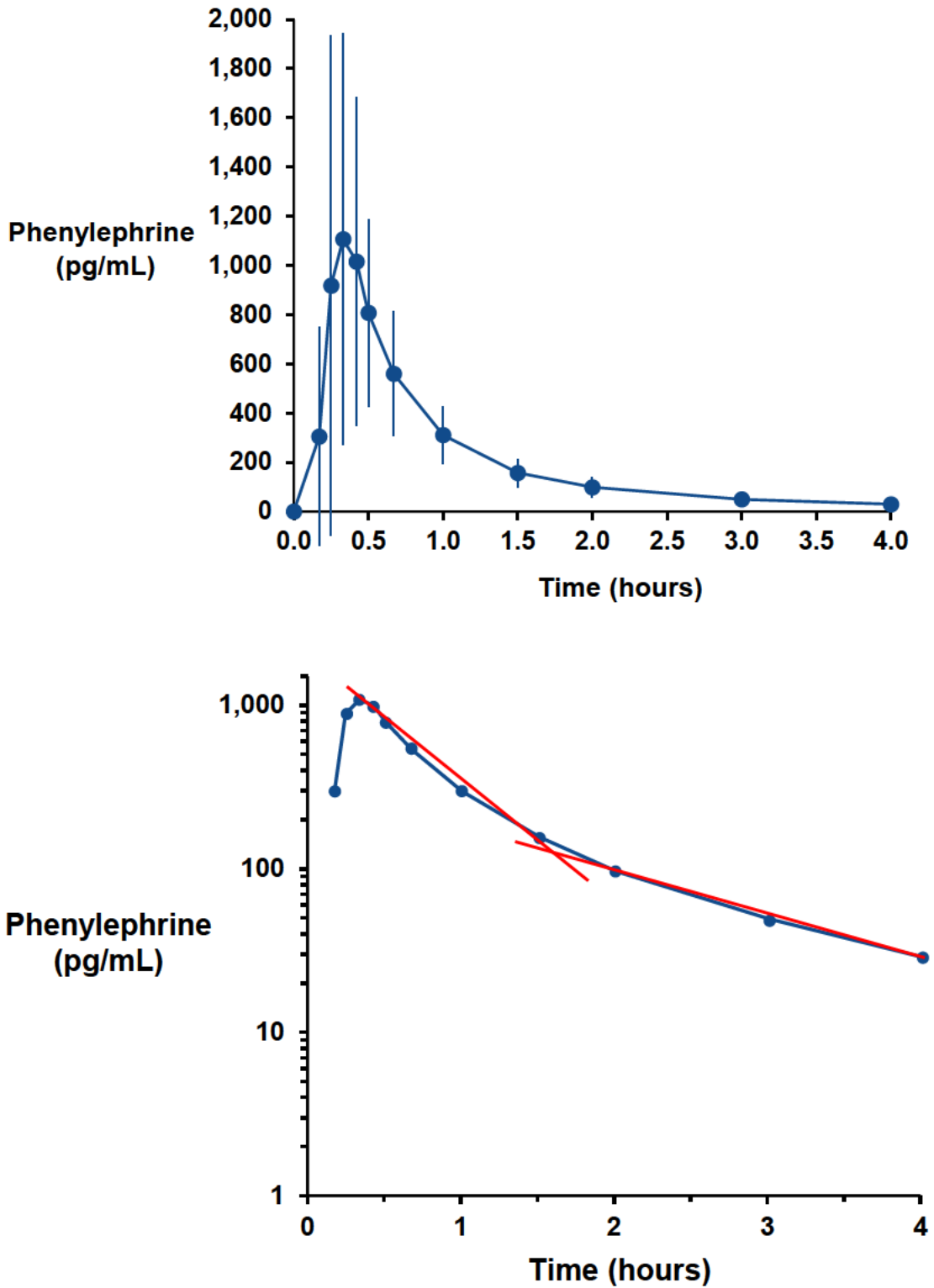
5.0 EFFICACY OF PHENYLEPHRINE AS A NASAL DECONGESTANT

Key Points

- Based on the totality of evidence for oral PE 10 mg from randomized, placebo-controlled clinical studies that used objective and subjective assessments of nasal congestion, the 1976 OTC Expert Panel recommended GRAS/E status. FDA agreed with the panel's recommendation, and this status was finalized in 1994.

    o The 2007 NDAC voted 11-1 that the evidence supports PE 10 mg as effective as a nasal decongestant but felt additional studies were needed to evaluate higher doses.

- Four randomized, placebo-controlled studies published since the 2007 NDAC did not detect treatment effects of PE in reducing nasal congestion in subjects with seasonal allergic rhinitis.

    o Certain methodological aspects of these studies (*i.e.*, inadequate blinding and concomitant use of an antihistamine) limit their predictive ability for assessing PE efficacy and render them inappropriate to negate the conclusions of previous efficacy determinations upon which FDA and the 2007 NDAC aligned.

    o Another important concern is that the enrolled population does not generally represent individuals with allergic rhinitis who would use OTC medicines "as needed" to manage their symptoms.

- PE 10 mg is an effective OTC ingredient for temporary relief of nasal congestion, and no changes are warranted to the monograph based on results from recent studies.

5.1   Objective and Subjective Assessments of Nasal Congestion

Nasal congestion is a major symptom of both the common cold and allergic rhinitis that is not always easily described by a patient and interpreted by a clinician.[48] The efficacy of nasal decongestants can be assessed either subjectively using symptom scales or objectively, typically using rhinomanometric measurements of nasal airway resistance.[49] Adequate blinding of subjects to their assigned treatments in placebo-controlled clinical studies is critically important to avoid any potential bias when implementing subjective assessments of

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[48] Davis SS, Eccles R. Nasal congestion: mechanisms, measurement and medications. Core information for the clinician. *Clin Otolaryngol* 2004;29:659-666.

[49] Zhang G, Solomon P, Rival R, *et al*. Nasal airway volume and resistance to airflow. *Am J Rhinol* 2008;22: 371–375.

nasal congestion.

Objective measurements require specialized equipment and trained technicians and, thus, are highly operator dependent and not easily amenable to multi-center clinical trials. Anterior and posterior rhinometry are used to calculate nasal airway resistance from the nasal airflow and pressure required to achieve that flow. Peak nasal airflow may be measured during inspiration (PNIF) and expiration (PNEF). Although these last two methods are quick and non-invasive, they are dependent on subject effort and may be affected by nasal secretions.

Most clinical studies have used variations of anterior or posterior rhinometry to measure nasal airway resistance. One challenge of utilizing these methods is the "nasal cycle" where congestion occurs in one nostril and alternates to the other, possibly due to changes in sympathetic tone.[49] If nostrils are measured bilaterally, the magnitude of improvements in unilateral congestion may not be fully appreciated. Also, the presence of mucus can affect measurements for both anterior and posterior rhinometry. Despite these challenges, topical (intra-nasal) and oral nasal decongestants have been shown to reduce nasal airway resistance.

Subjective assessments are also used to determine efficacy of nasal decongestants. However, subjective interpretation and temporal changes of congestion, which are associated with a variety of factors including the nasal cycle, posture, and mood, complicate the assessment of disease severity and treatment effectiveness in clinical trials.[48] The sensation of nasal congestion can be influenced by a number of factors including air temperature and cold receptors in the nasal airway.[50] All the above factors make the translation of sensation of congestion to subjective symptom score scales, typically used in clinical trials, challenging.

In general, most clinical efficacy trials for OTC oral nasal decongestants have used both subjective and objective endpoints for analysis with agreement reported in some studies. The FDA and clinical experts accept the importance of evaluating both objective and subjective endpoints in determining efficacy.

5.2   Efficacy Studies of Oral Phenylephrine

Over the past forty years, several clinical studies examined the efficacy of oral PE. They are listed in Table 5-1 and summarized in Sections 5.3 and 5.5 and Appendices 3 and 4. Results from 17 studies were previously reviewed by FDA and members of the 2007 NDAC. Since then, two additional clinical studies were published and are reviewed in Section 5.3.

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[50] Naclerio *et al*., 2010 Pathophysiology of Nasal Congestion *Int J Gen Med* 3:47-57.

Table 5-1 All Efficacy Studies of 10 mg Oral Phenylephrine Reviewed

Study Name	Relevant for PE 10 mg Indication	Included in 1976 Review	Included in 2007 Review	Published After 2007	Included in Kollar[76] Meta-analysis	Included in Hatton[75] Meta-analysis
Lands (1959)	X	X	X			
McLaurin (1961)	X		X			
AHR 7032 (1967)	X		X			
Elizabeth #2 (1968)	X	X	X		X	X
Cintest #1 (1969)	X	X	X		X	X
Huntingdon #1 (1969)	X	X	X		X	X
Huntingdon #2 (1969)	X	X	X		X	X
Elizabeth #5 (1970)	X	X	X		X	X
Cintest #2 (1970)	X	X	X		X	X
Cintest #3 (1970)	X	X	X		X	X
Cohen 72 (1972)	X		X			
Cohen 75 (1975)	X	X	X		X	X
AHR 4010-3 (1983)	X		X			
AHR-GIA (1973)	X	X	X			
Bickerman (1971)	X		X			
Day (2009)			X*	☒		
Horak (2009)			X*	☒		
Meltzer (2015)				X		
Meltzer (2016)				X		

X* = During the 2007 NDAC meeting, Day *et al.* (2009) was discussed as Drug Supply Trial 4822. Horak *et al.* (2009) was discussed as Schering-Plough Study P04579.

☒ = Results reviewed during 2007 NDAC but publication was released later.

5.3   Review of Efficacy Studies Published After the 2007 NDAC

The 2015 citizen petition requests that FDA remove oral PE from the final monograph for OTC nasal decongestants based in part on data from four randomized, placebo-controlled studies evaluating the nasal decongestion efficacy of PE in subjects with seasonal allergic rhinitis published after the 2007 NDAC meeting. Two of the studies (S-P 04579 and S-P 4822) were conducted in environmental allergy chambers and previously discussed at the 2007 NDAC. They were subsequently published with additional details as Horak *et al.*, 2009 and Day *et al.*, 2009, respectively,[10,11] and are described in this section, along with two field clinical studies not previously reviewed at the 2007 NDAC.[12,13]

A number of concerning methodological limitations associated with the studies are also described in this section, and they are summarized in Table 5-2. Based on these limitations, we believe the results from these clinical studies do not negate the previous findings that 10 mg oral PE is safe and effective for the temporarily relief of nasal congestion due to the common cold, hay fever, and other upper respiratory allergies, nor do they support a change in the categorization of PE as a GRAS/E ingredient.

5.3.1   *Allergy Chamber Study by Horak et al., 2009*

Also known by S-P P04579,[11] this study utilized a randomized, placebo-controlled, investigator-blind, three-way crossover design to examine the decongestant effect of PE 12 mg and pseudoephedrine 60 mg in response to grass pollen in an allergen-exposure unit. Subjects (n=39) having a history of seasonal allergic rhinitis received a single dose of PE 12 mg, pseudoephedrine 60 mg, or placebo on three different occasions. Subjective assessments of nasal congestion, PNIF, and rhinomanometry were recorded at 15 min intervals for more than 6 hours. The primary endpoint was subjective evaluation of nasal congestion expressed as an average change from baseline during the first 6 hours.

Phenylephrine did not separate from placebo in the primary efficacy comparison of subjective nasal congestion scores averaged over the course of 6 hours, and in the two objective measurements (PNIF and rhinomanometry). Overall reduction of nasal congestion scores for PE (-7.1%) was not different from placebo (-2.2%). The pseudoephedrine average reduction score (-21.7%) was statistically greater than placebo (p<0.01) and PE (p=0.01).

The authors noted that recall biases in the subjective nasal congestion scores due to a potential sequence effect in the crossover design may have adversely influenced the result for PE.[11] That is, when pseudoephedrine was taken before the other treatments, subjects may

have recalled its effect. Another critical contributing factor was that the three treatments were not double-blind in this study. In crossover designs where each subject receives each treatment and when the primary endpoint is subjective assessment of symptoms, adequate blinding is essential.[51] Because commercial products were used for both active treatments, some subjects may have been familiar with their respective dosage form and color. At the time of this study in 2005, the pseudoephedrine red tablet had been sold as a decongestant for many years in the United Kingdom, but the phenylephrine yellow capsule had only gained market authorization for about one year. The placebo capsule was blue.

Given the lack of blinding and crossover sequence effects that likely introduced bias, results of the subjective assessments in this study are not reliable. Regarding the objective endpoints, one important limitation was insufficient dosing of PE according to its OTC label (10 mg every 4 hours) for the 6-hour observation period. A second dose of PE 10 mg should have been administered at the 4-hour timepoint.

5.3.2   *Allergy Chamber Study by Day et al., 2009*

Also known as S-P 4822,[10] this study had a single-dose, double-blind, double-dummy, randomized, placebo-controlled, parallel-group design to evaluate loratadine-montelukast 10 mg/10 mg (L/M) and PE 10 mg in subjects (n=379) with SAR exposed to ragweed pollen in an environmental exposure unit. Subjects completed up to 6 priming visits where they were exposed to ragweed pollen for up to 3 hours to stimulate symptoms. At the treatment visit, subjects were initially exposed to ragweed pollen for 90 minutes in the unit to produce adequate symptoms. Subjects evaluated nasal congestion and other allergy symptoms and measured PNIF before dosing and at 20-minute intervals during the subsequent 8 hours of pollen exposure.

The primary efficacy endpoint was nasal congestion, expressed as a mean change from baseline averaged across all time points during the first 6 hours. L/M was more effective than both the placebo (p=0.007) and PE (p<0.001) in relieving nasal congestion and in improving PNIF, whereas PE was not different from placebo in the primary or secondary endpoints. However, similar to the previous allergy chamber study, the single dose of PE was insufficient for the 6-hour observation period. A second dose of PE 10 mg should have been administered at the 4-hour timepoint.

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[51] Allergic Rhinitis: Developing Drug Products for Treatment Guidance for Industry. FDA Center for Drug Evaluation and Research, September 2018.

Another important concern with this study is that we believe the enrolled population does not generally represent individuals who experience mild intermittent allergic rhinitis and use OTC medicines "as needed" to manage their symptoms.[52] This would include phenylephrine for the temporary relief of nasal congestion. Intermittent rhinitis is defined on the basis of symptoms that are present for less than 4 days per week or less than 4 weeks in duration.[53,54] Subjects in environmental chamber studies must have moderate-to-severe nasal congestion scores to enter the study after priming, *i.e.*, being exposed to antigen in the chamber. In FDA's guidance,[51] subjects must have sustained nasal congestion after a washout period. Neither of these scenarios is the same as sufferers who naturally get temporary nasal congestion.

5.3.3   *Clinical Study in Seasonal Allergic Rhinitis by Meltzer et al., 2015*

A Phase 2, open-label, placebo-controlled, randomized, parallel-group, study evaluated the nasal decongestion efficacy and safety of four doses of PE HCl (10, 20, 30, and 40 mg) and placebo in adults (n=539) with SAR for seven days.[12] All subjects were treated daily with 10 mg loratadine during the run-in and treatment periods. The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily reflective nasal congestion scores based on participant diaries. None of the PE treatment groups had a statistically significant change from baseline in instantaneous or reflective nasal congestion scores compared with the placebo group.

Adequate blinding of comparative treatments is critical when the primary endpoint is subjective assessment of symptoms. The authors deemed this study as open-label due to inadequate blinding: "Commercial PE 10-mg tablets were used. Both PE 10-mg and placebo tablets were red and concave, but not exactly matching."[12] This difference may seem trivial, but subjects are informed that they will receive either placebo or one of four PE doses during the written consent process. Figure 5-1 illustrates how bias can be introduced by not having the placebo exactly match the commercial 10-mg PE tablet when used to fill hypothetical blister dosing strips. Clearly, subjects receiving the 10-, 20-, and 30-mg doses know they are receiving an active treatment, and having two identical pairs would likely be the 20-mg dose.

[52] Greiner AN, Metzler EO. Pharmacologic rationale for treating allergic and nonallergic rhinitis. *J Allergy Clin Immunol* 2006;118:985-996.

[53] Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. 2001 *J Allergy Clin Immunol* 108 Suppl:147-334.

[54] Valero A, Ferrer M, Sastre J, *et al*. A new criterion by which to discriminate between patients with moderate allergic rhinitis and patients with severe allergic rhinitis based on the allergic rhinitis and its impact on asthma severity items. 2007 *J Allergy Clin Immunol* 120:359-65.

Figure 5-1 Hypothetical Blister Dosing Strips Illustrating Inadequate Blinding
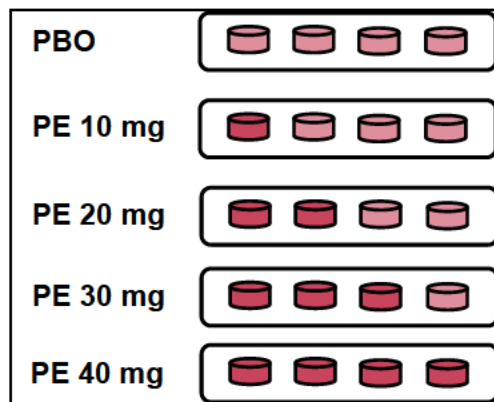
Another concerning limitation is the addition of daily loratadine to placebo and each PE treatment, which can provide a "halo effect" such that overall improvement in the subject's sense of well-being and reduced perception of the severity of other rhinitis symptoms biases the scoring of nasal congestion.[52] Daily use of loratadine is expected to decrease overall model sensitivity to detect differences in nasal decongestion between PE doses and placebo.

Finally, as discussed previously, we believe the subject population enrolled in this study does not generally represent individuals who experience mild intermittent[53] allergic rhinitis and use OTC medicines "as needed" to manage their symptoms.[52,54] By contrast, large numbers of individuals enrolled in clinical trials of seasonal allergic rhinitis are likely classified as having moderate-to-severe persistent allergic rhinitis, seek the care of healthcare specialists, and have been prescribed corticosteroids or leukotriene modifiers (*e.g.,* montelukast). In fact, research has shown that most individuals who visit general practitioners or specialists have moderate/severe intermittent and persistent rhinitis, as defined by the impact of symptoms on quality of life, sleep, daily activities, and work performance.[55,56] These practitioners and specialists are typically enlisted as trial investigators. Specific to this study, the inclusion criteria permitted enrollment of subjects who had taken corticosteroids after a washout period or who had previously initiated allergy immunotherapy.[12]

Limiting the number of years that individuals experienced allergic rhinitis would be one approach to identify an appropriate study population for studies that evaluate OTC

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[55] Bousquet J, Neukirch F, Bousquet PJ, *et al.* Severity and impairment of allergic rhinitis in patients consulting in primary care. J Allergy Clin Immunol. 2006 Jan;117(1):158-62.
[56] Bousquet J, Annesi-Maesano I, Carat F, *et al.* Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. Clin Exp Allergy. 2005 Jun;35(6):728-32.

ingredients for the temporary relief of symptoms. Having dealt with allergy symptoms for long durations is more likely to be associated with individuals seeking care from general practitioners/specialists. Indeed, research has shown a strong correlation between the number of years experiencing allergic rhinitis and diminished responses to an α_1/α_2-adrenergic decongestant.[57] In a prospective study of 312 adults with moderate-to-severe persistent allergic rhinitis, nasal airflow measured by anterior rhinomanometry before and after a decongestant test with naphazoline spray showed progressive impairment of response to decongestion with the number of years that an individual experienced allergic rhinitis.[57] These data corroborate our concern that the enrolled population in this study, and the following study, were not appropriate to evaluate PE 10 mg for temporary relief of nasal congestion.

5.3.4   *Clinical Study in Seasonal Allergic Rhinitis by Meltzer et al., 2016*

A Phase 3, double-blinded, placebo-controlled, randomized, parallel-group study evaluated the nasal decongestant efficacy and safety of the experimental PE modified-release tablet, 30-mg (PE-MR) compared with placebo in subjects with seasonal allergic rhinitis over 7 days.[13] Of 575 subjects, 288 received PE-MR and 287 received placebo every 12 hours. No significant difference was detected between PE-MR and placebo for the primary endpoint (mean change from baseline over 7 days of treatment in daily reflective nasal congestion scores). Likewise, no significant differences were observed for most secondary endpoints or quality of life.

Review of the study methods found that two design elements most likely decreased the assay sensitivity of this clinical model to detect a treatment effect by PE-MR on nasal congestion. The first was the significant concomitant use of loratadine by subjects to treat other allergy symptoms during the study. Out of seven treatment days, mean loratadine exposure was 3.8 ± 2.4 days for PE-MR and 3.8 ± 2.4 for placebo. As discussed previously, concomitant loratadine use provides a "halo effect" whereby a subject's improved well-being biases the scoring of nasal congestion. Further contributing to lower sensitivity was the enrollment of subjects who rated the severity of their nasal congestion as mild. As stated in FDA's Guidance for allergy trials,[51] enrollment of subjects should require at least moderate severity for all or the majority of individual symptoms. Without an active comparator, there is uncertainty whether lowering the entry criteria from moderate-to-mild severity for nasal congestion was appropriate.

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[57] Ciprandi G, Pistorio A, Tosca M, Cirillo I. Relationship between rhinitis duration and response to nasal decongestion test. *Laryngoscope.* 2008;118(7):1139-1141.

Finally, we believe that the enrolled population generally does not represent individuals with mild intermittent[53,56] allergic rhinitis who would use OTC medicines "as needed" to manage their symptoms.[52,54] For example, in this study, subjects who used nasal corticosteroids in the past were not excluded. Instead, individuals with moderate-to-severe persistent allergic rhinitis were likely enrolled because this population predominately visits general practitioners/specialists (*i.e.*, potential study investigators).[55,56] Also, this population is expected to have experienced allergic rhinitis for longer durations, which may further decrease assay sensitivity of the clinical model because diminished responsiveness to a nasal decongestant test has been shown to be highly correlated with the number of years that an individual has experienced allergic rhinitis.[57]

5.3.5   CHPA's Position Regarding the Studies Cited by the Petitioners

Although the Petitioners maintain that these clinical studies in subjects with seasonal allergic rhinitis prove that PE is not an effective nasal decongestant, it is CHPA's position that the results in these studies do not supersede the overall findings of the studies that previously demonstrated efficacy of PE and which support the labeled indication, that is for the temporary relief of nasal congestion.

- Results of the subjective assessments of nasal congestion are unreliable due to limitations observed with some study methodologies. Two concerning limitations were (i) inadequate blinding of active treatments and placebo that likely introduced bias, and (ii) concomitant use of an antihistamine in the field studies that likely decreased assay sensitivity of the clinical model.

- Another important concern across the studies was that the enrolled population does not generally represent individuals with mild intermittent allergic rhinitis who would use OTC medicines "as needed" to manage their symptoms. The selection criteria are based on historical precedence for the development of prescription drug products that establishes effectiveness over a longer duration in patients having more severe intermittent and persistent allergic rhinitis rather than provide temporary relief.

Therefore, we believe the results from these clinical studies do not negate the previous findings that 10 mg oral PE is safe and effective for the temporarily relief of nasal congestion due to the common cold, hay fever, and other upper respiratory allergies nor do they support a change in the categorization of PE as a GRAS/E ingredient.

Table 5-2 Methodological Limitations of the Four Studies Published after 2007

Limitation	Study	Comments
Inadequate Blinding	Horak 2009 Meltzer 2015	Adequate blinding of comparative treatments is critical when the primary endpoint is subjective assessment of allergy symptoms, which is underscored in FDA Guidance.[51] In these studies, results of the subjective assessments are not reliable due to inadequate blinding as the subjects' responses are likely biased.
Crossover Sequence Effect	Horak 2009	The researchers acknowledged a sequence effect where subjective assessments of nasal congestion for the PE in the first phase was directionally superior to placebo, but not in the remaining sequences. They state: "This finding suggests that bias may have been introduced because of patient recall of the pseudoephedrine effect in a previous phase".
Insufficient dosing of PE for the 6-hour Primary Endpoint	Horak 2009 Day 2009	Per its product labeling, PE 10 mg is dosed every 4 hours for the temporary relief of nasal congestion, so another dose of PE 10 mg should have been administered. Therefore, PE was underdosed compared with PSE and L/M for the averaged 6-hour assessment period.
Inappropriate Study Population	Day 2009 Meltzer 2015 Meltzer 2016	The study population does not reflect allergy sufferers who would use OTC PE 10 mg for the temporary relief of nasal congestion due to hay fever. Generally, individuals who experience mild intermittent allergic rhinitis use OTC medicines on "as needed" basis and manage their own care.[52] By contrast, individuals enrolled in SAR clinical trials generally experience moderate-to-severe persistent allergic rhinitis and may use corticosteroids or leukotriene modifiers under the care of healthcare professionals.
Daily Loratadine Use During Run-in and Treatment Periods	Meltzer 2015	PE doses were not compared with a true PBO treatment. Addition of daily loratadine to placebo and each PE treatment relieves other allergy symptoms, which can provide a "halo effect" whereby overall improvement in the subject's sense of well-being and reduced perception of the severity of other rhinitis symptoms biases the scoring of nasal congestion.[52] The daily use of loratadine during the study decreased overall model sensitivity to detect differences in nasal decongestion between PE doses and PBO.

Limitation	Study	Comments
Decreased Assay Sensitivity of SAR Model to Detect Decongestant Efficacy	Meltzer 2016	Two factors contributed to the decreased assay sensitivity of the SAR clinical model to detect a treatment effect on nasal congestion. The first was significant concomitant use of loratadine by subjects to treat other allergy symptoms during the study which, as discussed previously, provides a "halo effect" whereby a subject's improved well-being biases the scoring of nasal congestion.[52] Further contributing to this lower sensitivity was the enrollment of subjects who rated the severity of their nasal congestion as mild. As stated in the FDA Guidance[51] for allergy trials, enrollment of subjects should require at least moderate severity for all or the majority of individual symptoms. Without an active comparator, this modification to the standard design may not be sensitive enough to detect differences from placebo.
Rescue Medication Not Addressed in Analysis of Treatment Groups	Meltzer 2016	Mean loratadine exposure was 3.8 days (SD 2.35) for PE-MR and 3.8 days (SD 2.36) for placebo, which represents significant usage during the study. Except testing for statistical difference between treatment groups, the use of rescue medication in the efficacy analyses of treatment groups was not addressed. FDA Guidance[51] states that "If rescue medications are allowed during the trial, the protocol should document how rescue medication use will be analyzed in the different treatment groups." In addition, most published Phase 3 SAR trials of antihistamines and other agents did not permit the use of rescue medicine.
No Adjustments for Multiple Comparisons	Horak 2009 Day 2009	There were no statistical adjustments of p values for multiple comparisons, although overall statistical results are not expected to change if adjusted.

Key: L/M = loratadine plus montelukast, OTC = over- the-counter, PBO = placebo, PE = phenylephrine, PE-MR = phenylephrine modified release,

PSE = pseudoephedrine, SAR = seasonal allergic rhinitis, SD = standard deviation

5.4   Other Phenylephrine Clinical Studies After 2007

A search of the published literature and postings on Clinical Trials.gov revealed a number of clinical studies conducted outside the United States that included PE. The studies, except one, evaluated PE in combination products containing other OTC medicines. These studies on combination PE products reported positive efficacy findings,[58,59,60] but only one of them was placebo-controlled,[61] so they will not be discussed further.

The sole clinical study that included PE as a single ingredient and was placebo-controlled is posted on Clinical trials.gov (NCT03339726). This was a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy of an experimental extended-release (ER) formulation of PE-ER HCl, 30 mg, for the relief of nasal congestion in subjects with naturally occurring cold symptoms. The commercial PE HCl 12 mg tablet was included as a positive control. The study was terminated early at 43% enrollment due to the inability to enroll the planned number of subjects after the cold season, even after loosening an inclusion criterion. The incomplete data set was analyzed, and the posted results show that neither active treatment separated from placebo.

[58] Kiran M, Pawaskar L, Yadav P. Efficacy and Safety of a combination of Paracetamol, Chlorpheniramine maleate and Phenylephrine in the symptomatic treatment of Common Cold: Phase IV Clinical study. 2017 *The Indian Practitioner*. 70(2):10-5.

[59] Kiran MD, Pawaskar LJ. Safety and Efficacy of a combination of Paracetamol, Phenylephrine and Fexofenadine in adult patients of Common Cold and Allergic Rhinitis: Phase IV Study. 2017 *World J Pharm Res*. 16;6(4):1624-1634.

[60] Kiran M, Lotankar S, Pawaskar L. Efficacy and Safety of a Combination of Phenylephrine, Chlorpheniramine, and Dextromethrophan in Cold and Dry Cough in Children. 2017 *Inter J Innovative Pharm Sci Res* 13;5(12):116-25.

[61] Picon PD, Costa MB, da Veiga Picon R, *et al*. Symptomatic treatment of the common cold with a fixed-dose combination of paracetamol, chlorphenamine and phenylephrine: a randomized, placebo-controlled trial. 2013 *BMC Infect Dis*. 22;13:556.

5.5 Body of Evidence Before the 2007 NDAC Supports GRAS/E Status

On December 14, 2007, the Agency held a meeting of the Nonprescription Drugs Advisory Committee (NDAC) to discuss the safety and effectiveness of phenylephrine hydrochloride and phenylephrine bitartrate as OTC oral nasal decongestants to address a citizen petition filed on February 1, 2007.[3] In preparation for the 2007 NDAC meeting, a CHPA working group reviewed all available clinical trials, examining the efficacy of oral PE as a nasal decongestant for the temporary relief of nasal congestion. After a full day of presentations and discussion, the NDAC voted 11-1 that the evidence is supportive of the conclusion that PE 10 mg is effective but also felt additional studies were needed to evaluate higher doses.

This section provides an overview of the body of evidence for PE efficacy that was available before the 2007 NDAC and which supports the GRAS/E status of this ingredient as an OTC nasal decongestant.

By regulation, FDA's standard for effectiveness for GRAS/E monograph substances states:

> "Effectiveness means 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. Such recognition of effectiveness must be based on published and/or unpublished controlled clinical trials which can be supported by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing." [21 CFR 330.10 (3)(ii)][62]

The efficacy studies are organized such that the 14 studies reviewed by the OTC Expert Panel and FDA in the mid-1970's and used to establish GRAS/E status are presented first, followed by seven additional studies that were discussed at the 2007 NDAC meeting. When viewed in their entirety, results from these studies demonstrate that orally administered PE 10 mg is effective for the temporary relief of nasal congestion due to the common cold, hay fever, and other upper respiratory allergies, and continue to support the classification of PE as a GRAS/E ingredient.

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[62] 21 CFR 330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs. Accessed from https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-330/subpart-B/section-330.10 on July 23, 2023.

5.5.1 Studies Reviewed by the OTC Expert Panel and FDA in 1976

An FDA OTC Expert Advisory Panel reviewed study data and scientific publications regarding the safety and efficacy of oral PE as an OTC nasal decongestant. They reviewed a total of 14 studies for efficacy in 1976 (12 unpublished; 2 published).[63] A summary of the design, pertinent strengths, weaknesses, and findings from 12 of these studies is located in Appendix 3.[64,65]

For the discussion below and in Appendix 3, the studies are labeled by reference numbers that refer to the bibliography from the FDA OTC Review.[66] All studies enrolled subjects experiencing symptoms of the common cold and evaluated objective measures of nasal congestion by measuring reduction of nasal airway resistance using rhinometry methods. Furthermore, 11 of these 12 studies measured subjective responses on a 5-point severity scale of nasal congestion and one on a 6-category scale.

Five of the 12 studies (FDA References 5, 20, 21, 23, and 24 in Appendix 3) were negative or inconclusive, *i.e.,* PE at doses ranging from 5 mg to 75 mg did not significantly reduce nasal airway resistance compared to placebo. Three of these 5 studies (FDA References 21, 23, and 24) did not include a positive control group, making it impossible to evaluate the assay sensitivity of the rhinometry method. In another study (FDA Reference 5) the author noted that concerning the baseline nasal airway resistance measurements, "…*in the majority of cases there was no nasal congestion*." In addition, the positive control failed to separate from placebo, again suggesting that the methods used were not sensitive. The remaining negative study (FDA Reference 20) showed a statistically significant reduction in nasal airway resistance by the positive control (phenylpropanolamine, PPA) but not by 10 and 25 mg PE. Therefore, of these 5 negative/inconclusive studies, there was only one well-designed study that failed to demonstrate the efficacy of PE.

In contrast, 7 double-blind, randomized studies (FDA References 6, 7, 8, 9, 10, 22, and 26 in Appendix 3) were positive, *i.e.*, PE demonstrated a significant reduction in nasal airway

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[63] These studies are references 5-10 and 19-26 in the 1976 Advanced Notice of Proposed Rulemaking; published at 41 FR 38399-38400.

[64] Two of these studies (Blanchard 1964 and Rodgers 1973) are not reviewed here as one was a methodological paper that tested an oral combination product with unknown ingredients and the other was an abstract without clinical data. Blanchard CL, Borsanyi SJ, Grubb TC. Evaluation of nasal decongestant drugs. Eye, Ear, Nose and Throat Mon 1964;43:76-82. Rodgers JM, Reilly EB, Bickerman HA. Physiologic and pharmacologic studies on nasal airway resistance. *Clinical Pharmacology & Ther* 1973;14:146.

[65] See also Desjardins PJ and Berlin RG Efficacy of Phenylephrine. *Br J Clin Pharmacol* 2007 64(4):555-556.

[66] *Federal Register*, vol. 41, no. 176, pages 38399-38400, September 9, 1976.

resistance at the doses tested, ranging from 5 to 25 mg. Four of the studies (FDA References 7, 10, 22, and 26) included a 10 mg dose of PE. A fifth study included a 5 mg dose which also significantly reduced nasal airway resistance (FDA Reference 8).

The OTC Expert Panel concluded that PE at the 10 mg dose, given every four hours for children ≥12 years old and adults, is safe and effective for OTC use for the temporary relief of nasal congestion. Based on the review of these studies and consistent with the 21 CFR Part 330 standards for determining general recognition of safety and effectiveness for an OTC Monograph, FDA agreed with the expert panel recommendation that PE (10 mg) is GRAS/E for providing temporary relief of nasal congestion. The FDA decision was published in the 1976 Advanced Notice of Proposed Rulemaking.

5.5.2 Additional Studies Reviewed by the 2007 FDA NDAC

Seven additional efficacy studies of PE, which were not reviewed by the 1976 OTC Expert Panel, were discussed at the 2007 NDAC meeting. Results from these studies were mixed, with two being positive/supportive,[67,68] one inconclusive,[69] and four negative.[10,11,70,71] The positive, supportive, and inconclusive studies evaluated PE efficacy in subjects with nasal congestion due to the common cold, whereas the four negative studies evaluated PE efficacy in subjects with seasonal allergic rhinitis.

Two of the negative studies[10,11] were conducted in environmental allergy exposure units, and the results were presented at the 2007 NDAC meeting. These studies were subsequently published (Horak *et al.*, 2009 and Day *et al.*, 2009) such that more detail regarding the study methods and results became publicly available. Both studies were previously addressed in Sections 5.3.1 and 5.3.2, respectively. A summary of design, pertinent strengths, weaknesses, and findings from five of the remaining seven studies is located in Appendix 4.

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[67] Cohen BM. Clinical and physiologic "significance" of drug-induced changes in nasal flow/resistance. *Eur J Clin Pharmacol* 1972;5:81-86.
[68] Study Report: AHR-4010-3. December 14, 1983.
[69] McLaurin JW, Shipman WF, Rosedale R Jr. Oral decongestants: a double-blind comparison study of the effectiveness of four sympathomimetic drugs: objective and subjective. Laryngoscope 1961;71:54-67.
[70] AHR Study 7032.
[71] Bickerman HA. Physiologic and pharmacologic studies on nasal airway resistance (R_N). Presented at a conference sponsored by the Scientific Development Committee of the Proprietary Association. Washington, DC. December 8, 1971.

5.5.3   Studies Establishing Efficacy of Phenylephrine 10 mg

In this section, results from five positive well-controlled studies that were previously cited in Sections 5.5.1 and 5.5.2 as demonstrating the efficacy of oral PE 10 mg as a nasal decongestant are discussed in greater detail.

Cohen [1972][67] studied the efficacy of PE in 48 subjects with nasal congestion due to the common cold. This was a double blind, randomized, placebo controlled, incomplete two-way crossover[72] study that tested the effects of PE 10 mg (n=16), 15 mg (n=16) and 25 mg (n=16) on nasal airway resistance and subjective assessment of nasal congestion following a single dose. Nasal airway resistance was determined using electronic posterior rhinometry, and the average of three measurements was recorded at each timepoint for each subject at baseline, and from 15 to 120 minutes after the dose. Subjects assessed the severity of nasal congestion at the same timepoints using a 5-point categorical scale (from 0 = nose feels clear to 4 = completely blocked). Details regarding the statistical methods and measures of variability for the reported mean data were not provided in the publication.

The results of this study for both objective and subjective endpoints over the observation period are displayed in Figure 5-2. Each dose of PE was compared with its paired placebo and showed statistically significant reductions in mean nasal airway resistance at all timepoints, except at 15 minutes for the PE 10 mg dose. Furthermore, when the placebo data were pooled in a secondary analysis, a greater reduction in mean differences of nasal airway resistance from baseline (% reduction) was produced by PE 25 mg compared to the 10 mg and 15 mg doses.

The analysis approach for the subjective assessments was similar. Each dose of PE was compared with its paired placebo and showed statistically significant reductions in mean subjective assessment scores at all timepoints, except at 15 minutes for the PE 10 mg dose. There were no apparent differences in scores among the PE doses. This study, which was not included in the 1976 FDA review, clearly demonstrates the efficacy of PE on objective and subjective measures.

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[72] Each subject was randomized to a two-way crossover, receiving an active treatment and placebo in one of two possible sequences.

Figure 5-2 Time Course of Objective (top) and Subjective (bottom) Decongestant Effects from Cohen 1972
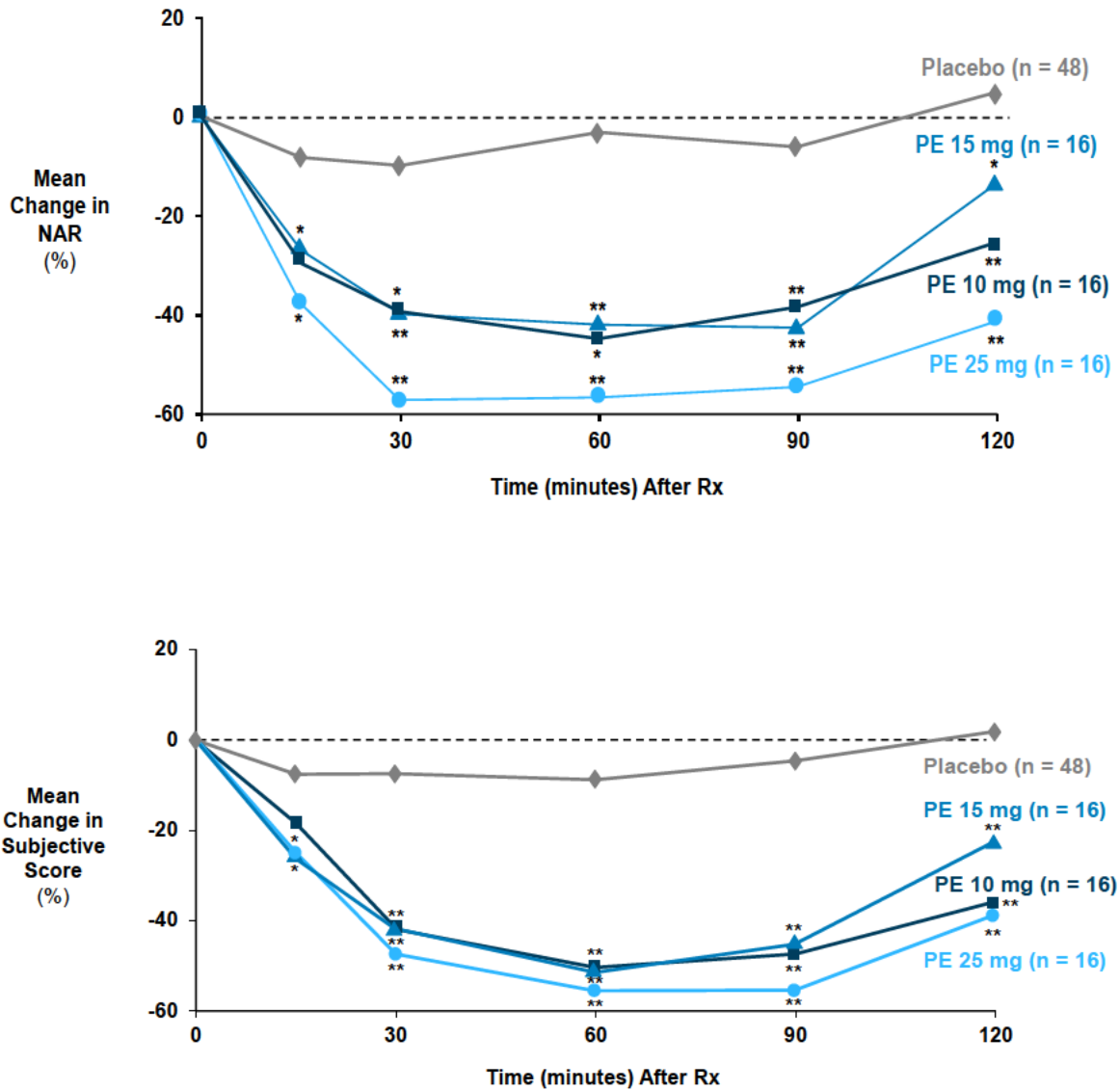
*p<0.05; **p<0.01 vs placebo

Note: Placebo data are pooled across groups for this display, but statistical testing vs placebo was only among subjects who received that particular dose.

Key: NAR = nasal airway resistance, PE = phenylephrine, Rx = administered dose

The "Elizabeth Biochemical Labs #2" study (Ref [#7] in: FDA OTC Volume 040298. January 12, 1968) was a randomized, double-blind, placebo-controlled, single-dose, incomplete two-way crossover[72] study in 38 subjects with congestion due to colds. Single oral doses of ephedrine 50 mg (n=6), and PE 10 mg (n=16), 15 mg (n=10), or 25 mg (n=6) were studied. Nasal airway resistance was measured at baseline, and from 15 to 120 minutes after a dose. Mean % reductions from baseline in nasal airway resistance were compared for each placebo-paired treatment using analysis of variance.

Results for the objective nasal airway resistance endpoint are illustrated in Figure 5-3. Each active dose statistically separated from placebo. PE 10 mg significantly reduced nasal airway resistance at all time points from 15 minutes through 2 hours (p=0.01). Maximal reduction was 40% at 45 and 60 minutes after the dose.

Using the Wilcoxon matched-pairs signed-ranks test, median subjective severity scores[73] for nasal congestion were significantly decreased for PE 10 mg vs placebo [-6, 0; p=0.01], PE 15 mg vs placebo [-6, -3; p=0.01] and for ephedrine 50 mg vs placebo [-8, -5; (p=0.05], but not for PE 25 mg vs placebo [-10, -6; p>0.05].

Figure 5-3 Time Course of Objective Decongestant Effects from Elizabeth Labs #2

*p<0.05; **p<0.01 vs placebo

Notes: Placebo data are pooled across groups for this display, but statistical testing vs placebo was only among subjects who received that particular dose. The ephedrine NAR curve is not shown but all observations were significant from 30 to 120 minutes.

Key: NAR = nasal airway resistance, PE = phenylephrine, Rx = administered dose

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[73] Sum of the differences from baseline in the severity of nasal congestion (0 = nose feels clear to 4 = completely blocked) measured at each timepoint.

The "Elizabeth Biochemical Labs #5" study (Ref #10 in: FDA OTC Volume 040298. May 27, 1970) was a randomized, double-blind, placebo-controlled, single-dose, incomplete crossover[72] study in 25 subjects with nasal congestion due to colds. Single oral doses of PE 10 mg (n=10), 15 mg (n=6) and 25 mg (n=9) were studied. Nasal airway resistance was measured at baseline, and from 15 to 240 minutes after a dose. Mean % reductions from baseline in nasal airway resistance were compared for each placebo-paired treatment using analysis of variance.

Results for the objective nasal airway resistance endpoint are illustrated in Figure 5-4. The % reduction in nasal airway resistance decreased significantly in all active groups compared to placebo as early as 30 minutes after dosing and lasted through 180 minutes. The maximum effect for PE 10 mg was at 60 minutes (29% decrease, p=0.01).

For the subjective endpoint, the difference from baseline in severity score for nasal congestion at each timepoint was summed for each subject. Using an analysis of variance model, the median of these sum differences was compared between each paired active and placebo treatments. No statistically significant differences were detected for any comparison: PE 10 mg vs placebo [-2.2, -1.2; SD 1.33, n=10], PE 15 mg vs placebo [-2.0, -2.2; SD 2.43, n=6], and PE 25 mg vs placebo [-4.8, -0.9; SD 3.40, n=9].

Figure 5-4 Time Course of Objective Decongestant Effects from Elizabeth Labs #5
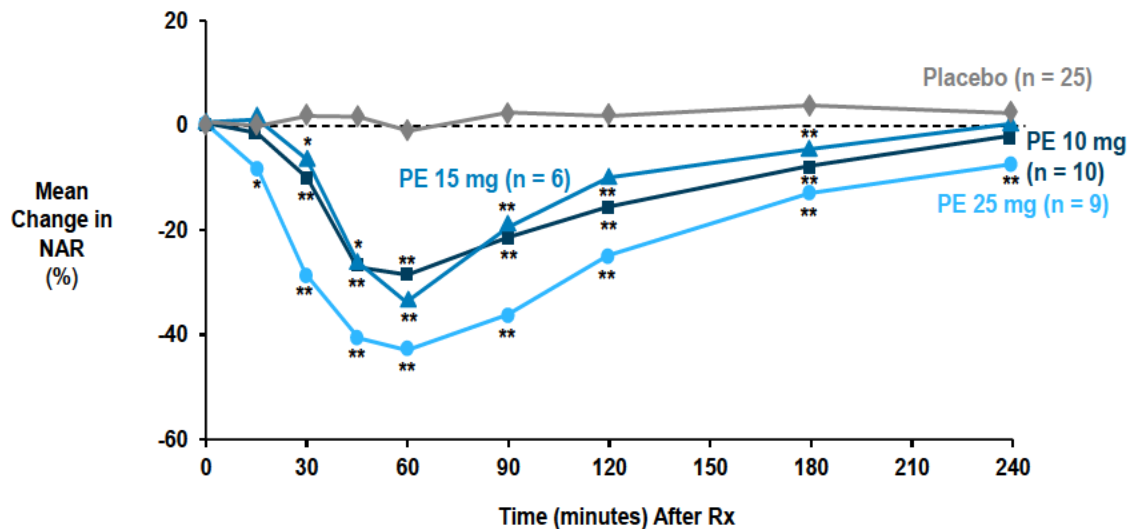
*p<0.05; **p<0.01 vs placebo

Note: Statistical testing vs placebo was among only subjects who received that particular dose
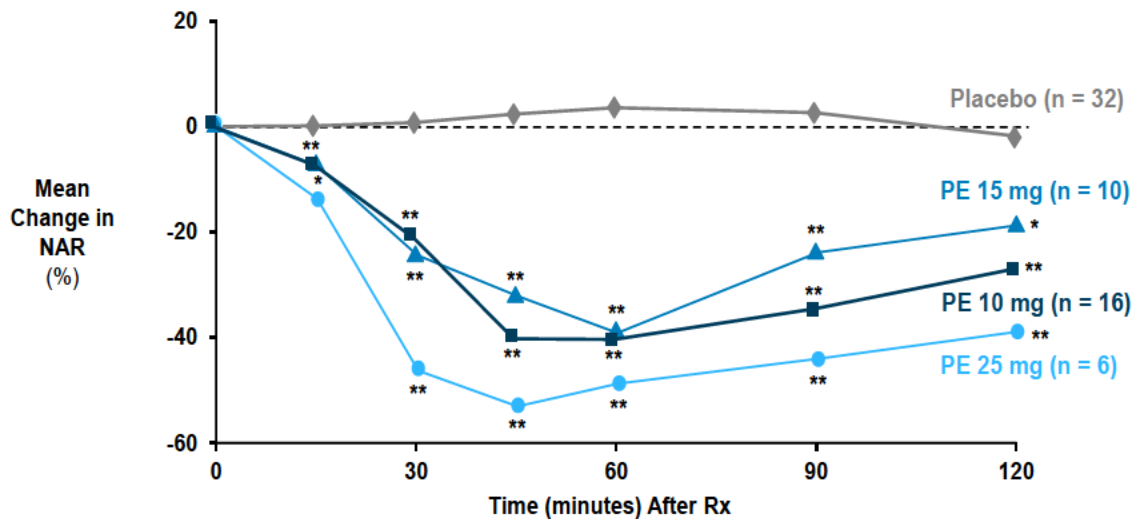
Key: NAR = nasal airway resistance, PE = phenylephrine, Rx = administered dose

Cintest Labs, Study #1 (Ref #22 in: FDA OTC Volume 040298. April 10, 1969), was a randomized, double-blind, placebo-controlled, single-dose, incomplete crossover[72] study in 47 subjects with congestion due to colds. Single oral doses of PE 10 mg (n=16) and 25 mg (n=16), and phenylpropanolamine 50 mg (n=15) were studied. Nasal airway resistance was measured at baseline, and from 15 to 240 minutes after a dose. Mean % reductions from baseline in nasal airway resistance were compared for each placebo-paired treatment using analysis of variance.

Results for the objective nasal airway resistance endpoint are illustrated in Figure 5-5. All active treatments decreased nasal airway resistance compared with placebo. The PE 10 mg dose produced a significant effect on nasal airway resistance at 90 to 180 minutes.

For the subjective endpoint, the difference from baseline in severity score for nasal congestion at each timepoint was summed for each subject. Using the Wilcoxon matched-pairs signed-ranks test, median subjective severity scores for nasal congestion were significantly decreased for PE 10 mg vs placebo [-7, -4; p=0.05] and phenylpropanolamine 50 mg vs placebo [-8, -3; p=0.01], but not for PE 25 mg vs placebo [-6, -4.6; p>0.1].

Figure 5-5 Time Course of Objective Decongestant Effects from Cintest Labs #1
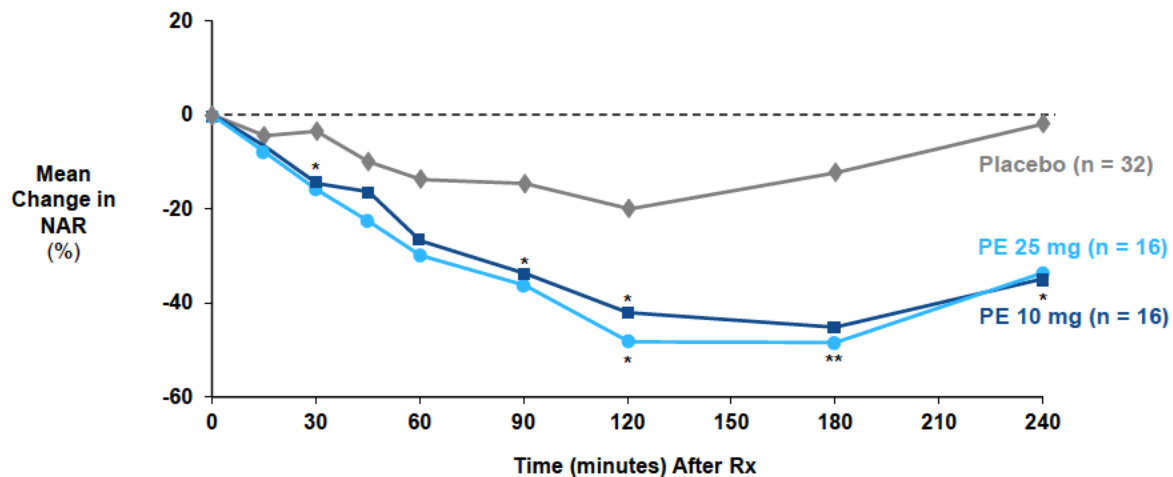
*p<0.05; **p<0.01 vs placebo

Notes: Placebo data are pooled across groups for this display, but statistical testing vs placebo was only among subjects who received that particular dose.

The phenylpropanolamine curve is not shown but observations at 90 and 120 minutes were significant.

Key: NAR = nasal airway resistance, PE = phenylephrine, Rx = administered dose

The efficacy of PE 10 mg was established in one multiple-dose study.

Cohen [1975] study (Ref #26 in: FDA OTC Volume 040298B. June 1975) was a randomized, double-blind, placebo-controlled, multiple-dose parallel group study of 200 subjects with nasal congestion due to the common cold.[74] 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 from at designated times over the 12-hours 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) had a mean age of 52.8 years [range 13-78 years]. The results for the objective nasal airway resistance endpoint are illustrated in Figure 5-6. 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 sneezing, runny nose, and stuffy nose (p< 0.05).

Figure 5-6 Time Course of Objective Decongestant Effects from Cohen 1975
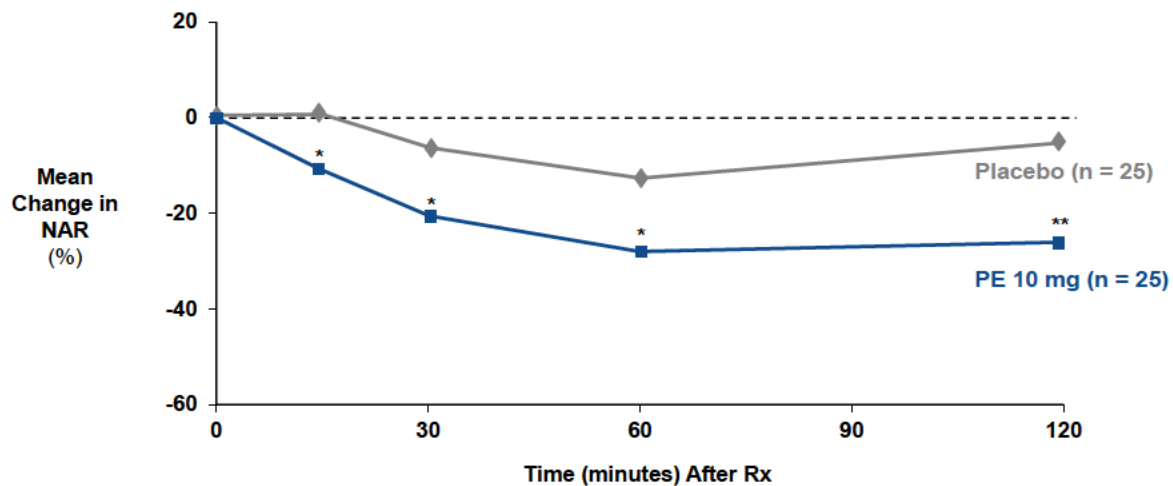
*p<0.05; **p<0.01 vs placebo
Key: NAR = nasal airway resistance, PE = phenylephrine, Rx = administered dose

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[74] Cohen BM. June 1975. Objective and subjective evaluation of phenylephrine HCl (5 mg) versus placebo tablets. In: FDA OTC Volume 040288B.

5.5.4   Meta-analyses of the Phenylephrine Efficacy Data

The drug approval process relies upon the principle of replication of results from well-designed, placebo-controlled, appropriately powered clinical trials to verify drug efficacy. In that aspect, multiple clinical trials have demonstrated the efficacy of PE 10 mg. In addition to individual clinical trials presented in the previous section, two meta-analyses of PE study data were published to synthesize results across studies. The first meta-analysis by the petitioners[75] argued that PE (10 mg) was not efficacious in reducing nasal congestion. The second meta-analysis was conducted on behalf of CHPA [Kollar 2007][76] and demonstrated statistically significant efficacy of PE 10 mg on nasal airway resistance (see Figure 5-7).

Although both analyses were conducted using data obtained primarily from the same studies, different statistical methodologies were employed, and different endpoints were evaluated. The two meta-analyses arrived at different stated conclusions about the efficacy of PE 10 mg as an oral decongestant but produced similar estimated effect sizes. In this section, the published meta-analyses are compared, and possible explanations for their different results are explored.

Study Selection Criteria

Hatton *et al.* selected randomized, placebo-controlled clinical studies evaluating the efficacy of oral PE as a single agent used as a nasal decongestant for inclusion in the primary analysis.[75] Studies that used combination products or compared PE with another oral decongestant were excluded. The meta-analysis was performed using aggregated treatment means and standard errors.

To be included in the Kollar analysis,[76] studies had to have used a single-dose, randomized, placebo-controlled design with an orally administered product in which PE 10 mg was the single active ingredient. These studies enrolled adult patients with acute nasal congestion due to the common cold; had the efficacy end point of nasal airway resistance; and contained sufficient data in the study report (*i.e.*, individual data for each patient and/or treatment group means and standard error of the mean, SE) to allow reanalysis and/or meta-analysis of PE 10 mg versus placebo. Studies not meeting these criteria were excluded. Meta-analyses

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[75] Hatton RC, Winterstein AG McKelvey RP, Shuster J, and Hendeles L. Efficacy and safety of oral phenylephrine: systematic review and meta-analysis. *Ann Pharmacother* 41(3):381-390.

[76] Kollar C, Schneider H, Waksman J, Krusinska E. Meta-analysis of the efficacy of a single dose of phenylephrine 10 mg compared with placebo in adults with acute nasal congestion due to the common cold. *Clin Ther* 2007;29(6):1057-1069.

were performed using individual data for each patient which facilitated more sophisticated modeling, including covariate adjustment for individual subject values.

Both meta-analyses included the same seven crossover studies. Hatton also included one parallel-group study.[74] While Kollar included this study in their re-analyses of individual studies, the results were not included in their original meta-analysis due to its different (parallel) design. Nonetheless, Kollar noted the parallel-group study itself provided significant evidence of the effectiveness of PE 10 mg.

Consideration of Endpoints

In the Hatton meta-analysis, the sole endpoint analyzed was the maximum percentage reduction in nasal airway resistance during the first 120 minutes after dosing (the most commonly studied period in the studies).[75] Based on this endpoint, Hatton concluded that PE 10 mg was ineffective as an oral nasal decongestant.

While understanding a drug's maximum effect is one measure of clinical interest, more clinically relevant endpoints to evaluate are those that examine treatment response over time. Such a time-point analysis is in accordance with the FDA Guidance on allergic rhinitis [FDA 2000].[77] This was the approach used in the Kollar meta-analysis, which analyzed the treatment effect of PE at all available time-points (from 15 to 120 minutes after dosing in the 7 studies, and up to 240 minutes after dosing in 5 studies). This analysis showed that PE 10 mg was significantly more effective than placebo at 30, 60, and 90 minutes.

Data at later time points of 120 and 240 minutes is more limited, with only five studies reporting results at these times. Two of the five studies demonstrated statistical significance at these time points. Of the three studies without statistical significance at these later time points, two did not contain a positive control.

In order to possibly explain the differences between the two analyses, CHPA attempted to replicate the Hatton meta-analysis using the same data from the same eight studies and the identical statistical methodology, evaluating both the maximal effect variable used by Hatton and the endpoints used by Kollar. Rather than re-analyzing all the individual time points, a single endpoint that best combines the results of the individual time points is area-under-the-curve (AUC), which takes into account the results over the individual time points. Because

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[77] FDA Draft Guidance "Allergic Rhinitis: Clinical Development Programs for Drug Products" (April 2000) was replaced by FDA Guidance for Industry "Allergic Rhinitis: Developing Drug Products for Treatment" (Sept 2018). See 81 *Fed. Reg.* 7816-7817 (Docket No. FDA-2000-D-0277). April 2000 Draft Guidance can be downloaded at https://www.regulations.gov/document/FDA-2000-D-0277-0002 (accessed on July 23, 2023).

the treatment effect over time is derived from multiple assessments, it is less variable, and therefore more sensitive, than the maximum effect, which is derived from a single assessment that can occur at different times. Further details on the AUC methodology are described in Appendix 5.

The CHPA re-analysis using the maximum effect endpoint yielded point estimates that differed slightly from those reported by Hatton, but only by approximately 2%, with a p-value of 0.15 (no significant treatment effect for PE 10 mg). When AUC was used as the endpoint, it yielded a p-value of 0.02 (significant treatment effect for PE 10 mg). Since the endpoint was the only difference between the two meta-analyses, these results indicate that the clinical endpoint selected is a major factor for the difference in conclusions between the Hatton and Kollar meta-analyses (see Figure 5-7).

Figure 5-7 Kollar Meta-Analysis Demonstrates Efficacy of Oral Phenylephrine

	PE 10 mg (N)	Difference in NAR AUC Treatment Difference vs Placebo	Treatment Difference (95% CI)
Elizabeth #2	16		29.8 (22.1, 37.5)
Elizabeth #5	10		18.6 (14.4, 22.8)
Cintest #1	16		11.6 (-0.4, 23.6)
Cohen 75	25*		15.0 (8.4, 21.6)
Cohen 72	16		31.7 (24.0, 39.4)
AHR 4010-3	12*		14.3 (4.8, 23.8)
Huntingdon #1	16		-1.6 (-16.3, 13.1)
AHR 7032	8		20.4 (-2.7, 43.5)
Lands	15		-10.7 (-19.9, -1.5)
McLaurin	88		9.5 (-2.4, 21.4)
Huntingdon #2	25		-3.2 (-11.2, 4.8)
Cintest #2	15		0.6 (-9.4, 10.6)
Cintest #3	15		0.1 (-12.5, 12.7)
Bickerman	20		4.9 (-4.3, 14.1)
Combined (8 studies used by Hatton)	138		9.5 (1.3, 17.6)
Combined (all 14 studies)	297		10.2 (3.4, 17.0)

-50 -40 -30 -20 -10 0 10 20 30 40 50
▶ Favors PE 10 mg

*Parallel study, the same number of subjects were in the placebo group
Key: AUC = area under curve, NAR = nasal airway resistance

5.5.5 *Examination of Dose-Response Across Studies*

Some studies evaluated more than one dose of PE, so where data on the percentage reduction of nasal airway resistance were available, they were further analyzed to determine whether a dose-response relationship could be demonstrated for PE. The efficacy of a 10 mg dose of PE was compared to a 25 mg dose in four studies in which model sensitivity was demonstrated (i.e., positive studies versus placebo). Results from this analysis show that there was a statistically significant difference between the 10 mg and 25 mg treatment groups in only one

study. Thus, the evidence is insufficient to conclude that PE 25 mg is a more effective dose. Additional details of this analysis are available in Appendix 6.

5.6   Overall Efficacy Conclusions

Several randomized, placebo-controlled studies provide evidence for the efficacy of PE 10 mg in the symptomatic treatment of nasal congestion, using objective measures (nasal airway resistance) and subjective assessments of symptom improvement. Of these studies summarized above and in Appendix 3 and Appendix 4, eight studies evaluating PE for nasal congestion show benefit in doses ranging from 5 mg to 25 mg on both objective and subjective measures. Five of these eight clinical studies found the PE 10 mg dose to be superior to placebo on objective measures of nasal airway resistance. Furthermore, four of the latter five studies also demonstrated statistically significant improvements in subjective symptoms of nasal congestion.

Many studies also included a positive control that separated from placebo, establishing the assay sensitivity of the clinical model. These results are also supported by the meta-analysis conducted by Kollar,[76] which evaluated nasal airway resistance at multiple timepoints as an AUC endpoint and demonstrated that PE 10 mg was superior to placebo. Furthermore, when the same statistical analysis as used by the Petitioners was applied to the Kollar AUC endpoint, the results confirmed again that PE 10 mg was superior to placebo.

6.0 OVERALL CONCLUSIONS

- The body of clinical data collected since the 1960's is broadly relevant and supports that PE 10 mg is a safe and effective OTC oral nasal decongestant. As such, PE 10 mg continues to meet the regulatory status of GRAS/E and should remain readily available to consumers for the temporary relief of nasal congestion.

- Concerns regarding methodologies and limitations of the four clinical studies that were published since the 2007 FDA NDAC meeting do not negate the findings of the 1976 OTC Expert Panel that PE provides temporary relief of nasal congestion based on evidence from the collection of earlier clinical studies.

For the reasons outlined in this briefing book, studies published since 2007 do not negate the conclusions of previous studies demonstrating that PE provides temporary relief of nasal congestion caused by colds or allergic rhinitis. These more recent clinical studies had important limitations (*e.g.*, inadequate blinding and concomitant use of an antihistamine) and were conducted using a study population that is not appropriate to evaluate the efficacy of PE for OTC use.

No changes to the CCABADP were suggested following the 2007 NDAC meeting, and the final monograph has remained unchanged since that time. The CHPA Phenylephrine Task Group continues to believe that, despite the newer studies cited in the Hendeles and Hatton citizen petition (2015)[7] and supported by others (Wilson *et al*., 2015),[8] the conditions of use for PE as an OTC oral nasal decongestant for the temporary relief of congestion due to the common cold or allergic rhinitis should remain.

APPENDICES

Appendix 1. Overview of Regulatory Activities Related to Phenylephrine

In 1976, oral phenylephrine hydrochloride was initially proposed to be Category 1 or GRAS/E by FDA's expert review panel after collectively assessing clinical data and scientific literature on oral phenylephrine available at that time. FDA accepted the expert review panel's findings that oral phenylephrine hydrochloride met the regulatory standards to be GRAS/E as a nasal decongestant active ingredient. Over a span of 18 years, as part of the formal rulemaking process, interested parties provided feedback to FDA on which ingredients should be included in the OTC monograph. The Agency would have reviewed all information and data submitted to the regulatory docket, and suggested changes, at each stage of the rulemaking process.

On August 23, 1994, FDA issued the final monograph for the original active ingredients and labeling for OTC nasal decongestants for multiple ingredients commonly found in cough, cold, and allergy medications. It included oral phenylephrine hydrochloride as an OTC ingredient that is safe and effective for temporary relief of nasal congestion due to the common cold and allergies. For adults and children ≥12 years old, 10 milligrams of oral phenylephrine hydrochloride can be used every 4 hours, not to exceed 60 milligrams in 24 hours. Phenylephrine bitartrate (effervescent dosage form) was added to the CCABADP monograph as a permitted oral nasal decongestant active ingredient over a decade later (on August 1, 2006).[78]

Table A1-1 Summary of Citizen Petitions and Supporting Documents Related to OTC Phenylephrine

Date Filed	Petitioners	FDA Response
February 1, 2007	Hendeles, Hatton, and Winterstein	None
November 4, 2015	Hendeles and Hatton[79,80]	Decision pending
June 19, 2023 (Withdrawal of 2007 citizen petition)	Hendeles and Hatton	Holding September 11-12, 2023, NDAC Meeting

Key: NDAC = Nonprescription Drugs Advisory Committee, OTC = over-the-counter, PE = phenylephrine

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[78] Cold, Cough, Allergy Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use, Amendment of Monograph for OTC Nasal Decongestant Drug Products (Final Rule). Accessed from https://www.govinfo.gov/content/pkg/FR-2006-08-01/pdf/E6-12265.pdf on August 7, 2023.

[79] Wilson *et al.* (November 6, 2015) filed a letter supporting the Hendeles-Hatton citizen petition.

[80] Hendeles & Hatton (May 2022) filed a supplement to their 2015 citizen petition under Docket No. FDA-2015-P-4131.

Appendix 2. Supplemental Information on Pharmacokinetic Studies

Table A2-1 Clinical Pharmacology Studies Published after 2007

[Study] Reference	Healthy Subjects	Design	Treatments (Doses in milligrams)	Objectives/Comparisons
[Atkinson 2015][14]				
Bioequivalence Study 1 *Jordan*	28 M / 0 F 28 ± 6.55 y	OL, single-dose, randomized CO	A (T): PE 10, APAP 1000, IBU 300 tablet; fasted B (R): PE 10 tablet; fasted C (R): APAP 1000, IBU 300 tablet; fasted	Bioequivalence of a new combination formulation to commercial products
Bioavailability Study 2 *Jordan*	30 M / 0 F 28 ± 6.85 y	OL, single-dose, randomized CO	D (T): PE 10, APAP 1000 tablet; fasted E (R): PE 10 tablet + APAP 500 tablet; fasted	Bioavailability of PE 10 combined with 500 or 1000 APAP
Bioavailability Study 3 *Jordan*	6 M / 0 F 28 ± 4.37 y	OL, single-dose, randomized CO	F (T): PE 5, APAP 1000 tablet; fasted G (R): PE 10 tablet; fasted	Bioavailability of PE 5 combined with 1000 APAP relative to PE 10
Bioequivalence Study 4 *Jordan*	26 M / 0 F 30 ± 6.10 y	OL, single-dose, randomized CO	H (T): PE 5, APAP 1000 tablet; fasted I (R): PE 10 tablet; fasted J (R): PE 10, APAP 1000 tablet; fasted	Bioequivalence of a new combination formulation to commercial products
[Gelotte 2015][15] Pharmacokinetic Study *Canada*	13 M / 15 F 32 ± 6.6 y	OL, single-dose, randomized CO	A: PE 10 (1 x 10 tablet + 2 PBO tablets); fasted B: PE 20 (2 x 10 tablets + 1 PBO tablet); fasted C: PE 30 (3 x 10 tablets); fasted D: Placebo (3 PBO tablets); fasted	Pharmacokinetics, metabolism, and cardiovascular safety of three doses of PE
[Gelotte 2018][16] Bioequivalence Study *United States*	10 M / 10 F 27 ± 11.1 y	OL, single-dose, randomized CO	A (T): PE tannate 25, GUA 200 ER tablet; fasted B (T): PE 10, APAP 625 tablet; fasted C (T): PE 10 tablet; fed D (R): PE 10 tablet; fasted	Effect of salt form, APAP, and food on the pharmacokinetics and metabolism of PE

Key: APAP = acetaminophen, BA = bioavailability, BE = bioequivalence, CO = crossover, ER = extended-release, F = female, GAU = guaifenesin, IBU = ibuprofen, M = male, OL = open-label, PBO = placebo, PE = phenylephrine, PK = pharmacokinetics, R = reference, T = test

Table A2-2 PE Pharmacokinetic Results[a] from Studies Published after 2007

Study [Reference]	Treatments (Doses in milligrams)	AUC∞ (pg·h/mL)	Cmax (pg/mL)	Tmax (h)	t½ (h)
Atkinson 2015[14]					
Bioequivalence Study 1	A: PE 10, APAP 1000, IBU 300	2311 (682)	3220 (1537)	0.67 (0.25)	1.23 (0.76)
	B: PE 10	**1105 (272)**	**874 (266)**	**0.76 (0.34)**	**1.35 (0.81)**
	C: APAP 1000, IBU 300	----	----	----	----
Bioavailability Study 2	D: PE 10, APAP 1000	2192 (586)	2546 (1264)	0.56 (0.27)	1.73 (0.95)
	E: PE 10, APAP 500	1780 (510)	2077 (863)	0.56 (0.19)	1.91 (1.35)
Bioavailability Study 3	F: PE 5, APAP 1000	1842 (968)	1598 (785)	0.83(0.30)	6.91 (2.83)
	G: PE 10	**1916 (825)**	**1132 (675)**	**0.71 (0.37)**	**5.91 (2.87)**
Bioequivalence Study 4	H: PE 5, APAP 1000	1479 (457)	1851 (686)	0.46 (0.15)	4.19 (1.38)
	I: PE 10	**1489 (516)**	**1119 (596)**	**0.55 (0.34)**	**3.56 (0.82)**
	J: PE 10, APAP 1000	2646 (848)	3696 (2495)	0.52 (0.25)	3.02 (0.92)
Gelotte 2015[15] Pharmacokinetic Study	**A: PE 10**	**956 (279)**	**1354 (954)**	**0.33 [0.22–1.0]**	**1.89 (0.82)**
	B: PE 20	2346 (984)	2959 (2122)	0.46 [0.25–1.0]	1.93 (0.85)
	C: PE 30	3900 (1764)	4492 (1978)	0.50 [0.27–1.0]	1.64 (0.43)
Gelotte 2018[16] Bioequivalence Study	A: PE tannate 25, GUA 200	943 (225)	926 (398)	0.63 [0.33-3.0]	1.51 (1.05)
	B: PE 10, APAP 625	1246 (281)	2458 (1287)	0.42 [0.25-1.5]	1.14 (0.63)
	C: PE 10 after high-fat meal	741 (120)	(591 (231)	0.50 [0.33-2.0]	1.20 (0.55)
	D: PE 10	**816 (465)**	**1053 (845)**	**0.33 [0.25-0.83]**	**1.22 (0.60)**

a: Reported as mean (standard deviation) except for Tmax, which is reported as median [range] in both Gelotte studies.

Key: APAP = acetaminophen, BA = bioavailability, BE = bioequivalence, GAU = guaifenesin, IBU = ibuprofen, PE = phenylephrine, PK = pharmacokinetics.

Bolded text reflects data from 10 mg dose of PE.

Phenylephrine Metabolism

The principal routes of PE metabolism are sulfate conjugation (mainly in the intestinal wall) and oxidative deamination by both the A and B forms of monoamine oxidase to aldehydes, which are further metabolized to m-hydroxymandelic acid (MHMA) and m- hydroxyphenyl-glycol-sulfate (MHP-S).[46,81]

In an early published study,[81] metabolites following a 30-mg PE dose excreted into urine included phenylephrine-sulfate (PE-S), phenylephrine-glucuronide (PE-G), MHMA, and MHP-S at 47%, 12%, 30%, and 6% of the dose, respectively. In two recent studies,[15,16] differences in the excreted percentages of metabolites were observed, and Table A2-3 summarizes data from a few of the treatment arms in these studies to highlight the new learnings.

- Compared with the early study, PE-G was excreted at <0.1 % for all PE doses instead of 6%; and the percentages of PE-S and MHMA for the PE doses were in a comparable range.
- The percentage of PE-S decreased about 10 points when the PE 10 mg dose was increased to 30 mg and when it was administered with acetaminophen 650 mg. These decreases can be explained by saturation of, or competitive inhibition with, pre-systemic sulfate conjugation during absorption. Consequently, more unchanged PE is absorbed, leading to higher overall drug exposure (AUC∞ and Cmax).

Table A2-3 Urinary Metabolites Reported as Mean (SD) Percentages of Dose

Administered Dose	[Gelotte 2015][15]		[Gelotte 2018][16]	
	PE 10 mg	PE 30 mg	PE 10 mg	PE 10 mg + APAP 650 mg
Phenylephrine (PE)	0.44 (0.11)	0.44 (0.12)	0.47 (0.10)	0.52 (0.09)
Phenylephrine sulfate (PE-S)	46.6 (12.4)	36.2 (9.2)	43.3 (12.6)	33.5 (6.74)
Phenylephrine glucuronide (PE-G)	0.033 (0.013)	0.033 (0.023)	0.002 (0.007)	0.025 (0.15)
m-hydroxmandelic acid (MHMA)	25.3 (10.9)	30.2 (7.8)	32.1 (7.53)	36.6 (8.60)
m-hydroxyphenylglycol-sulfate (MHP-S)	na	na	na	na
Total % of Dose Collected in Urine	---	---	75.6 (12.3)	70.7 (8.59)

Key: APAP = acetaminophen, MHMA = m-hydroxmandelic acid, MHP-S = m-hydroxyphenylglycol-sulfate, na = not assayed, PE = phenylephrine, PE-G = phenylephrine-glucuronide, PE-S = phenylephrine-sulfate, SD = standard deviation

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[81] Ibrahim KE, Midgley JM, Crowley IR, and Willaims CM. The mammalian metabolism of R-(-)-m-synephrine. J Pharm Pharmacol. 1983;35:144-147.

Appendix 3. Summary of Efficacy Studies Evaluated by 1976 OTC Expert Panel

Study Reference #[a]	Basis of Review	Results/Comments
Reference 5 Memo to Lands from Luduena. April 23, 1959	DB, PC, incomplete[b] crossover study. Topical PE and oral PE dose tested 10, 25, 50, 75 mg and PPA 25, 50 mg. n=14-15 volunteers/arm Post-dose Obs at 1-5 h	**Inconclusive study.** With the exception noted below, oral active controls were not significantly different from PBO for NAR. PPA 50 mg was significant only at 1 hour. Analysis: Inadequate assay sensitivity, no systemic drugs demonstrated any effect. Volunteers did not appear to have congestion at baseline.
Reference 6 Memo to Suter from Hulme. June 27, 1967 Elizabeth Biochemical Labs #1	DB, PC, R, incomplete crossover study in 25 subjects with congestion due to colds. Studied oral EPH. 8 mg (n=13) and PE 25 mg (n=12) Post-dose Obs at 15-120 min	**Positive study.** Both PE 25 mg and EPH significantly ↓'d NAR and subjective scores of nasal congestion compared to PBO.
Reference 7 Memo to Wessinger from Hulme. Jan 12, 1968 Elizabeth Biochemical Labs #2	DB, PC, R, incomplete crossover study in 38 subjects with congestion due to colds. Studied oral ephedrine 50 mg (n=6) and PE 10 mg (n=16), 15 mg (n=10), 25 mg (n=6) Post-dose Obs at 15-120 min	**Positive study.** 10 mg, 15 mg and 25 mg PE significantly decreased NAR vs PBO. 10 mg PE significantly reduced NAR at all time points from 15 min through 2 hours (p=0.01); maximal reduction was 40% at 45- and 60-min post dose. Subjective scores for nasal congestion significantly ↓'d for PE 10 mg and 15 mg, and not for PE 25 mg.
Reference 8 Memo to Blackmore from Hulme. June 2, 1969 Elizabeth Biochemical Labs #3	DB, PC, R incomplete crossover study in 42 subjects with congestion due to colds for 2 consecutive days. Studied oral PE doses of 5 mg (n=16), 15 mg (n=8) and 25 mg (n=9) and PPA 50 mg (n=9) Post-dose Obs at 15-240 min	**Positive study.** All actives significantly ↓'d NAR compared to PBO. No demonstration of dose-response. Only PE 15 mg and PPA 50 mg significantly reduced subjective scores of nasal congestion (p=0.05).
Reference 9 Memo to Blackmore from Hulme. August 11, 1969 Elizabeth Biochemical Labs #4	DB, PC, R incomplete crossover study in 20 subjects with congestion due to colds. PE 15 mg (n=6), 20 mg (n=5), and PE 25 mg (n=9) Post-dose Obs at 15-240 min	**Positive study.** 15 mg, 20 mg, and 25 mg PE significantly ↓'d NAR compared to PBO as early as 45 min post dose. Only 20 mg PE significantly ↓'d subjective scores of nasal congestion.
Reference 10 Memo to Blackmore from Hulme. May 27, 1970 Elizabeth Biochemical Labs #5	DB, PC, R incomplete crossover study in 25 subjects with congestion due to colds. Studied oral PE doses of 10 mg (n=10), 15 mg (n=6) and 25 mg (n=9) Post-dose Obs at 15-240 min	**Positive study.** All actives significantly ↓'d NAR compared to PBO as early as 30 minutes after dosing. PE 10 mg duration up to 180 min, peak effect at 60 min (29%↓, p=0.01). Subjective: only 25 mg PE significantly reduced subjective scores of nasal congestion.

Study Reference #[a]	Basis of Review	Results/Comments
Reference 20 Memo to Blackmore from Hulme. May 13, 1969 Huntingdon Research Center #1	DB, PC, R, incomplete crossover study in 48 subjects with congestion due to colds. Oral PE 10, 25 mg, and PPA 50 mg. n=16/arm Post-dose Obs at 15-240 min	**Negative study.** Neither PE dose separated from PBO on NAR. PPA significantly ↓'d NAR at 45 and 60 minutes. Subjective results not reported due to lack of objective effect.
Reference 21 Memo to Blackmore from Hulme. June 26, 1969 Huntingdon Research Center #2	DB, PC, R incomplete crossover study in 49 subjects with congestion due to colds. Oral PE 10 mg (n=25), and 20 mg (n=24). Post-dose Obs at 15-240 min	**Inconclusive study.** No doses separated from PBO on NAR. No positive control. Author cited possible reasons for failure: 1) larger variability (compared to other congestion studies), 2) insufficient training of technicians, 3) use of different technicians pre- and post-dosing. Subjective results not reported due to lack of effect on NAR.
Reference 22 Memo to Blackmore from Hulme. Apr 10, 1969 Cintest Labs #1	DB, PC, R incomplete crossover study in 47 subjects with congestion due to colds. PE 10 (n=16), and 25 mg (n=16), PPA 50 mg (n=15). Post-dose Obs at 15-240 min	**Positive study.** 10, 25 mg PE and PPA significantly ↓'d NAR compared to PBO. PE 10 mg effect on NAR seen at 90 to 180 minutes. PE 10 mg and PPA significantly reduced subjective scores for nasal congestion (p=0.05, p=0.01, respectively).
Reference 23 Memo to Blackmore from Hulme. Jan 23, 1970 Cintest Labs #2	DB, PC, R incomplete crossover study in 46 subjects with congestion due to colds. Oral PE 10 mg (n=15), 15 mg (n=16), and 20 mg (n=15). Post-dose Obs at 15-240 min	**Inconclusive study.** No doses separate from PBO on objective and subjective measures. No positive control. No evidence of assay sensitivity
Reference 24 Memo to Blackmore from Hulme. May 18, 1970 Cintest Labs #3	DB, PC, R incomplete crossover study in 47 subjects with congestion due to colds. Oral PE 10 mg (n=15), 15 mg (n=16), and 25 mg (n=16). Post-dose Obs at 15-120 min	**Inconclusive study.** No dose of PE separated from PBO for NAR. No positive control. PE 15 mg significantly ↓'d subjective scores of nasal congestion (p=0.05).
Reference 26 OTC volume 040288B (Cohen, 1975)	DB, PC, parallel group study of 200 subjects with nasal congestion due to head cold. Oral PE 10 mg every 4 h for 4 doses versus PBO Post-dose Obs at 15-120 min for NAR (n=25 per group), subjective assessments through 12 h	**Positive study.** Significant reduction in NAR by PE 10 mg from 15-120 min compared to PBO (11-28%, p≤0.05). Subjective: PE was significantly better than PBO for sneezing, runny nose, and stuffy nose, (p <0.05).

Study Reference #[a]	Basis of Review	Results/Comments

[a] Reference # refers to the bibliography from the FDA OTC Review (*Federal Register*, vol. 41, no. 176, pages 38399-38400, September 9, 1976)

[b] Denoted incomplete crossover since subjects received multiple treatments but not all of them. Specifically, each subject received one of the active treatments and placebo.

Key: DB = double-blind, EPH = ephedrine, NAR = nasal airway resistance, PBO = placebo, PC = placebo-controlled, PE = phenylephrine, PPA = phenylpropanolamine, R = randomized

Appendix 4. Summary of Additional Efficacy Studies Available Before 2007

Seven additional efficacy studies of PE that were not reviewed by the 1976 OTC Expert Panel were discussed at the 2007 NDAC meeting. Results from these studies were mixed, with two being positive/supportive,[67,68] one inconclusive,[69] and four negative.[10,11,70,71] Five of these seven studies are summarized in this appendix, whereas the remaining two studies[10,11] published by Day *et al*., 2009 and Horak *et al*., 2009, are summarized in Sections 5.3.1 and 5.3.2, respectively.

The Cohen [1972] study[67] was a double-blind, randomized, placebo-controlled, incomplete two-way crossover study that examined the effects of PE (10, 15, 25 mg) on nasal airway resistance and improvement of subjective assessment of nasal congestion in 48 subjects with nasal congestion due to the common cold. Post-dose observations were made at 15 to 120 minutes. All doses of PE significantly reduced nasal airway resistance and improved subjective scores of nasal congestion compared to placebo. Subjective symptom scores separated from placebo for all PE groups, without notable differences between them. This study clearly demonstrates the efficacy of PE on objective and subjective measures.

Study AHR-4010-3[68] was a randomized, 6-center, multiple-dose, double-blind, parallel group study conducted in 274 subjects (aged 18 to 77 years) with nasal congestion due to an upper respiratory infection (URI). Subjects took study medication every 4 hours over a 72-hour period. The study evaluated PE 10 mg, phenylpropanolamine 25 mg, PE 5 mg plus phenylpropanolamine 12.5 mg, and placebo. Subjective symptom evaluations were provided by the subject at baseline, and at 24, 48 and 72 hours after taking the first dose of study medication, and by the investigator at baseline and at 72 hours. Both the subject and investigator provided an overall evaluation of therapeutic effect at the end of the evaluation period. Only subjects (n=48; 12 in each of the 4 groups) enrolled at one study site underwent objective assessments at 15, 30, and 45 minutes, and 1 to 4 hours after the first dose of medication. PE 10 mg and phenylpropanolamine 25 mg were found to be statistically significantly better than placebo for nasal airway resistance at 30 to 180 minutes after the first dose and PE 10 mg was statistically significantly better than placebo for subjective symptom assessments at 72 hours. The pooled data from the remaining 5 sites failed to show significant differences among the 4 treatments by subjective assessments. Based on the nasal airway resistance outcomes, this study is supportive of the efficacy of PE 10 mg for nasal congestion.

The McLaurin [1961] study[69] assessed the oral decongestant efficacy of PE 10 mg, phenylpropanolamine 25 mg, pseudoephedrine 60 mg and ephedrine 25 mg compared with placebo in a mixed population of patients with rhinitis. The quality of this study is questionable for a number of reasons including that the study population consisted of patients with rhinitis of mixed etiologies (common cold, sinusitis, allergy, vasomotor rhinitis, hypothyroidism); the method of balancing the treatment order, if performed, was not clear; and a large number of patients (42 of 130 enrolled subjects) were discontinued from the study and not included in the analysis, potentially biasing the results. Only ephedrine 25 mg was found to significantly reduce nasal airway resistance compared to placebo. Subjective assessment of nasal congestion did not reveal any significant treatment effects resulting from any of the 4 active treatments. The validity and assay sensitivity of the model were thus not clearly demonstrated; therefore, this study is inconclusive and cannot be considered as showing a lack of PE efficacy.

AHR Study 7032[70] conducted in 1967 was a randomized, single-dose, single-blind, placebo controlled, full-factorial, 8-way crossover, single-center study conducted in 8 subjects (ages 18-60) with stable or chronic nasal congestion due to allergy. Each subject received each of the following treatments in random order on 8 separate treatment days: PE 10 mg, phenylpropanolamine 10 mg, brompheniramine 8 mg, PE and phenylpropanolamine, PE and brompheniramine, phenylpropanolamine and brompheniramine, and PE with phenylpropanolamine and brompheniramine and placebo. During each treatment period, nasal airway resistance was measured at baseline and at 30, 60, and 120 minutes after dosing. Subjects were required to have a nasal airway resistance reading of at least 10 mm at baseline. Changes in nasal airway resistance were not statistically significant between the four treatments including PE and the four treatments without PE. PE alone was not compared to the other groups.

Bickerman [1971][71] evaluated the efficacy of oral PE 10 mg, pseudoephedrine 60 mg and phenylpropanolamine 40 mg compared to placebo in an unknown number of patients with chronic non-seasonal rhinitis using an objective measure (nasal airway resistance). The publication associated with this study is generally lacking in detail and appears to be more of a description and validation of a rhinometric method where a number of baseline measurements were made in patients with upper respiratory tract infections. Pseudoephedrine and phenylpropanolamine but not PE reduced nasal airway resistance from 30 minutes to 4 hours post dose. No subjective assessments of nasal congestion were made.

Table A4-1 Further Details on the Additional Efficacy Studies Available Before 2007

Study	Basis of Review	Results/Comments
Cohen, 1972	DB, PC, R incomplete two-way crossover study of 48 subjects with nasal congestion due to the common cold. Each subject received oral PBO and PE 10 mg (n=16) or 15 mg (n=16) or 25 mg (n=16). Post-dose observations at 15-120 min	**Positive study.** All active doses significantly reduced NAR compared to PBO. For PE 10 mg, significant reduction was seen from 30-120 min (p≤0.01- 0.05). Peak reduction of ~40% at 60 min post dose. All doses significantly reduced subjective scores of nasal congestion from 30-120 minutes. Mean % reduction in subjective scores paralleled reduction in NAR for each dose.
AHR-4010-3 December, 1983	R, PC, DB, parallel, multiple dose (every 4 hours), 3-day study in 274 patients with nasal congestion due to URI of less than 48 hours in duration <u>Treatments (n for NAR)</u> PE 5 mg + PPA 12.5 mg (n=12) PE 10 mg (n=12) PPA 25 mg (n=12) PBO (n=12) <u>Assessments</u> NAR (electronic posterior rhinometry) at 15, 30, 45, 60, 120, 180, and 240 min after first dose Subjective symptomatic measures (4-point categorical scale) at 24, 48 and 72 hours; Investigator symptomatic evaluation at 72 hours; Overall (global) evaluation by both subject and Investigator at 72 hours	**Supportive study.** Only 1 of 6 sites measured NAR (n=48). PE 10 mg significantly reduced NAR at 30-180 minutes compared to PBO, PE 10 mg was essentially equal to PPA at all timepoints. In the analysis of the subjective assessment for this site, PE was significantly better than PBO for subjects' assessment of stuffy nose at 72 hours. For the most part, both PE and PPA provided similar relief of runny nose, nasal congestion, and sneezing, although the severity of the subjects' stuffy nose for PE was significantly lower than PPA at 72 hours. A significant treatment-by-site interaction was observed for subject and investigator's overall evaluations at 72 hours. When the site that measured NAR was excluded, pooled data from the remaining 5 sites failed to show significant differences among the four treatments.
McLaurin, 1961	Cross-over study in 88 subjects with nasal congestion due to a variety of causes including colds, sinusitis, allergy, vasomotor rhinitis, and hypothyroidism. Compared oral PBO, PE 10 mg, PSE 60 mg, PPA 25 mg and EPH 25 mg. Measured NAR at baseline and 60 minutes post dose. Subjective change of the nasal airway (6-category scale) recorded 60 min post dose and the following a.m. after taking a second dose 1 h prior to bedtime the previous evening. Vital signs.	**Inconclusive study.** PSE did not separate from PBO. Only ephedrine was found to significantly (p=0.05) lower NAR (38%). No significant differences in subjective assessments between PBO and the other treatment groups at either of the 2 time points. Significant methodologic issues: Almost 1/3 of the subjects (42/130) who entered the study dropped out before completion and were excluded from all analyses. This could have severely biased the results because, to some extent, only responders (*i.e.,* patients who returned the completed series of comparison tests) were analyzed. Statistical methods were not provided.

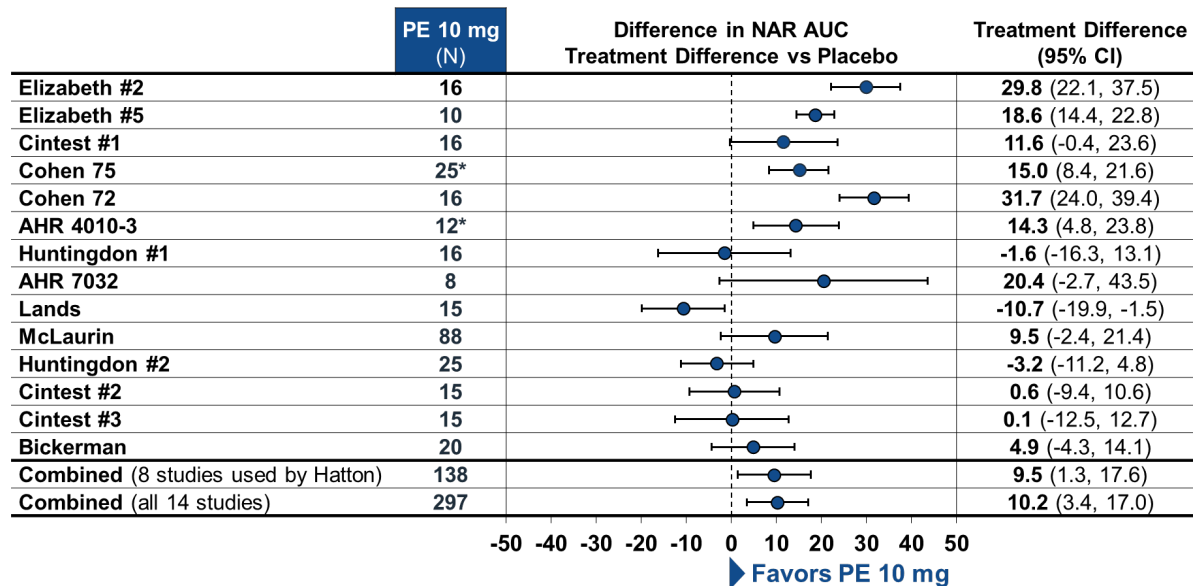| Study	Basis of Review	Results/Comments
AHR Study 7032 November, 1967	R, PC, SB, single dose, single-center crossover, 2-hour evaluation period in 8 subjects with stable or chronic nasal congestion Treatments PBO, PE 10 mg, PPA 10 mg, BROM 8 mg, PE + PPA, PE + BROM, PPA + BROM, PE + PPA + BROM (n=8) Assessments Inspiratory and expiratory NAR Post-dose observations at 30-120 min	**Negative Study** PE 10 mg monotherapy produced reductions ($p<0.10$) in inspiratory and expiratory nasal airway resistances at 1 hour after dosing. Readings at 30 minutes and 2 hours after dosing were numerically better, but not statistically different from placebo.
Bickerman, 1971	This study was described by the author as a "Representative DB crossover study". An unknown number of subjects with chronic non-seasonal rhinitis received oral PBO, PSE 60mg, PPA 40 mg or PE 10 mg. Post-dose observations at 30-240 min	**Negative Study.** PE did not separate from PBO. PSE and PPA showed significant reduction of NAR compared to PBO at all post-dose time points (30 min – 4 hours) whereas PE did not. No subjective assessments of nasal congestion were made.

Key: BROM = brompheniramine, DB = double-blind, EPH = ephedrine, NAR = nasal airway resistance, PBO = placebo, PC = placebo-controlled,
PE = phenylephrine, PPA = phenylpropanolamine, PSE = pseudoephedrine, R = randomized, SB = single-blind

Appendix 5. Kollar[76] Meta-analysis Methods

Area-under-the curve (AUC), which is essentially a weighted average across the time points, is a useful, single endpoint to capture the % reduction in nasal airway resistance (NAR) data over a time period. To directly compare this endpoint with the maximum % reduction endpoint that Hatton *et al.*[75] used, we analyzed this AUC endpoint over the same 2-hour interval with the same eight placebo-controlled, randomized studies (7 crossover studies and 1 parallel study), and using the Petitioners' methodology.

We summarized the results of the studies using a random effects meta-analysis model with the aggregated treatment means and standard errors. For the crossover studies, we used the mean and standard error of the within-subject difference between the relative change in nasal airway resistance during the PE and placebo periods, and for the parallel-group study, we used the difference between the mean changes and the pooled standard errors. Again, this is exactly the method that Hatton *et al*. used, except that our endpoint is the AUC of the relative changes, and their endpoint was the maximum relative change. The individual study data were analyzed by the within-group t-test on the within-subject differences in the changes from baseline for the crossover studies and the independent groups t-test on the within-subject changes from baseline for the parallel study; apparently Hatton *et al*. did the same. All pairwise tests were two-sided. The results are shown in Figure A5-1 below.

Figure A5-1 Kollar Meta-Analysis Demonstrates Efficacy of Oral Phenylephrine

	PE 10 mg (N)	Difference in NAR AUC Treatment Difference vs Placebo	Treatment Difference (95% CI)
Elizabeth #2	16		**29.8** (22.1, 37.5)
Elizabeth #5	10		**18.6** (14.4, 22.8)
Cintest #1	16		**11.6** (-0.4, 23.6)
Cohen 75	25*		**15.0** (8.4, 21.6)
Cohen 72	16		**31.7** (24.0, 39.4)
AHR 4010-3	12*		**14.3** (4.8, 23.8)
Huntingdon #1	16		**-1.6** (-16.3, 13.1)
AHR 7032	8		**20.4** (-2.7, 43.5)
Lands	15		**-10.7** (-19.9, -1.5)
McLaurin	88		**9.5** (-2.4, 21.4)
Huntingdon #2	25		**-3.2** (-11.2, 4.8)
Cintest #2	15		**0.6** (-9.4, 10.6)
Cintest #3	15		**0.1** (-12.5, 12.7)
Bickerman	20		**4.9** (-4.3, 14.1)
Combined (8 studies used by Hatton)	138		**9.5** (1.3, 17.6)
Combined (all 14 studies)	297		**10.2** (3.4, 17.0)

-50 -40 -30 -20 -10 0 10 20 30 40 50
► **Favors PE 10 mg**

*Parallel study, the same number of subjects were in the placebo group

Appendix 6. Additional Information on PE Dose-Response

The efficacy of a 10 mg dose of PE was compared to a 25 mg dose in the four studies in which model sensitivity was demonstrated (*i.e.*, the positive studies versus placebo). The doses were compared based on their relative effects over placebo, where the effect was based on the AUC of the % nasal airway resistance improvement over baseline. In three studies, the effects were compared by analysis of covariance with dose and treatment as fixed effects, baseline nasal airway resistance as a covariate, and subject as a repeated measure (each subject received placebo and either PE 10 mg or PE 25 mg). The fourth study [Cohen 1972],[67] provided neither raw data nor summary data to estimate standard errors; so only the effect size estimates are presented. Results are summarized in Table A6-1.

Table A6-1 Change in Nasal Airway Resistance (AUC) PE 10 mg versus PE 25 mg

Study	PE 10 mg LS Mean % change in AUC ± S.E.	PE 25 mg LS Mean % change in AUC ± S.E.	Difference (PE 25 mg – PE 10 mg) LS Mean % change in AUC ± S.E.	p
Elizabeth #2	29.3 ± 3.6	38.8 ± 5.9	9.4 ± 6.9	0.19
Cintest #1	11.6 ± 6.0	9.9 ± 6.0	-1.7 ± 8.4	0.84
Elizabeth #5	18.1 ± 2.5	31.0 ± 2.7	12.9 ± 3.7	0.003
Cohen (1972)*	31.7	38.6	6.9	

*The article provided insufficient information to compute standard errors
Key: AUC = area under curve, LS = least square, PE = phenylephrine, SE = standard error

In summary, these results show that in only one study was there a statistically significant difference between the 10 mg and 25 mg dose groups. Thus, the evidence is insufficient to conclude that 25 mg is a more effective dose. While suggestive of some incremental response with increasing doses of PE, limited data comparing PE 10 mg against higher doses do not strongly support the presence of a dose-response for reduction in nasal airway resistance or improvement in symptoms of nasal congestion. Only one [Elizabeth #5 1970] of the four studies demonstrated improved subjective response when the dose was increased to 25 mg. Based on the available study data, doses greater than PE 10 mg do not consistently produce greater decongestant effect as measured by nasal airway resistance.

Appendix 7. Safety Review of Phenylephrine

Key Points

- The safety of oral phenylephrine (10 mg) as an oral nasal decongestant is well established based on existing placebo-controlled clinical trial data and monitoring of post-marketing adverse event reports. This has been confirmed repeatedly over the past 45+ years, beginning with the OTC Cough-Cold Advisory Review Panel in 1976.

- In a 2007 review, 15 placebo-controlled studies were identified which collected vital sign information (pulse rate, systolic blood pressure, diastolic blood pressure) for phenylephrine (5-100 mg). In studies that included a 10 mg dose, there was no discernable relationship between changes in pulse and blood pressure, nor was there a clear pattern of vital sign changes at different time points.

- More recent placebo-controlled studies conducted post-2007 have shown phenylephrine to be well-tolerated at doses up to 30 mg. Dose related changes in systolic blood pressure, which resolved post-treatment, were observed in 2 studies (Meltzer *et al*., 2015; 2016).[12,13]

A7.1 Placebo-Controlled Studies (conducted before 2007)

Fifteen of 20 placebo-controlled studies of PE conducted prior to 2007 reported safety data. Of the 8 studies collecting data on adverse events, 4 studies reported no adverse events in subjects treated with single doses of PE ranging from 5 mg to 25 mg. In the other 4 studies, most adverse events reported by PE-treated subjects were reported at a frequency similar to placebo-treated subjects. Nervousness was reported more frequently with PE 15 mg and 25 mg than with PE 10 mg or placebo.

Fifteen studies collected data on vital signs for PE doses ranging from 5 mg to 100 mg. Many studies reported no change in vital signs for various doses of PE at various time points, and both increases and decreases for pulse and blood pressure were observed. In studies that included a 10 mg PE dose, there was no discernable relationship between changes in pulse and blood pressure, nor was there a clear pattern of vital sign changes at different time points.

Statistically significant differences from placebo in pulse were reported more frequently with doses of PE greater than 10 mg; some of the largest mean increases from baseline in pulse were observed with PE 25 mg. Mean increases from baseline in systolic blood pressure were

larger with increasing PE dose. However, all mean increases in pulse compared to baseline were ≤ 11 beats per minute and mean increases in blood pressure compared to baseline were less than 5 mm Hg and may not be clinically relevant.

A7.2 Placebo-Controlled Studies (conducted after 2007)

More recent placebo-controlled studies conducted after 2007 have shown PE to be well-tolerated at doses up to 30 mg. Dose related changes in systolic blood pressure, which resolved post-treatment, were observed in 2 studies (Meltzer *et al*., 2015; 2016).[12,13]

A7.3 Post-Marketing Safety Data for Phenylephrine

Disproportionality analysis reporting odds ratios (ROR; 95% CI) for adverse event cases reported in association with use of PE (single ingredient) versus PE/acetaminophen (combination products) were performed in two adverse event databases (independent analysis by the Procter & Gamble Company).[82] The rationale for these comparisons is that when combined with acetaminophen (500-1000 mg), both Cmax and AUC∞ for PE are increased.

In a review of adverse event data from Uppsala Monitoring Centre (1968-2017), no meaningful differences (*i.e.,* no events with ROR above 2) were observed between PE alone and PE with acetaminophen for events of a cardiovascular nature or of potential sympathomimetic effects. A similar approach using data from the FDA FAERS database (2004-2023) also found no meaningful differences (*i.e.,* no events with ROR above 2) between PE alone and PE with acetaminophen for events of a cardiovascular nature or of potential sympathomimetic effects.

These results lend further support to the established safety profile of PE.

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[82] Procter & Gamble 2023, Disproportionality Analysis for reported cases of phenylephrine alone versus phenylephrine in combination with acetaminophen in the Uppsala Monitoring Centre (1968-2017) and FDA Adverse Event Recording System (FAERS; 2004-2023) Databases.

Appendix 8. Clinical Classifications of Allergic Rhinitis

Allergic rhinitis has been classified by the

- allergen causing symptoms: seasonal, perennial, and episodic allergic rhinitis;
- duration of symptoms: intermittent and persistent allergic rhinitis; and
- severity of symptoms: mild, moderate, and severe.[83]

The classification by allergen is the oldest one, and still useful in the clinical setting.[83] This classification is popular in the USA, and used to define populations studied in drug clinical trials per FDA's Allergy Guidance.[51] Seasonal allergic rhinitis develops during times of the year that correspond to pollination of plants and trees, perennial allergic rhinitis develops anytime during the year when conditions in a patient's environment (e.g., dust, pet fur, and mold) cause symptoms, and episodic allergic rhinitis is caused by exposure to a specific airborne allergen on a sporadic and short-term basis.[84] This classification scheme is often inconsistent because sensitization to multiple seasonal allergens can result in year-round disease; whereas sensitization to perennial allergens (*e.g.*, animal dander) can result in symptoms during a limited time period.[52]

Subsequently, classifications by duration of symptoms and severity have been developed through the initiative, Allergic Rhinitis and its Impact on Asthma (ARIA), in collaboration with the World Health Organization. Their treatment guidelines based on the following classifications have evolved over 20 years and been endorsed by many national and international scientific societies and organizations.[53,54,55,56] According to ARIA,

- Intermittent allergic rhinitis is defined on the basis of symptoms that are present for less than 4 days per week or less than 4 weeks in duration.
- Persistent allergic rhinitis is defined on the basis of symptoms that occur more than 4 days per week and more than 4 weeks of the year.
- Allergy symptoms are classified as mild when quality of life is not affected.
- Allergy symptoms are moderate to severe when at least one of the following quality of life indicators are affected: sleep disturbance, impairment of daily activities, sports, or leisure, impairment of school or work, or troublesome symptoms.[53]

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[83] Emeryk A, Emeryk-Maksymiuk J, Janeczek K. New guidelines for the treatment of seasonal allergic rhinitis. 2019 *Postepy Dermatol Alergol.* 36(3):255-260.

[84] Seidman MD, Gurgel RK, Lin SY*, et al.* Clinical practice guideline: allergic rhinitis executive summary. 2015 *Otolaryngol Head Neck Surg* 152: 197-206.

The following schematic by Emeryk and colleagues,[83] illustrates how both intermittent and persistent allergic rhinitis may have a mild or moderate/severe clinical course and different forms of the disease may pass into one another (See Figure A8-1).

Figure A8-1 ARIA Classification of Allergic Rhinitis and Relationships Between Forms

Allergic rhinitis → Intermittent / Persistent → Mild ↔ Moderate/severe
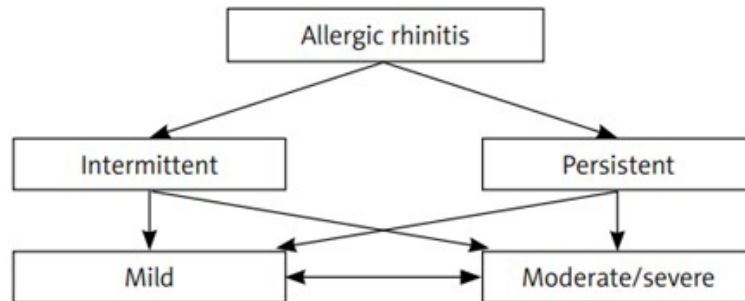
Recently, the severity classification of allergy symptoms has been further refined by ARIA because of the heterogenicity of the moderate/severe patient population. The presence of symptoms with moderate severity is defined as affecting from 1 to 3 of the quality-of-life indicators, whereas all 4 indicators are affected with severe symptoms.[54]

Based on the ARIA classifications, treatment guidelines have been proposed and developed,[52] including integrated care pathways (ICPs), which are structured multi-disciplinary care plans detailing the key steps of patient care.[85,86] Figure A8-2 shows the ICPs for allergic rhinitis. It has been modified from its published version by removing care pathways specific for asthma in order to focus on allergic rhinitis.[86]

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[85] Campbell H, Hotchkiss R, Bradshaw N, *et al.* Integrated care pathways. 1998 *BMJ*. 316(7125):133–137.
[86] Bousquet JJ, Schünemann HJ, Togias A, *et al.* Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases. 2019 *Clin Transl Allergy*. 9:44.

Figure A8-2 Integrated Care Pathways for Allergic Rhinitis[86] (Modified)