U.S. Food and Drug Administration

Center for Drug Evaluation and Research

Office of New Drugs

Office of Nonprescription Drugs

Scientific Review Supporting Proposed Administrative Order

November 4, 2024

Order ID:	OTC000036
Order Title:	Amending Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use
OTC Monograph:	M012
Active Ingredients:	Phenylephrine hydrochloride and phenylephrine bitartrate
Dosage Forms:	Phenylephrine hydrochloride: liquid and tablet Phenylephrine bitartrate: effervescent dosage form
Route of Administration:	Oral
Purpose of Review:	Review of efficacy

I. Introduction

This scientific review describes the findings and proposals supporting Proposed Administrative Order (OTC000036), amending the requirements for cold, cough, allergy, bronchodilator, and antiasthmatic (CCABA) drug products for over-the-counter (OTC) human (CCABA drug products), as currently described in Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (OTC Monograph M012). OTC Monograph M012 describes the conditions under which OTC CCABA drug products are generally recognized as safe and effective (GRASE).[1,2] Under OTC Monograph M012, orally administered phenylephrine hydrochloride (PEH) and phenylephrine

[1] OTC Monograph M012 is set forth in Final Administrative Order OTC000026 Over-the-Counter Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use, available via the OTC Monographs@FDA portal at https://dps.fda.gov/omuf.

[2] 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. See 21 CFR part 330.10(a)(4)(ii).

bitartrate (PEB) in an effervescent dosage form are generally recognized as safe and effective as nasal decongestant active ingredients (see §§ M012.20(a)(1) and (4) of OTC Monograph M012). In this evaluation, FDA considered scientific data on the efficacy, pharmacology, and safety of oral phenylephrine (PE)[3] to inform a determination under section 505G(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) whether oral PE is GRASE for adult and pediatric populations[4] as an oral nasal decongestant within the dosage limits and dosage forms allowed under OTC Monograph M012 (see Table 1 and § M012.80(d)(1)).[5]

Table 1. OTC Monograph M012: Dosage and Dosage Limits of Oral Phenylephrine

Age Range	Phenylephrine Hydrochloride	Phenylephrine Bitartrate
Adults and children 12 years of age and over	10 mg every 4 hours, not to exceed 60 mg in 24 hours	15.6 mg every 4 hours, not to exceed 62.4 mg in 24 hours
Children 6 to under 12 years of age	5 mg every 4 hours, not to exceed 30 mg in 24 hours	7.8 mg every 4 hours, not to exceed 31.2 mg in 24 hours
Children 2 to under 6 years of age	2.5 mg every 4 hours, not to exceed 15 mg in 24 hours	Consult a doctor
Children under 2 years of age	Consult a doctor	Consult a doctor

Source: OTC Monograph M012 § M012.80.
Abbreviation: OTC, over-the-counter.

II. Scientific Review of Efficacy Data

FDA conducted a comprehensive review of clinical data regarding the effectiveness of oral PE as a nasal decongestant. FDA reviewed clinical data on PE that have become available since FDA's review of data to support the GRASE determination for oral PE as a nasal decongestant in the 1994 final rule.[6] In order for FDA to understand this newer clinical data within the context of the long history of oral PE use, FDA also reviewed the historical data that were used by FDA to make the GRASE determination for oral PE as a nasal decongestant.

[3] When not otherwise specified, all doses and dosages are for PEH. However, the implication for effectiveness applies to both PEH and PEB because the inclusion of PEB in OTC Monograph M012 was based solely on bioavailability data that PEB was comparable to PEH (see 71 FR 83358). Therefore, in general, "oral PE" is used throughout the document to refer to both orally administered phenylephrine hydrochloride and orally administered phenylephrine bitartrate in an effervescent dosage form.

[4] In OTC Monograph M012, FDA's GRASE determination on the doses of oral PE for ages less than 12 years old was based entirely on historical use and not clinical data in those age groups. Since all of the GRASE determination was based on extrapolation of efficacy and dosing from adult data, FDA evaluates these pediatric issues by addressing the adult data under the pediatric extrapolation principles set forth in the draft guidance for industry (CDER 2022b)) and in the draft guidance (CDER 2022a) Guidances are updated periodically. For the most recent version of a guidance, visit https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[5] This proposed administrative order review applies to oral PE as a nasal decongestant and therefore does not apply to the following: (1) intravenous PE approved under an NDA; (2) GRASE status of topically administered PE under OTC Monograph M015: Anorectal Drug Products for Over-the-Counter Human Use; (3) GRASE status of ophthalmically administered PE under OTC Monograph M018: Ophthalmic Drug Products for Over-the-Counter Human Use; and (4) GRASE status of intranasally administered PE for nasal congestion under OTC Monograph M012.

[6] See 59 FR 43409 (Aug. 23, 1994). Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Nasal Decongestant Drug Products (1994 Final Rule).

This comprehensive review on the effectiveness of oral PE included:

- Review of historical data (prior to 1994) regarding efficacy
- Review of two environmental exposure unit (EEU) studies
- Review of three more recent (post-1994) clinical trials on the efficacy of oral PE

A. Review of Historical Data Regarding Efficacy

FDA reviewed the historical data that was used by FDA to support FDA's GRASE determination for oral PE in the 1994 final rule.

1. Background

In the *Federal Register* of September 9, 1976 (41 FR 38312), FDA issued an advance notice of proposed rulemaking (ANPR) proposing to establish the conditions under which OTC CCABA drugs are GRASE, based on the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products (Panel). The Panel reviewed safety and efficacy data for oral PE that included 14 studies with clinical efficacy data,[7] and concluded that oral PE is effective as a nasal decongestant[8] (see Table 2 and Table 3 for a listing of the 14 studies, with a more detailed summary in Appendix A).

[7] See 41 FR 38312 at 38340, Reference 5: Ludena to Lands. Comparative study of the effects of Neo-Synephrine HCl and Propadrine HCl [phenylpropanolamine hydrochloride] on nasal airway resistance (NAR), blood pressure, and pulse rate of volunteers. Unpublished report from Sterling-Winthrop Labs, dated April 23, 1959.Reference 6: Hulme to Suter. Nasal Decongestant Study – Elizabeth Biochemical Laboratories No. 1 (Elizabeth 1); Reference 7: Stander to Hulme. Neo-Synephrine Oral Study – Elizabeth Biochemical Laboratories No. 2 (Elizabeth 2); Reference 8: Hulme to Blackmore. Oral Neo-Synephrine – Elizabeth Biochemical Laboratories Study No. 3 (Elizabeth 3); Reference 9: Hulme to Blackmore. Oral Neo-Synephrine – Elizabeth Biochemical Laboratories Study No. 4 (Elizabeth 4); Reference 10: Hulme to Blackmore. Neo-Synephrine – Elizabeth Biochemical Laboratories Study No. 5 (Elizabeth 5); Reference 19: (Blanchard et al. 1964). This is cited in the ANPR as being among a group listed as one of five studies conducted at the same laboratory (Elizabeth) over a 3-year period. However, it was not. It was conducted at the University of Maryland; Reference 20: Hulme to Blackmore. Oral Neo-Synephrine – Huntingdon Research Center Study No. 1 (Huntingdon 1); Reference 21 Hulme to Blackmore. Oral Neo-Synephrine – Huntingdon Research Center Study No. 2 (Huntingdon 2); Reference 22: Hulme to Blackmore: Oral Neo-Synephrine – Cintest Labs Study No. 1 (Cintest 1); Reference 23: Hulme to Blackmore: Oral Neo-Synephrine – Cintest Labs Study No. 2 (Cintest 2); Reference 24: Hulme to Blackmore: Oral Neo-Synephrine – Cintest Labs Study No. 3 (Cintest 3); Reference 25: (Rogers 1973). The study population included patients with chronic nonseasonal rhinitis; Reference 26: Study report from Burton Cohen at Bio-Evaluation, Inc., for Study BEI 1025 and 1025a, conducted for Whitehall Laboratories, June 1975.

[8] See 41 FR 38312 at 38399.

2. Considerations When Reviewing Historical Studies

a. Design and Methodology Issues

In the studies reviewed by the Panel, nasal airway resistance (NAR), an indirect measure of the level of congestion, was used as the primary endpoint to assess the effectiveness of oral PE as a nasal decongestant. However, since the efficacy data was originally evaluated to support the 1994 final rule, FDA has recommended that the preferred measures of efficacy in allergic rhinitis trials are patient self-rated instantaneous and reflective total nasal symptom scores.[9]

The measurement of NAR has inherent variability and methodological issues. Measurement of NAR to assess nasal airway patency is a complex procedure that is subject to multiple methodological issues. This includes subject training and experience with the procedure (including variability in inspiratory effort); day-to-day fluctuations and within-day cyclic variations in nasal congestion; procedural differences; differences in the equipment and mechanical measurement accuracy; and technician and evaluator experience.[10]

NAR has not been clinically validated as an endpoint. Data are lacking to support a correlation between improvement in NAR and clinical improvement in nasal congestion symptoms. Study P04579[11] was conducted in 2009 to evaluate the effects of oral PE compared with those of placebo and pseudoephedrine (PSE) on nasal congestion in subjects with seasonal allergic rhinitis. The study included information for both NAR and symptom scores for nasal congestion and therefore allowing for some comparison. However, the study results did not support a correlation between NAR and clinical improvement in nasal congestion symptoms (see Section II.B.1.c.i Study P04579 (NCT00276016)).

Therefore, the primary endpoint of NAR should not be used as a substitute for direct measurement of symptom scoring for nasal congestion to support efficacy of a drug product as a nasal decongestant.

b. Disease Context Issues

Nasal decongestants are used to treat nasal congestion associated with the common cold and allergic rhinitis. All but one of the studies reviewed by the Panel evaluated subjects in the setting of the common cold.[12] The common cold platform for studying nasal congestion is known to be highly variable, thereby introducing additional difficulty in obtaining consistent results in and across studies. Use of allergic rhinitis for studying nasal congestion is a far more stable platform even for single-dose or short-term studies because patients with allergic rhinitis often have congestion for considerable periods of time.

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[9] Since the 1990s, all of the topical intranasal drugs and second generation H_1 blockers (antihistamines) approved by FDA have used nasal symptom scores as the primary endpoint. See the guidance for industry (CDER 2018).

[10] In an effort to standardize the technique, several methodologies were published, including one referred to as the Butler-Ivy technique (see (Butler 1943). Four of the seven positive studies (i.e., studies reporting positive findings demonstrating efficacy for PE) specifically mention use of a modified version of the Buter-Ivy technique.

[11] (Horak et al. 2009). See also https://clinicaltrials.gov/ct2/show/NCT00276016.

[12] See 41 FR 38312 at 393400, Reference 25: (Rogers 1973). The study population included patients with chronic nonseasonal rhinitis.

c. Statistical Issues

FDA found statistical issues in the studies reviewed by the Panel. The majority of studies were small, crossover, single-center studies. Other than blinding, study reports did not discuss methodology to reduce bias. Statistical analyses appear to have been performed at each time point without adjustment for multiplicity. None of the study reports explicitly presented statistical endpoints and methodology.

All of the studies evaluated very small sets of subjects (n<50)[13] (see also Table 2, which shows the small sample sizes in the 10 Sterling-Winthrop studies). None of the study reports discussed a sample size calculation. Due to the inherent variability and methodological issues with NAR, FDA cannot perform a retrospective sample size calculation for studies that used NAR as the primary endpoint. Further, FDA has no current experience to ascertain the magnitude of difference between study drug (PE) and control (placebo) that might be statistically or clinically meaningful, and FDA has not been able ascertain this information from the literature. However, based on FDA's experience with inherent variability in endpoints, FDA believes that the magnitude of the variability is great. Given the variability of NAR and difficulty in studying subjects with the common cold, a reasonable sample size calculation would likely yield the need for sample sizes that are many times larger than those employed in any of the studies to show meaningful statistical or clinical difference between study drug (PE) and control (placebo).

3. Review of Studies with Efficacy Information

FDA reviewed each of the 14 study reports and/or publications reviewed by the Panel to support the effectiveness of oral PE as a nasal decongestant. However, only 12 of the studies provided efficacy information that could be evaluated. Sterling-Winthrop Research Institute, on behalf of Sterling-Winthrop Labs (Sterling-Winthrop),[14] submitted 10 studies providing efficacy information for PE (Table 2). Four other PE efficacy studies were also submitted (Table 3). However, two of those studies failed to provide useful efficacy information (see Section II.A.3.d Efficacy Studies With No Useful Efficacy Information).

[13] See 41 FR 38312 at 38399, Reference 26: Study report from Burton Cohen at Bio-Evaluation, Inc., for Study BEI 1025 and 1025a, conducted for Whitehall Laboratories, June 1975. BEI 1025 was the largest study evaluated by the Panel and the study only evaluated 25 subjects per arm (in a parallel design) with NAR as the primary endpoint.

[14] Sterling-Winthrop labs was the manufacturer of Neo-Synephrine, oral and intranasal products containing PE.

Table 2. Doses (mg) and Numbers of Subjects in the 10 Sterling-Winthrop Oral PE Efficacy Studies Submitted to FDA

			Phenylephrine (n)					PPA	Ephedrine	
Site	**Ref #**	**Study Date**	**5 mg**	**10 mg**	**15 mg**	**20 mg**	**25 mg**	**50 mg**	**8 mg**	**50 mg**
Elizabeth 1	6	6-28-67					12*		13*	
Elizabeth 2	7	1-12-68		16*	10*		6*			6*
Cintest 1	22	4-10-69		16*		16*		15*		
Huntingdon 1	20	5-13-69		16			16	16^		
Elizabeth 3	8	6-2-69	16*		8*		9*	9*		
Huntingdon 2	21	6-26-69		25		24				
Elizabeth 4**	9	8-11-69			6*	5*	9*			
Elizabeth 5**	10	5-27-70		10*	6*		9*			
Cintest 2	23	1-23-70		15	16	15				
Cintest 3	24	5-18-70		15	16		16			
Total subjects		Positive	16	42	30	21	45	24	13	6
		Negative	0	71	32	39	32	16	0	0

Source: Adapted from oral PE studies submitted to the docket.
Reference numbers refer to the reference numbers in 41 FR 38399 at 38340.
Bolded studies (Elizabeth 2 and Cintest 1) were considered the most "positive" studies i.e., studies reporting positive findings demonstrating efficacy for PE.
*Grey highlighting denotes significance reported for NAR results for specific doses by the FDA statistician, Dr. Stan Lin, PhD, in his 2007 statistical review, available in the meeting materials for the NDAC meeting, December 14, 2007, accessed at https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs (accessed February 21, 2024).
Studies considered to be "positive" studies, are also highlighted in grey.
^ Denotes that active control was not effective (even though it would be expected to have been).
** Elizabeth 4 and 5 did not enroll the expected number of subjects, either because the common cold season had ended (Elizabeth 4) or because they were unable to recruit sufficient numbers of subjects (Elizabeth 5).
Abbreviations: NAR, nasal airway resistance; PE, phenylephrine; PPA, phenylpropanolamine; ref, reference; FDA, U.S. Food and Drug Administration; FR, *Federal Register*; NDAC, Nonprescription Drugs Advisory Committee.

Table 3. Doses (mg) and Numbers of Subjects in the Four Oral PE Efficacy Studies Submitted to FDA

			Phenylephrine (n)				PSE	PPA		Ephedrine	
Study	**Ref #**	**Year**	**10 mg**	**15 mg**	**20 mg**	**25 mg**	**60 mg**	**25 mg**	**50 mg**	**25 mg**	**50 mg**
Sterling-Winthrop	5	1959	15			15				15	14
Whitehall Laboratories (BEI 1025)	26	1975	25/75								
Columbia University		1971	57				57	40 mg n = 57			
University of Maryland	19	1964	NA								

Source: Adapted from oral PE studies submitted to the docket.
Notes: All studies used placebo arms (not shown). Study BEI 1025 was a parallel-group study; all others were of a crossover design. Study BEI 1025 evaluated 50 subjects for NAR (n=25 PEH, n=25 placebo) and symptoms, with an additional 150 (n=75 PEH, n=75 placebo) subjects evaluated only for symptoms (total of 200 subjects, n=100 PEH, n=100 placebo), as shown in the table above.
Study highlighted in grey indicate arms that were considered "positive" with regard to NAR results.
The studies are presented in order of the date of the study report.
Abbreviations: NA, not available; NAR, nasal airway resistance; PE, phenylephrine; PEH, phenylephrine hydrochloride; PPA, phenylpropanolamine; PSE, pseudoephedrine; ref, reference; FDA, U.S. Food and Drug Administration; FR, *Federal Register*.

a. Sterling-Winthrop Efficacy Studies

Sterling-Winthrop submitted 10 studies providing efficacy information for oral PE.[15] Six studies were considered positive studies for oral PE with regard to NAR (i.e., studies reporting positive

[15] 41 FR 38312 at 38400 (Sep. 9, 1976), References 6 to 10 and 20 to 24. The ANPR mistakenly noted Reference 19 as having been one of those studies.

findings that demonstrate efficacy for PE), five of which were performed in a single research laboratory, Elizabeth Biochemical (Elizabeth). The six positive studies for oral PE include Elizabeth 1, 2, 3, 4, and 5[16] and Cintest 1.[17] These studies represent six of the seven studies[18] considered by the Panel to have demonstrated the efficacy of oral PE. Additionally, four studies submitted by Sterling-Winthrop were considered negative studies for oral PE with regard to NAR (i.e., studies did not report positive findings demonstrating efficacy for PE), including Huntingdon 1 and 2[19] and Cintest 2 and 3.[20]

i. Review of Efficacy Studies

The 10 efficacy studies submitted by Sterling-Winthrop were conducted at three different research laboratories, Elizabeth,[21] Cintest Division of Hill Top Laboratories in Cincinnati (Cintest),[22] and Huntingdon Research Center (Huntingdon).[23] All of the study reports were prepared by the Sterling-Winthrop in Rensselaer, NY. The study reports were all unpublished,

[16] 41 FR 38312 at 38400 Reference 6: Hulme to Suter. Nasal Decongestant Study – Elizabeth Biochemical Laboratories No. 1 (Elizabeth 1); Reference 7: Stander to Hulme. Neo-Synephrine Oral Study – Elizabeth Biochemical Laboratories No. 2 (Elizabeth 2); Reference 8: Hulme to Blackmore. Oral Neo-Synephrine – Elizabeth Biochemical Laboratories Study No. 3 (Elizabeth 3); Reference 9: Hulme to Blackmore. Oral Neo-Synephrine – Elizabeth Biochemical Laboratories Study No. 4 (Elizabeth 4); Reference 10: Hulme to Blackmore. Neo-Synephrine – Elizabeth Biochemical Laboratories Study No. 5 (Elizabeth 5).

[17] 41 FR 38312 at 38400, Reference 22: Hulme to Blackmore: Oral Neo-Synephrine – Cintest Labs Study No. 1 (Cintest 1).

[18] The other study considered by the panel to demonstrated efficacy of oral PE was Whitehall Laboratories Study (BEI 1025). For more information on this study, see Section II.A.3.b Whitehall Laboratories Study (BEI 1025) of this document.

[19] 41 FR 38312 at 38400, Reference 20: Hulme to Blackmore. Oral Neo-Synephrine – Huntingdon Research Center Study No. 1 (Huntingdon 1); Reference 21 Hulme to Blackmore. Oral Neo-Synephrine – Huntingdon Research Center Study No. 2 (Huntingdon 2).

[20] 41 FR 38312 at 38400 Reference 23: Hulme to Blackmore: Oral Neo-Synephrine – Cintest Labs Study No. 2 (Cintest 2); Reference 24: Hulme to Blackmore: Oral Neo-Synephrine – Cintest Labs Study No. 3 (Cintest 3).

[21] Five studies were conducted at Elizabeth and cited as references in 41 FR 38312 at 38400 (Sep. 9, 1976), Reference 6: Hulme to Suter. Nasal Decongestant Study – Elizabeth Biochemical Laboratories No. 1 (Elizabeth 1); Reference 7: Stander to Hulme. Neo-Synephrine Oral Study – Elizabeth Biochemical Laboratories No. 2 (Elizabeth 2); Reference 8: Hulme to Blackmore. Oral Neo-Synephrine – Elizabeth Biochemical Laboratories Study No. 3 (Elizabeth 3); Reference 9: Hulme to Blackmore. Oral Neo-Synephrine – Elizabeth Biochemical Laboratories Study No. 4 (Elizabeth 4); Reference 10: Hulme to Blackmore. Neo-Synephrine – Elizabeth Biochemical Laboratories Study No. 5 (Elizabeth 5).

[22] Three studies were conducted at Cintest and cited as references in 41 FR 38312 at 38400 (Sep. 9, 1976), Reference 22: Hulme to Blackmore: Oral Neo-Synephrine – Cintest Labs Study No. 1 (Cintest 1); Reference 23: Hulme to Blackmore: Oral Neo-Synephrine – Cintest Labs Study No. 2 (Cintest 2); Reference 24: Hulme to Blackmore: Oral Neo-Synephrine – Cintest Labs Study No. 3 (Cintest 3).

[23] Two studies were conducted at Huntingdon and cited as references in 41 FR 38312 at 38400, Reference 20: Hulme to Blackmore. Oral Neo-Synephrine – Huntingdon Research Center Study No. 1 (Huntingdon 1); Reference 21 Hulme to Blackmore. Oral Neo-Synephrine – Huntingdon Research Center Study No. 2 (Huntingdon 2).

and therefore were not peer-reviewed. Additionally, to FDA's knowledge, none of the study protocols were submitted to FDA for the FDA or the Panel to review.[24]

The 10 studies were small, single-dose, double-blind, placebo-controlled, single-center, two-way crossover studies in subjects with the common cold. The studies used similar protocols and methodology. However, the studies evaluated various doses of oral PE (between 5 mg and 25 mg) (see Table 2). The oral PE doses and number of completed subjects at each oral PE dose level in each of the studies are shown in Table 2. Additionally, some of the studies included an active comparator (phenylpropanolamine (PPA) or ephedrine), including Elizabeth 1, 2, 3, Cintest 1, and Huntingdon 1 (see Table 2). Across the studies, oral PE at any given dose level failed to show efficacy in approximately half of the total number of subjects studied (see Table 2).

The 10 studies had significant methodological and statistical issues. The studies all used the same primary endpoint of NAR (see also Section II.A.2.a Design and Methodology Issues). The total number of subjects enrolled in the studies at any given dose was small; far below the number needed to demonstrate efficacy of oral PE (see also Section II.A.2.c Statistical Issues). Further, two studies did not enroll the planned number of subjects (Elizabeth 4 and 5). The studies all used the same population of subjects with common cold, rather than also include subjects with allergic rhinitis (see Section II.A.2.b Disease Context Issues). There was also significant heterogeneity of results both within and among the three study centers (see Section II.A.3.a.ii Other Issues.

ii. Other Issues

The results from studies at the Elizabeth site could not be duplicated by studies at the two other Sterling-Winthrop sites (Cintest and Huntingdon), with the exception of Cintest 1. Additionally, the results from studies at the Elizabeth site could also not be duplicated by other investigators, including the study conducted at Columbia University[25] (see in Section II.A.3.c Columbia University Study (Columbia)) and in two environmental exposure unit (EEU) studies that were conducted by Schering-Plough[26] (see Section II.B.1 Review of Environmental Exposure Unit Studies).

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[24] In the *Federal Register* of 88 FR 44370 (Jul. 23, 2023), FDA announced a Nonprescription Drugs Advisory Committee meeting on September 11-12, 2023, and the establishment of a docket for public comment, FDA-2023-N-2653. The purpose of the meeting was for the committee to discuss new data regarding the GRASE status of oral PE as a nasal decongestant that have become available since FDA last examined the issue. To FDA's knowledge, the study protocols were first submitted to FDA by Consumer Health Product Association to the 2023 meeting docket.

[25] See 41 FR 38312 at 38399. 41 FR 38312 at 393400, Reference 25: (Rogers 1973).

[26] See the (2007) Schering-Plough Merck Briefing Document for NDAC Meeting (December 14, 2007). The Effects of Phenylephrine on the Symptoms of Allergic Rhinitis. 2007-4335b1-02-Schering-Plough-Merck.pdf. Available at https://wayback.archive-it.org/7993/20170404050450/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-00-index.htm. Slides available at https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm (accessed February 21, 2024). The results of both studies presented at the 2007 meeting of the NDAC were subsequently published in 2009. See (Day et al. 2009), (Horak et al. 2009).

The study reports from Cintest 2 and Huntingdon 1 attempted to address why the study results differed from the study results at the Elizabeth site. The Cintest 2 study report noted that, having failed to duplicate any of the Elizabeth results, researchers visited the Elizabeth site to observe testing in an effort to understand why they were unable to duplicate the results from the studies at the Elizabeth site. The Huntingdon 1 study report contains a table comparing the standard deviations (SDs) in the studies that had been conducted at the Elizabeth, Cintest, and Huntingdon sites (see Table 4). While it is unclear how this table was derived, it shows that the magnitude of the SDs for the results from studies conducted at the Elizabeth site were considerably smaller than the results from the studies conducted at the Cintest and Huntingdon sites, regardless of the drug or dose studied.

Table 4. Comparison of Standard Deviation Values for Decongestant Studies Conducted at Elizabeth, Cintest, and Huntingdon

Product/Dose	Time Point (Minutes) and SD								
Lab	0	15	30	45	60	90	120	180	240
PPA 50 mg									
Elizabeth	1.3	0.7	0.9	0.9	1.5	1.8	2.1	2.6	2.3
Cintest	4.1	12	13	18	20	17	18	23	45
Huntingdon	6.5	27	20	16	25	37	36	38	38
Neo-Synephrine 10 mg									
Cintest	7.3	12	14	16	21	21	23	27	42
Huntingdon	7.7	12	18	18	28	22	58	79	166
Neo-Synephrine 25 mg									
Cintest	5.4	14	22	23	21	22	22	22	30
Huntingdon	10	22	29	32	38	44	45	35	44
Neo-Synephrine 15 mg									
Elizabeth	0.8	0.3	1.0	1.7	2.1	1.5	1.5	1.4	2.3

Source: Huntingdon 1 study report, Table II. in 41 FR 38312 at 38400, Reference 20: Hulme to Blackmore. Oral Neo-Synephrine—Huntingdon Research Center Study No. 1.
Abbreviation: PPA, phenylpropanolamine; ANPR, advance notice of proposed rulemaking; SD, standard deviation; FR, *Federal Register*.

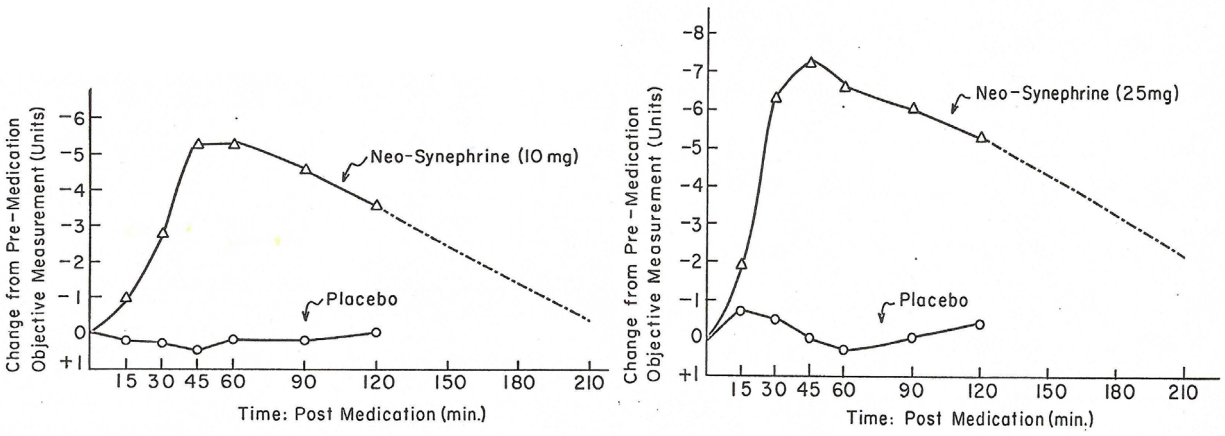
FDA cannot make a meaningful interpretation when comparing the results from each of the Sterling-Winthrop studies. The results were highly inconsistent between two of the five studies conducted at the Elizabeth site (Elizabeth 1 to 5) and between four of the five studies conducted at the Cintest and Huntingdon sites (Cintest 2 and 3 and Huntingdon 1 and 2), the exception being Cintest 1.

Three of the positive studies, Elizabeth 2, Elizabeth 5, and Cintest 1 (see Table 2), all appear to have been outliers because their results do not match the results obtained in the other studies. The NAR results from Elizabeth 2, Elizabeth 5, and Cintest 1 are not consistent with what is now known about the overall systemic bioavailability and pharmacodynamic (PD) effects of orally administered PE (see Section III Scientific Review of Pharmacology Data). The mechanism of action for PE as a nasal decongestant is believed to be due to vasoconstriction of the vascular bed in the nose. In order for an oral drug to have systemic effects on the vascular bed of the nose, it would also be expected to cause vasoconstriction in other blood vessels of the body. These studies included measurements of PD effects, and positive NAR results even though there were no clinically relevant changes in blood pressure (BP) or heart rate (HR).

Additionally, the NAR response curves do not match current data about the area under the curve (AUC) (systemic exposure) after an orally administered dose of PE, including the timing of the peak and the duration of systemic exposure to the active parent PE (see Section III Scientific Review of Pharmacology Data). Based on current data about the AUC after administration of oral PE, FDA expects that the decongestant effect, if present, would occur at an early timepoint and be very short-lived. However, the results in the Elizabeth 2, Elizabeth 5, and Cintest 1 are not consistent with current data about AUC after administration of oral PE. Additionally, no change from baseline was observed for placebo. The results of Cintest 1 also raise concern because the onset and duration of effect were later and more sustained (see Figure 3) than other studies and cannot be easily explained by current scientific data on the PD effect of oral PE (see Section III Scientific Review of Pharmacology Data). To illustrate this, graphical representations of the results are shown for Elizabeth 2 (positive study) in Figure 1; Elizabeth 5 (positive study) in Figure 2; Cintest 1 (positive study) in Figure 3; and Cintest 3 (negative study) in Figure 4.[27]

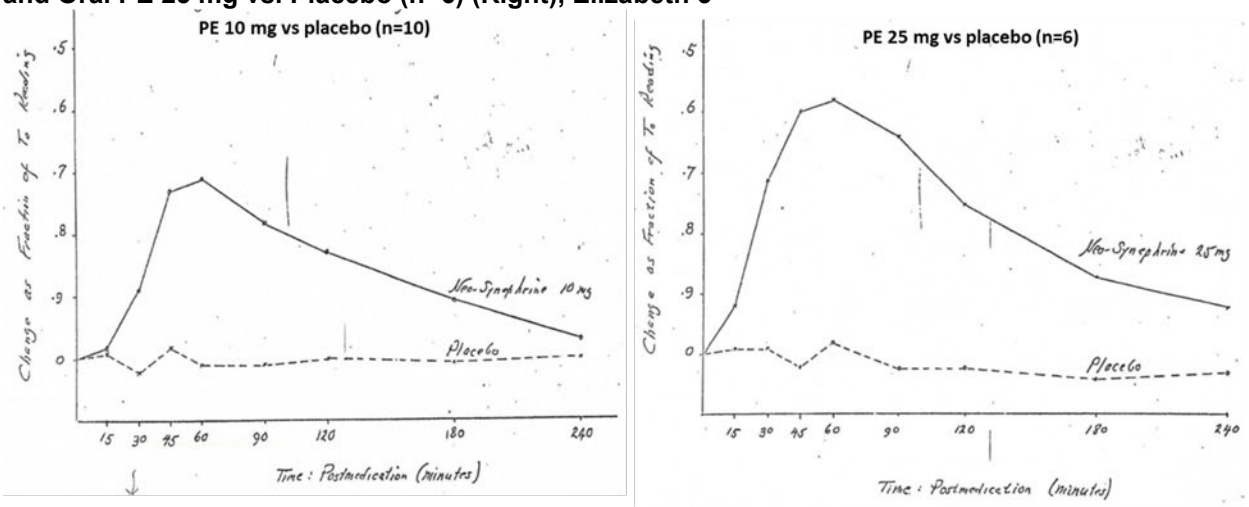
[27] When reviewing the figures, note the differences in the y-axis. Elizabeth 2 reported absolute change from baseline, whereas studies at the Cintest site reported the change in percentage of the baseline reading. As a result, the sets of figures from the two sites cannot be directly compared. However, the slopes, AUCs, and differences between study (PE) and control (placebo) arms are visually apparent.

Figure 1. Absolute Change From Baseline, NAR Results, Oral PE 10 mg vs. Placebo (n=16) (Left) and Oral PE 25 mg vs. Placebo (n=6) (Right), Elizabeth 2



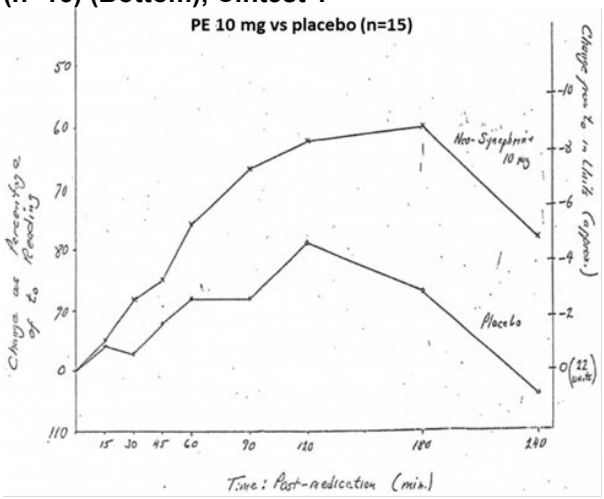
Source: Elizabeth 2 study.
Results beyond 120 minutes are extrapolated.
Abbreviation: NAR, nasal airway resistance; PE, phenylephrine; min, minute(s).

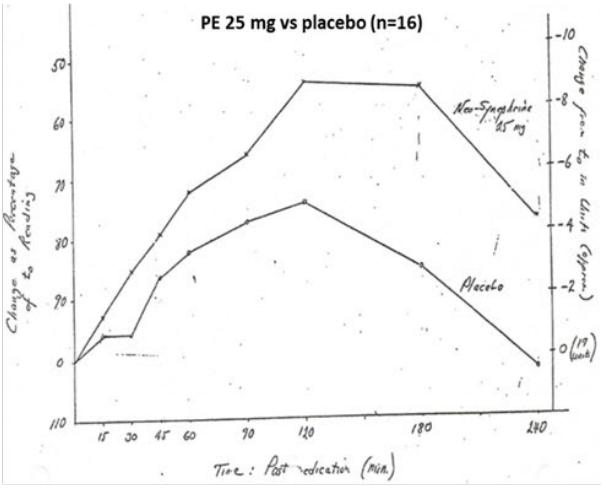
Figure 2. Absolute Change From Baseline, NAR Results, Oral PE 10 mg vs. Placebo (n=10) (Left) and Oral PE 25 mg vs. Placebo (n=6) (Right), Elizabeth 5

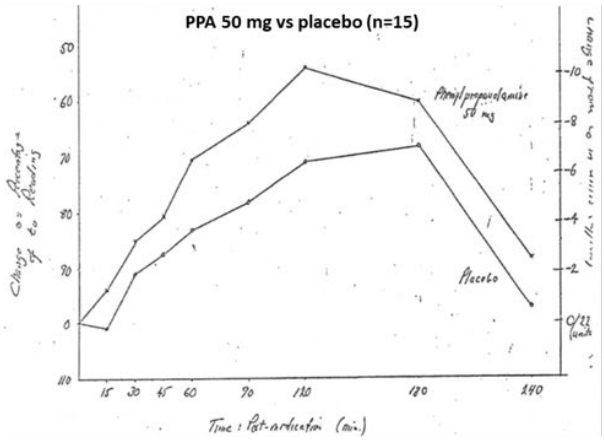


Source: Elizabeth 5 study.
Abbreviations: NAR, nasal airway resistance; PE, phenylephrine.

Figure 3. Change in Percentage of Baseline Reading, NAR Results, Oral PE 10 mg vs. Placebo (n=15) (Top Left), Oral PE 25 mg vs. Placebo (n=16) (Top Right), and Oral PPA 50 mg vs. Placebo (n=15) (Bottom), Cintest 1

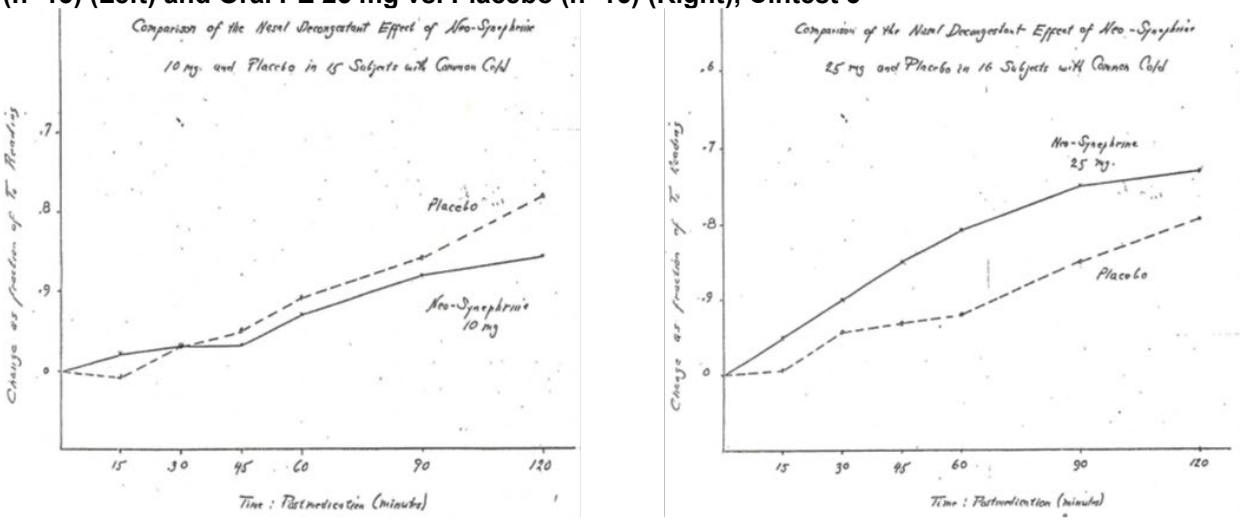






Source: Cintest 1 study.
Abbreviations: NAR, nasal airway resistance; PE, phenylephrine; PPA, phenylpropanolamine; min, minute(s).

Figure 4. Change in Percentage of Baseline Reading, NAR Results, Oral PE 10 mg vs. Placebo (n=15) (Left) and Oral PE 25 mg vs. Placebo (n=16) (Right), Cintest 3



Source: Cintest 3 study.
Abbreviations: NAR, nasal airway resistance; PE, phenylephrine.

Additionally, FDA reviewed a 2010 article that discussed concerns about Elizabeth 2 (Shuster et al. 2010).The authors note the lack of variability in the Elizabeth 2 and Elizabeth 5 results when compared with other studies. The authors performed a statistical analysis of the variability in Elizabeth 2 and 5 results, by evaluating digit preference in the third [last] significant digit (tenths column) of the reported data results (see Table 5).[28,29] While the authors did not express concern with Elizabeth 5 from a statistical perspective, they noted that Elizabeth 2 had a disproportionately high occurrence of the digit "5" (see Table 5) that was consistent across time points, which they believe provides "sufficient statistical evidence to cast doubt upon the results of Study 1" (Elizabeth 2) (Shuster et al. 2010).

Table 5. Appearance of Digits in the Tenths Column, Elizabeth 2 and 5

	Frequency of Digit Appearance										
Study	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Total**
1 (Elizabeth 2)	2	4	2	6	2	**23**	8	9	3	5	64
2 (Elizabeth 5)	5	2	1	9	4	7	5	10	3	4	50

Source: Table AI in (Shuster et al. 2010).
X^2=55.6 ($P<10^{-8}$) for study 1 (Elizabeth 2).
X^2=15.2 (P=0.060) for study 2 (Elizabeth 5).

[28] The actual raw data are not in the study report. The study report included mean data for each subject, timepoint, and nostril, which is stated to represent the mean of five measurements. For each subject and timepoint, the data for the two nostrils were averaged to obtain results for each subject and timepoint, such that each data point that was used for the forensic evaluation presented in Table 5 represents the mean of 10 NAR measurements.

[29] The authors followed a forensic recommendation discussed in (Buyse et al. 1999).

b. Whitehall Laboratories Study (BEI 1025)

BEI 1025, of which Study 1025a was a substudy, was conducted for Whitehall Laboratories.[30] The study report was unpublished, and therefore was not peer-reviewed. Additionally, to FDA's knowledge, the study protocol was not submitted to FDA for the FDA or the Panel to review.[31]

BEI 1025 was a double-blind, placebo-controlled, parallel-group study. This was the only study reviewed by the Panel with a parallel group design. It was the only non-Sterling-Winthrop study that was considered to be positive. It was conducted in 200 adult subjects with nasal congestion associated with the common cold. All subjects received four doses of 10 mg of PE or placebo over 12 hours. Subjects were followed for 12.5 hours (30 minutes beyond the fourth dose). All 200 subjects' symptoms were evaluated at various time points over the treatment period. Subjects and investigators subjectively assessed symptoms of stuffy nose (i.e., congestion), runny nose, sneezing, itching (eyes and nose), coughing, and muscle ache. However, the primary endpoint of rhinometry evaluations (i.e., NAR) over 2 hours post the first dose (at 15, 30, 60, and 120 minutes) was only evaluated/performed in 50 subjects (25 per arm). These measurements were performed at 0, 15, 30, 60 and 120 minutes after the first dose.

The study report noted changes in both NAR (Table 6 and Figure 5) and for the symptoms of nasal congestion, runny nose, and sneezing, which they judged to be significant compared with placebo, with no improvements in cough or muscle ache. The study report said that NAR results (Table 6 and Figure 5) "demonstrated that a single oral 10 mg dose of phenylephrine led to a reduction in NAR, averaging 11 percent at 15 minutes, 21 percent at 30 minutes, 28 percent at 60 minutes, and 26 percent at 120 minutes."[32] However, that percent change tends to exaggerate any differences, whereas the absolute change in NAR (see Figure 5) was far more modest. Likewise, the study report said that the "phenylephrine treatment group experienced relief of nasal congestion, runny nose and sneezing throughout the 12 -hour observation period" and differed from that of placebo.[33] However, no differences were seen between PE versus placebo groups in systolic or diastolic BP (see Figure 6), implying that a PD effect was not seen in this study.

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[30] 41 FR 38312 at 38399, Reference 26: Study report from Burton Cohen at Bio-Evaluation, Inc., for Study BEI 1025 and 1025a, conducted for Whitehall Laboratories, June 1975.

[31] In the *Federal Register* of 88 FR 44370 (Jul 23, 2023), FDA announced a Nonprescription Drugs Advisory Committee meeting on September 11–12, 2023, and the establishment of a docket for public comment, FDA-2023-N-2653. The purpose of the meeting was for the committee to discuss new data regarding the GRASE status of oral PE as a nasal decongestant that have become available since FDA last examined the issue. To ONPD's knowledge, the study protocols were first submitted to FDA by Consumer Health Product Association to the 2023 meeting docket.

[32] 41 FR 38312 at 38399, Reference 26: Study report from Burton Cohen at Bio-Evaluation, Inc., for Study BEI 1025 and 1025a, conducted for Whitehall Laboratories, June 1975.

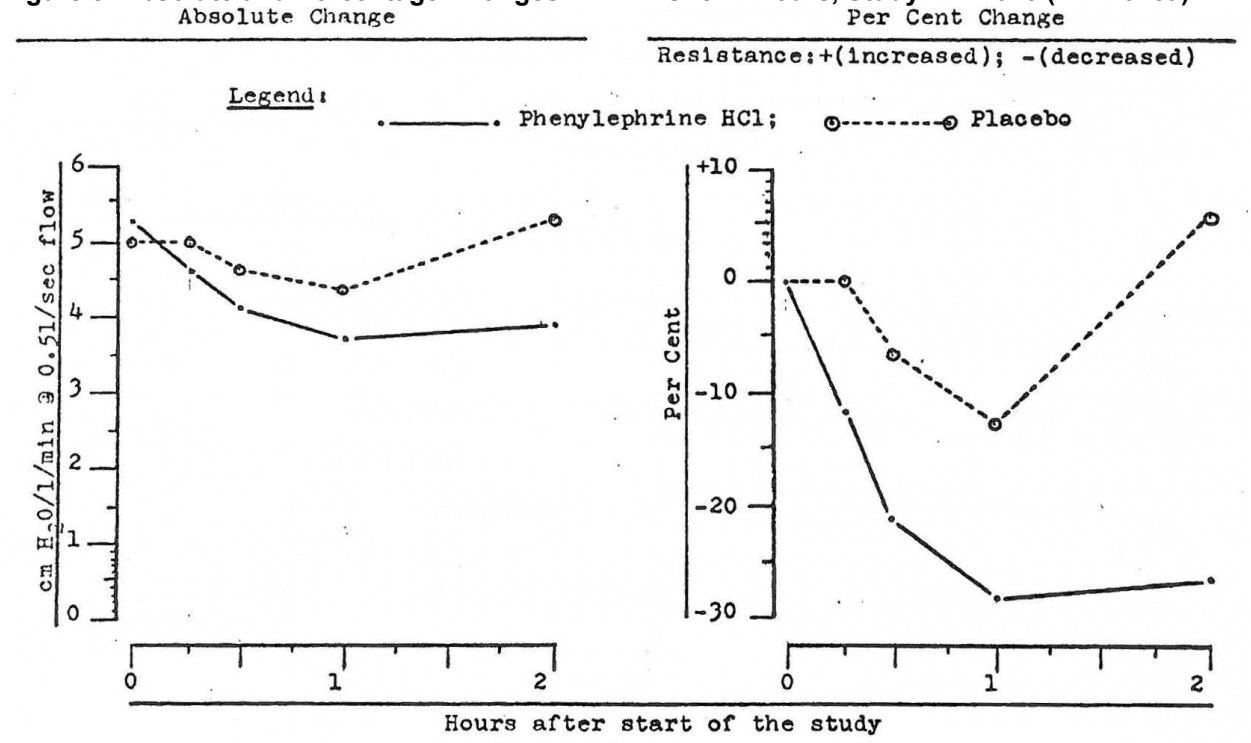
[33] Ibid.

Table 6. Percentage Change in NAR Over 2 Hours, Study BEI 1025 (BEI 1025a)

Time (Minutes)	PEH 10 mg	Placebo
15	-11.37	+0.15
30	-20.62	-6.33
60	-28.25	-12.67
120	-26.18	+5.50

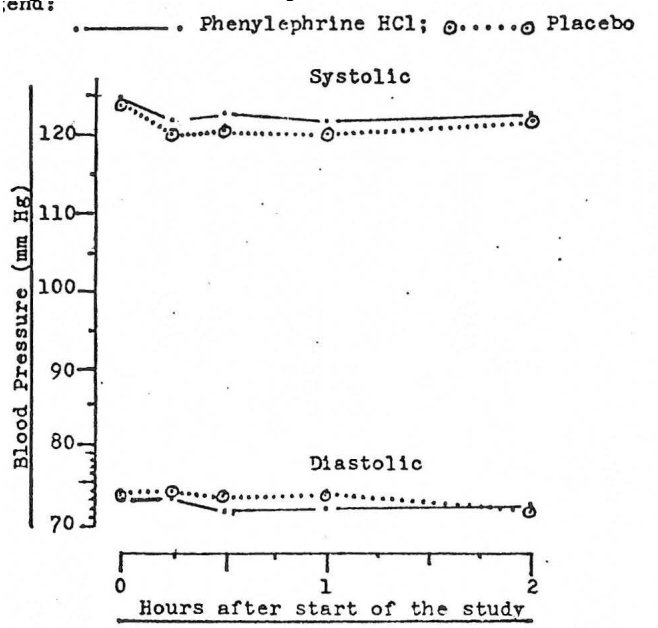
Source: Study BEI 1025. 41 FR 38312 at 38399, Reference 26: Study report from Burton Cohen at Bio-Evaluation, Inc., for Studies BEI 1025 and 1025a.
Abbreviation: NAR, nasal airway resistance; PEH, phenylephrine hydrochloride; FR, *Federal Register.*

Figure 5. Absolute and Percentage Changes in NAR Over 2 Hours, Study BEI 1025 (BEI 1025a)



Source: Study BEI 1025a. 41 FR 38312 at 38399, Reference 26: Study report from Burton Cohen at Bio-Evaluation, Inc., for Studies BEI 1025 and 1025a, conducted for Whitehall Laboratories, June 1975.
Abbreviations NAR, nasal airway resistance; PEH, phenylephrine hydrochloride; FR, *Federal Register.*

Figure 6. Results for Systolic and Diastolic BP Following PEH 5 mg or Placebo, Study BEI 1025



Source: Study BEI 1025. 41 FR 38312 at 38399, Reference 26: Study report from Burton Cohen at Bio-Evaluation, Inc., for Studies BEI 1025 and 1025a, conducted for Whitehall Laboratories, June 1975.
Abbreviations: BP, blood pressure; PEH, phenylephrine hydrochloride; FR, *Federal Register.*

Similar to the issues with the Sterling-Winthrop studies, there were methodological and statistical issues with the study. The methodology to reduce bias and the scoring methodology were not specified, and no adjustments were made for multiplicity.

Since FDA was unable to review the protocol, an assessment of how symptoms were rated cannot be made. Baseline symptoms appear to be evaluated by both the subjects and the investigators and rated on a five-point scale, from mild to very severe, with improvement rated on a two-point scale with 0 being no change and 2 being much improved. However, FDA does not know the frequency of the scoring, whether it was instantaneous or reflective, and how much weight was placed on investigator judgement. While the study report notes that subjects who experienced the largest magnitude of changes in NAR also experienced the largest magnitude of changes in symptom scores, it is unknown how much the investigator reporting of symptoms influenced those results.

Additionally, the primary endpoint of NAR over 2 hours following the first dose was reported as percent change from baseline (Figure 5). In Figure 5, percent change is on the right and absolute change is on the left. The percent reduction at each timepoint is shown in Table 6. In general, percent change tends to magnify any differences, whereas absolute measurements do not. The magnitude of difference in absolute changes seen in NAR results (left side of Figure 5) were quite small. Even at 1 hour, the timepoint with the largest effect size, subjects appeared to continue to have significant nasal airflow obstruction (4 on a scale of 5, where 5 was considered to be significant obstruction). The study did not specify what difference in absolute change might be clinically meaningful.

c. Columbia University Study (Columbia)

The Columbia study was a double-blind, crossover study in 20 subjects with chronic rhinitis. It was considered a negative study and therefore did not support the effectiveness of oral PE.[34] The study evaluated and found that 10, 20, and 40 mg of oral PE demonstrated no effect on NAR compared to placebo over a 4-hour observation period, whereas pseudoephedrine (PSE) 60 mg and PPA 40 mg each produced significant NAR reductions persisting for at least 3 hours.

FDA could not conduct an analysis of the study because the reference is an abstract to the study, which included no dosing information or specific data to support the reported study findings. However, the ANPR discussed the negative results from the study in a manner that matches a previous 1971 publication from one of the authors of the Columbia study, Bickerman.[35,36] Therefore, FDA reviewed the 1971 publication from Bickerman (see results in Table 7 and Figure 7), in which the 1971 publication from Bickerman attempted to address NAR measurement variability.

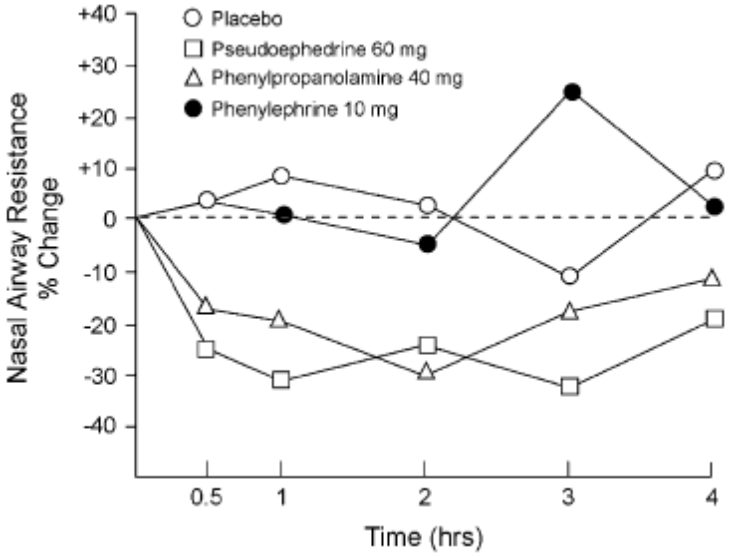
While the investigators attempted to address inherent variability in NAR measurements, NAR is not a validated primary endpoint (see discussion in Section II.A.2.a Design and Methodology Issues). Further, the data showed lack of efficacy of the oral PE 10 mg, particularly in light of the two positive controls that were also studied, oral PSE 60 mg, and oral PPA 40 mg.

[34] See 41 FR 38312 at 38399. 41 FR 38312 at 393400, Reference 25: (Rogers 1973).

[35] (Bickerman 1971).

[36] In the *Federal Register* of January 15, 1985 (50 FR 2220), FDA issued a notice of proposed rulemaking in the form of a tentative final monograph (TFM) that would establish conditions under which OTC nasal decongestant drug products used for relieving the symptoms of nasal congestion caused by acute or chronic rhinitis are GRASE and not misbranded. TFM Comment 11 noted that the ANPR had cited a study (1973 Rogers) that did not contain the information cited by the Panel. After a review, FDA explained in the TFM that it determined that the cited information should have been attributed to another study (1971 Bickerman). See 41 FR 38312 at 38400 Reference 25: (Rogers 1973) (1973 Rogers) and (Bickerman 1971) (1971 Bickerman). Based on our review, we believe that 1973 Rogers is an update for the 1971 publication and study, with additional arms that had not been previously included in the 1971 publication.

Figure 7. Effects of Phenylephrine, Phenylpropanolamine, and Pseudoephedrine on Nasal Airway Resistance Over 4 Hours



Source: Adapted from (Bickerman 1971). Figure published by (Hendeles 1993) and (Hendeles and Hatton 2006).

Table 7. Effect on Nasal Airway Resistance of Four Oral Drugs in Patients With Chronic Nasal Congestion (0.2 L/s Expiration)*

Drug	Control	0.5 hour	1 hour	2 hours	3 hours	4 hours
Placebo	1.68	1.74	1.83	1.71	1.47	1.85
PSE 60 mg	2.18	1.61	1.49	1.65	1.46	1.75
PPA 40 mg	2.16	1.78	1.73	1.51	1.75	1.91
PE 10 mg	1.99	2.06	2.00	1.89	2.49	2.14

Source: (Bickerman 1971), Figure 25.
* After obtaining poor correlation using the Butler-Ivy technique of anterior rhinometry, measurements were performed using a modified full-face Navy diving mask fitted to a heated pneumotachograph to record nasal airflow and a mouthpiece with a pressure tap to record the pressure differential between the mask and the oropharynx. Permanent records were made by photographing the oscilloscope tracing. A total of 104 subjects (57 with mostly nonatopic chronic rhinitis and 47 healthy) were evaluated over a 3-year period to assess healthy versus chronic rhinitis differences, day-to-day fluctuations, in-day cyclic variations (including variations between the two sides versus measuring both sides in unison), differences between sexes, and day-to-day changes in subjects as they developed an upper respiratory infection. Pharmacologic studies were then performed using a double-blind crossover design in subjects with chronic nonseasonal rhinitis, including topical placebo, oxymetazoline, and PE nasal sprays, and oral PSE, PPA, PE, and placebo. Results are shown in the table and graphically in Figure 7.
Abbreviations: N, not stated; PE, phenylephrine; PPA, phenylpropanolamine; PSE, pseudoephedrine.

d. Efficacy Studies With No Useful Efficacy Information

Two studies failed to provide useful efficacy information.

i. Sterling-Winthrop

One study submitted by Sterling-Winthrop was an unpublished, preliminary descriptive study focused primarily on safety and not efficacy, and therefore provides no useful efficacy information.[37] The preliminary study preceded Sterling-Winthrop's 10 other studies (see Section II.A.3.a Sterling-Winthrop Efficacy Studies).

[37] 41 FR 38312 at 38399 (Sep. 9, 1976), Reference 5: Ludena to Lands. Comparative study of the effects of Neo-Synephrine HCl and Propadrine HCl [phenylpropanolamine hydrochloride] on nasal airway resistance (NAR), blood pressure, and pulse rate of volunteers. Unpublished report from Sterling-Winthrop Labs, dated April 23, 1959.

ii. University of Maryland

One study was conducted at the University of Maryland in hundreds of subjects with the common cold or hay fever over a 3-year period.[38] However, they failed to adequately identify the active ingredients and doses studied. Therefore, the study provided no evaluable efficacy information.

4. Proposal Based on Review of Historical Data

FDA proposes that due to significant issues with study design, methodology, disease context, conduct, and statistical analysis, the studies cannot be relied upon to provide evidence of effectiveness of oral phenylephrine as a nasal decongestant.

B. Review of Efficacy Data Available After the Publication of the 1994 Final Rule

FDA reviewed data on the efficacy of PE as a nasal decongestant that have become available since the publication of the 1994 final rule.[39]

1. Review of Environmental Exposure Unit Studies

In the *Federal Register* of October 24, 2007 (72 FR 60377), FDA announced the meeting of a public advisory committee to discuss the safety and effectiveness of phenylephrine as an OTC oral nasal decongestant and to address the 2007 citizen petition. On December 14, 2007, FDA convened a meeting of the Nonprescription Drugs Advisory Committee (2007 meeting).[40]

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[38] 41 FR 38312 at 38399 (Sep. 9, 1976), Reference 19: (Blanchard et al. 1964) This is cited in the ANPR as being among a group listed as one of five studies conducted at the same laboratory (Elizabeth) over a 3-year period. However, it was not. It was conducted at the University of Maryland. Elizabeth is in Reference 10, not 19.

[39] See 59 FR 43409 (Aug. 23, 1994). Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Nasal Decongestant Drug Products.

[40] The FDA uses committees and panels to obtain independent expert advice on scientific, technical, and policy matters. The Nonprescription Drugs Advisory Committee reviews and evaluates available data concerning the safety and effectiveness of nonprescription human drug products, or any other FDA-regulated product, for use in the treatment of a broad spectrum of human symptoms and diseases and advise the Commissioner either on the promulgation of OTC monographs establishing conditions under which these drugs are generally recognized as safe and effective and not misbranded or on the approval of new drug applications for such drugs. For more information on Nonprescription Drugs Advisory Committee, see https://www.fda.gov/advisory-committees/human-drug-advisory-committees/nonprescription-drugs-advisory-committee.

Schering-Plough Merck conducted two environmental exposure unit (EEU) studies and presented the results for the two EEU studies at the 2007 meeting.[41,42] The results of both studies were subsequently published in 2009 (Day et al. 2009); (Horak et al. 2009). The two EEU studies compared oral PE with placebo and either PSE (active comparator) or a combination of loratadine/montelukast (study drug).

FDA reviewed the results of the two environmental exposure unit (EEU) studies conducted by Schering-Plough Merck.

a. Study Review Considerations

An allergen challenge chamber is a type of Environmental Exposure Unit (EEU) study and is an artificial setting. However, it is well documented and accepted that an EEU study provides a reasonable initial assessment of the PD properties of a drug, including an estimate of the dose, onset of action, and duration of effect (Day et al. 2006a; Day et al. 2006b).

EEU studies are generally considered late phase 1 or early phase 2 proof-of-concept studies. However, they may also be used to provide evidence of a dose and dosing interval to be carried into additional phase 2 and 3 clinical trials.

The study design and methodology, study populations, and endpoints used for these two studies were appropriate and consistent with EEU studies presented to FDA as part of other drug development programs for pulmonary-allergy products. Both studies used repeated instantaneous clinical symptom scores of nasal congestion, rhinorrhea, nasal itch, and sneezing over a set time period, a methodology that has been used as proof-of-concept and early dose finding in prescription allergy drug development.

Further, the two studies were performed at well-known EEU study centers.

b. Review of Studies

i. Study P04579 (NCT00276016)

The study was a single-center, randomized, investigator-blind, active- and placebo-controlled, three-way crossover, single-dose study that evaluated the efficacy of oral PE compared to PSE and placebo in 39 adult subjects with seasonal allergic rhinitis (SAR) exposed to grass pollen in

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[41] See the Schering-Plough Merck Briefing Document for NDAC Meeting (December 14, 2007). The Effects of Phenylephrine on the Symptoms of Allergic Rhinitis. 2007-4335b1-02-Schering-Plough-Merck.pdf. Available at https://wayback.archive-it.org/7993/20170404050450/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-00-index.htm. Slides available at https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm (accessed February 21, 2024). Based on the two EEU studies, Schering-Plough concluded that a single 10 mg or 12 mg dose of oral PE failed to provide any benefit over placebo. However, a single 60 mg oral dose of PSE provided relief of congestion symptoms.

[42] Many of the presentations, including those by the petitioners of the CP, CHPA, and FDA, included meta-analysis or analysis of the studies reviewed by the Panel. Meeting materials for the NDAC meeting, December 14, 2007 are available at https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs (accessed February 21, 2024).

the EEU setting. The study was conducted in January of 2006, at the University of Vienna, Vienna, Austria, and funded by Schering-Plough Research Institute, Kenilworth, New Jersey (Schering-Plough).[43]

Subjects who met minimum symptom scores during a 120 minutes predose challenge were treated with immediate release (IR) oral PE 12 mg (European Union–approved product), PSE 60 mg (positive control), or placebo. Symptoms were monitored and recorded every 15 minutes over 6 hours post dosing. Measurements of NAR, peak nasal inspiratory flow (PNIF), and nasal secretions for weight were collected at 30-minute intervals over the 6-hour study period. The publication does not explain the methodology used for the NAR and PNIF measurements.

The primary efficacy assessment was mean change from baseline in nasal congestion score over 6 hours. The study noted that "pairwise comparisons were made using linear contrasts of the treatment means obtained from an analysis of variance model that extracts sources of variation due to treatment, patient, and phase. The primary comparison for all of the secondary end points was PE versus placebo tested at 2-sided $\alpha = .05$; PSE was also compared with placebo (Horak et al. 2009).

A total of 39 subjects were randomized; and 38 subjects completed treatment. Subjects were predominantly White (97 percent), and female (59 percent), with a mean age of 27 years. Baseline nasal congestion scores were 2.20 for PE and placebo and 2.26 for PSE.

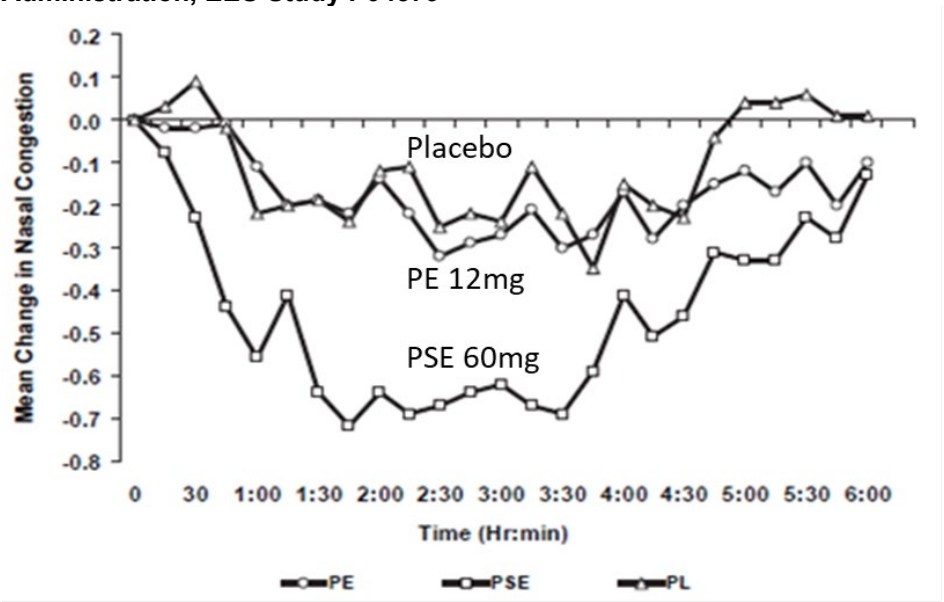
Results for symptom scores and NAR/PNIF measurements over the course of the EEU exposure after treatment are shown in Figure 8 and Figure 9, respectively. There was no difference in nasal congestion scores for PE when compared to placebo, but PSE treatment resulted in an average 6-hour mean percentage decrease from baseline in nasal congestion score of 21.7 percent. No adverse events (AEs) were reported in the study.

The data failed to demonstrate efficacy of oral PE using either endpoint of NAR or nasal congestion symptoms. PSE was effective compared with placebo when evaluated by nasal congestion scores (Figure 8). However, there was no clear separation between PSE and placebo for either PNIF (right side of Figure 9) or NAR (left side of Figure 9).

The results in this study do not support a correlation between NAR and clinical improvement in nasal congestion symptoms. This further supports that NAR is not a validated clinical endpoint and NAR results cannot be used as a substitute for direct measurement of symptom scoring for nasal congestion to support efficacy of a drug product for nasal congestion (see discussion in Section II.A.2.a Design and Methodology Issues).

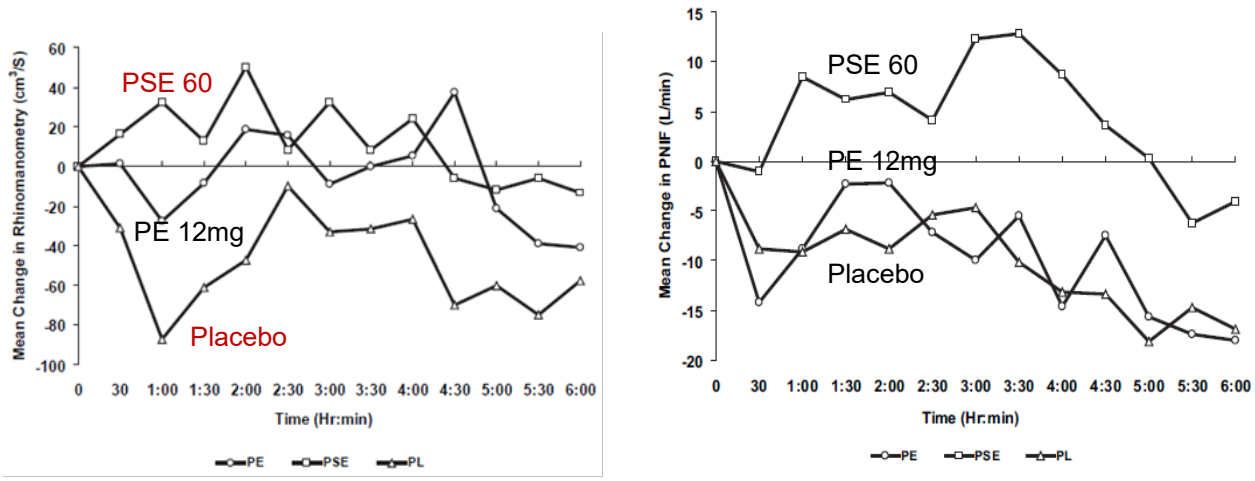
[43] The study results were presented at the 2007 NDAC meeting. See the Schering-Plough Merck Briefing Document for NDAC Meeting (December 14, 2007). The Effects of Phenylephrine on the Symptoms of Allergic Rhinitis. 2007-4335b1-02-Schering-Plough-Merck.pdf. Available at https://wayback.archive-it.org/7993/20170404050450/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-00-index.htm. Slides available at https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm (accessed February 21, 2024). The study results were subsequently published in (Horak et al. 2009) The study results are also available at https://clinicaltrials.gov/ct2/show/NCT00276016.

Figure 8. Mean Change in Subjective Nasal Congestion Scores at 15 Minute Intervals After Drug Administration, EEU Study P04579



Sources Schering-Plough Merck Briefing Document for NDAC Meeting (December 14, 2007). The Effects of Phenylephrine on the Symptoms of Allergic Rhinitis. 2007-4335b1-02-Schering-Plough-Merck.pdf. Available at https://wayback.archive-it.org/7993/20170404050450/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-00-index.htm Slides available at https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm (accessed February 21, 2024) and (Horak et al. 2009).
Abbreviations: EEU, environmental exposure unit; NDAC, Nonprescription Drugs Advisory Committee; PE, phenylephrine; PSE, pseudoephedrine; hr, hour(s); min, minute(s).

Figure 9. Mean Change in Nasal Rhinometry (Left) and Peak Nasal Inspiratory Flow (Right) at 30 Minute Intervals After Drug Administration, EEU Study P04579



Sources: Schering-Plough Merck Briefing Document for NDAC Meeting (December 14, 2007). The Effects of Phenylephrine on the Symptoms of Allergic Rhinitis. 2007-4335b1-02-Schering-Plough-Merck.pdf. Available at https://wayback.archive-it.org/7993/20170404050450/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-00-index.htm. Slides available at https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm (accessed February 21, 2024) and (Horak et al. 2009).
Abbreviations: EEU, environmental exposure unit; NDAC, Nonprescription Drugs Advisory Committee; PE, phenylephrine; PSE, pseudoephedrine; PL, placebo; PNIF, peak nasal inspiratory flow; hr, hour(s); min, minute(s).

ii. Study P04822 (NCT00423995)

The study was conducted to evaluate the efficacy of the combination loratadine-montelukast (L/M) on nasal congestion in patients with SAR in an EEU. The study was a single-center, randomized, double-blind, double-dummy, placebo-controlled, three-arm parallel-group single-dose study that compared the efficacy of an oral L/M, oral PE, and placebo in adult patients with SAR who were exposed to ragweed pollen in the EEU setting. In this study, L/M was the study drug whereas PE was included as a positive control. The study was conducted in 2007, at Kingston General Hospital, Kingston, Ontario, Canada, and funded by Schering-Plough/Merck Pharmaceuticals, Kenilworth, New Jersey (Day et al. 2009).[44]

Subjects completed a screening visit, up to six priming visits (to expose subjects to ragweed pollen and stimulate symptoms), and one treatment visit. At each visit, evaluations were made of four nasal symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) and three non-nasal symptoms (itching/burning eyes, tearing/watery eyes, and itching of ears/palate) using a 0 to 3 severity scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) at 30-minute intervals.

To qualify for the treatment visit, subjects had to meet a minimum symptom score (≥2 for nasal congestion, ≥7 for combined nasal symptoms, ≥3 for combined non-nasal symptoms, and ≥10 for total symptoms) at 90 minutes, after which a single dose of treatment was administered at 120 minutes. Treatments included IR L/M 10 mg/10 mg tablets, PE-IR 10 mg syrup, and corresponding placebo tablets and flavor-disguised syrup, administered in a double-dummy fashion. Subjects were then followed for an additional 8 hours, with nasal symptom scores and PNIF measurements evaluated at 20-minute intervals. The primary endpoint was change from baseline in nasal congestion scores averaged across all time points during the first 6 hours after treatment. Because the primary objective of this study was to evaluate the efficacy of L/M in comparison with placebo, with PE administered as an active comparator, the primary comparison was between L/M and placebo.

A total of 379 subjects were randomized to treatment (127, 126, and 126, in the L/M, PE, and placebo groups, respectively). The study population was primarily female (53 to 61 percent), White (94 to 100 percent), nonasthmatic (83 to 89 percent), and approximately 33 years of age. The data demonstrates that L/M is more effective in relieving nasal congestion and other symptoms compared to placebo and PE. However, there was no statistical difference between PE and placebo, both in mean change from baseline and at most timepoints starting at 1 hour posttreatment (Figure 10) and PNIF (Figure 11). Therefore, the data fails to demonstrate efficacy of oral PE for nasal congestion.

c. Proposal Based on Review of EEU Studies

In both EEU studies, oral PE failed to demonstrate benefit over placebo. Therefore, FDA proposes that these studies demonstrate that oral PE (10 and 12 mg) is not effective as a nasal decongestant.

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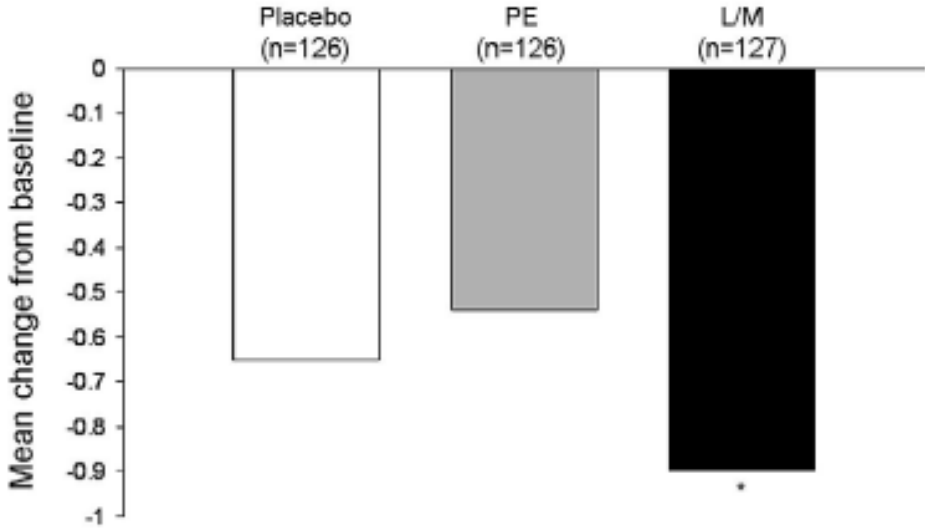
[44] Schering-Plough and Schering-Plough Merck each presented under their respective names at the 2007 NDAC meeting. The name of the company that is listed as having performed this EEU study was changed from Schering-Plough Healthcare Products to MSD Consumer in 2011. Whether Schering-Plough and Schering-Plough Merck were the same or different companies is unknown.

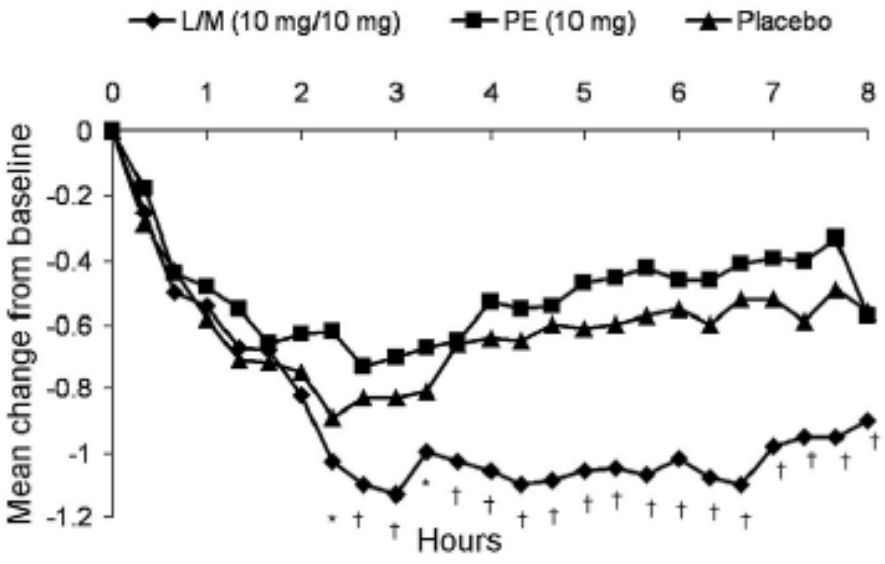
Figure 10. Mean Change From Baseline During First 6 Hours After Treatment (A) and Across Time (B) in Nasal Congestion Scores for Loratadine-Montelukast, Phenylephrine, and Placebo Groups, Study P04822

A.



*P=0.007 vs placebo, P<0.001 vs PE.
0 = none; 1 = mild; 2 = moderate; 3 = severe.

B.

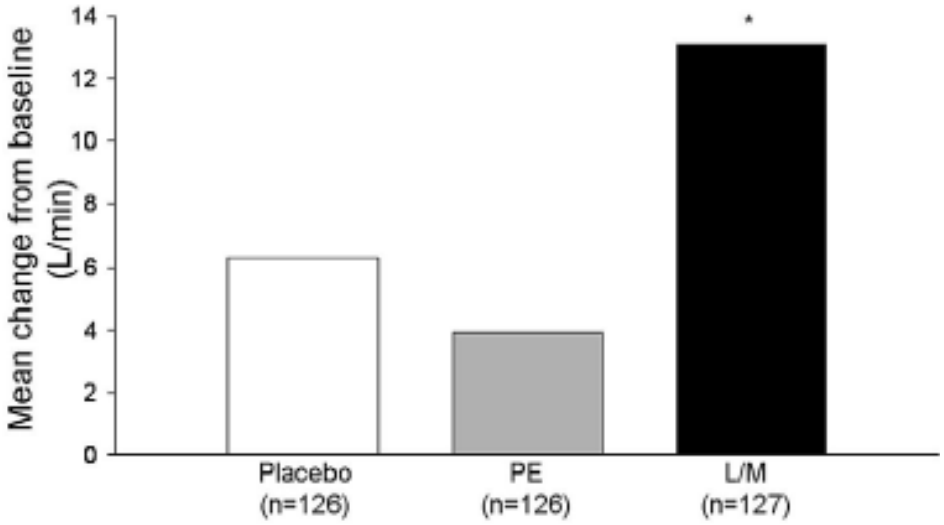


*P<0.01 L/M vs PE. †P<0.01 L/M vs PE and placebo.

Source: (Day et al. 2009).
Abbreviations: L/M, loratadine-montelukast; PE, phenylephrine.

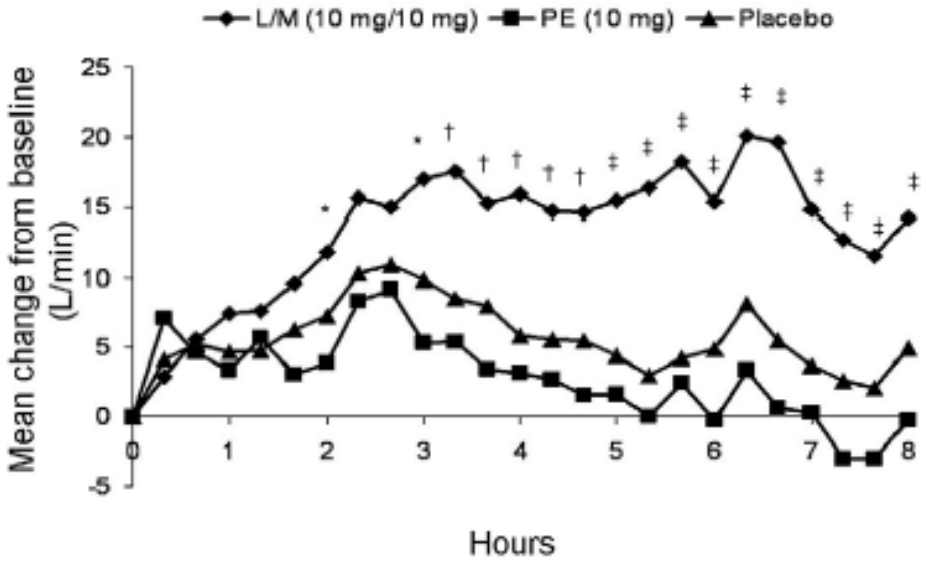
Figure 11. Mean Change From Baseline During First 6 Hours After Treatment (A) and Across Time (B) in Peak Nasal Inspiratory Flow for Loratadine-Montelukast, Phenylephrine, and Placebo Groups, Study P04822

A.



*P=0.024 vs placebo, P=0.002 vs PE.

B.



*P<0.05 L/M vs PE. †P≤0.05 L/M vs PE and placebo. ‡P<0.01 L/M vs PE and placebo.

Source: (Day et al. 2009)
Abbreviations: L/M, loratadine-montelukast; PE, phenylephrine.

2. Review of Clinical Trials on Efficacy of Oral PE

At the 2007 meeting, the Nonprescription Drugs Advisory Committee recommended that additional trials be conducted to evaluate the safety and efficacy of oral PE as a nasal decongestant and provided recommendations as to how the trials should be conducted. FDA reviewed three relevant clinical trials on the efficacy of oral PE that were conducted after the 2007 meeting.

a. Review of Studies

FDA reviewed two clinical trials completed by Merck to support the efficacy of doses of oral PE, other than doses of 10 mg. Additionally, FDA reviewed a clinical trial completed by Johnson & Johnson Consumer, Inc. (J&J).

i. Study P08156 (NCT01330017)

Merck conducted a dose-ranging trial to study the effects of oral PE on nasal congestion in participants with SAR. It was a multicenter, randomized, unmatched dummied and partially blinded, placebo-controlled, five-arm, parallel-group dose-ranging trial that evaluated fixed dosages of 10, 20, 30, and 40 mg of oral PE or placebo in 539 otherwise healthy adults with a documented history of SAR caused by spring allergens. The trial was conducted between March and June 2011, at multiple centers in the United States. The study was funded by Merck, Kenilworth, New Jersey. The results were published in a peer-reviewed journal in 2015 (Meltzer et al. 2015) and posted at clinicaltrials.gov.[45]

FDA reviewed both the results of the trial posted at clinical trials.gov and the publication. FDA considers the trial to be a late-phase 2 study.

After a 4-day run-in, subjects were randomized to one of five treatment groups of 10, 20, 30, and 40 mg of oral PE tablets or unmatched placebo tablets. The PE or placebo tablets were administered every 4 hours with not more than six doses in 24 hours for a period of 7 days. The investigators followed-up with the subjects at the end of treatment and by phone at 3 to 4 weeks. Loratadine 10 mg oral tablets were used as background treatment for allergic rhinitis during both the run-in and treatment periods. Loratadine has been shown to not have any significant effect on congestion symptoms, therefore allowing assessment of nasal congestion while still treating the underlying condition (SAR).

The trial was partially blinded. All subjects received oral PE 10 mg tablets (up to four tablets per dose), placebo tablets (up to five tablets per dose), and loratadine tablets (one tablet daily). Because the oral PE 10 mg and placebo tablets were red and concave but not exactly matching, the publication referred to the trial as having been a phase 2, "open-label" trial. However, the listing at clinicaltrials.gov explains that all subjects, regardless of treatment allocation, received up to five tablets of (unmatched) placebo. The trial used a so-called "single-dummy" technique to assist with blinding. The exact numbers of tablets the subjects received of active (PE) and control (placebo) tablets depended upon randomization to study treatment.

[45] Available at https://clinicaltrials.gov/ct2/show/NCT01330017.

Subjects rated the severity of congestion symptoms. Reflective nasal congestion symptom scores (i.e., self-evaluation of symptom severity) were assessed on a four-point, 0 to 3 scale (where 0 = absent and 3 = severe) and captured on a paper diary every 12 hours prior to the next dose during the run-in and treatment periods. Reflective assessment was recorded prior to the morning (AM) (8 AM) dose and approximately 12 hours later prior to the evening (PM) (8 PM) dose. Instantaneous congestion symptom scores, assessed on a four-point, 0 to 3 scale (where 0 = absent and 3 = severe), were captured once daily prior to the morning dose over the treatment period.

The primary endpoint was the mean change from baseline over the entire treatment period (i.e., 7 days) in daily reflective nasal congestion symptom scores, which is consistent with FDA's recommendations discussed in its guidance for industry.[46] The baseline for reflective nasal congestion symptom scores was defined as the average of the daily scores over the four consecutive 24-hour periods prior to randomization.

The secondary endpoint was the mean changes from baseline in:

- AM and PM symptom scores for the reflective symptom assessment
- Instantaneous symptom scores over the entire treatment period
- Daily reflective symptom scores during the treatment period
- Daily instantaneous symptom scores

Additionally, a secondary endpoint was time to maximal effect, defined as the earliest time that the nasal congestion symptom score demonstrates the greatest numerical difference from the placebo in change from baseline. The baseline for instantaneous symptom assessment score was the Day-1 predose assessment.

Safety endpoints were AEs, treatment-emergence adverse events (TEAEs), serious AEs, vital signs, physical examination, and 12-lead electrocardiograms (ECGs). ECGs were measures at screening and Day 8.

The study was powered, and a statistical analysis was completed. Using a two-sided test with 5 percent significance level and a standard deviation of 2.0 units, 100 subjects per arm were calculated to provide a 94 percent power to detect a difference of at least 1 unit between PE and placebo for the primary endpoint. An analysis of covariance model (ANCOVA) was used for analysis of the mean change from baseline versus placebo for all end points, with adjustments for the baseline score, investigative site, age, and sex. Control for multiple comparisons between each of the four PE doses and placebo for the primary end point was achieved via a closed family of tests, each at the $p = 0.05$ level of significance, proceeding in sequence from the highest to the lowest dose.

[46] See the guidance for industry (CDER 2018).

Demographics and baseline characteristics of the treatment groups were similar.[47] Overall, 325 of 539 (60.3 percent) subjects were female, 422 of 539 (78.3 percent) subjects were White, and 447 of 539 (82.9 percent) subjects were non-Hispanic/Latino. The mean (SD) age was 38.7 (12.04) years.

Efficacy results for the intent-to-treat (ITT) population (defined as all randomized subjects who received at least one dose of study drug) are summarized in Table 8 and shown graphically by treatment group and day in Figure 12. The primary endpoint of mean (SD) change from baseline in reflective nasal congestion scores for the ITT population was -0.460 (0.5374), -0.499 (0.5042), -0.508 (0.5618), -0.461 (0.5308), and -0.428 (0.5530) for the 10 mg PE, 20 mg PE, 30 mg PE, 40 mg PE, and placebo groups, respectively. None of the PE treatment groups had a statistically significant change from baseline in reflective nasal congestion symptom scores compared to placebo. The observations for the efficacy evaluable population for the primary endpoint were consistent with the findings for the ITT population. The time to maximal effect was 5.5 days for all PE treatment groups.

The only statistically significant secondary endpoint was the change from baseline in PM reflective nasal congestion symptom scores for the 20 mg PE group compared to placebo ($p = 0.0188$) on Day 6. All other comparisons were not statistically significant. The response rate increased over time in all treatment groups, including placebo, and the only response rate that was significant was for the 20 mg PE group compared with the placebo group on Day 6 ($p = 0.031$). The time to maximal effect was 5.5 days for all PE treatment groups. The mean change from baseline for the instantaneous symptom assessment score was not significantly different from placebo on any day for any PE treatment group.

There were no meaningful differences in the safety endpoints of vital signs, physical examinations, and 12-lead ECGs, and no new or unexpected safety issues were identified. However, there were minor differences between treatment groups for AEs. Overall, the system organ class with the most TEAEs was nervous system disorders, reported in 30 of 539 (5.6 percent) of all treatment groups, but only in 2 of 103 (1.9 percent) of placebo-treated subjects. The most common TEAE was headache. However, it was not dose related, occurring in 5.5 percent (6/109), 3.7 percent (4/108), 2.8 percent (3/107), and 2.7 percent (3/112) of the 10, 20, 30, and 40 mg treatment groups, respectively, but in none (0/103) of the subjects in the placebo group. At the 40 mg PE dose, 2.7 percent (3/112) and 3.6 percent (4/112) of subjects experienced gastrointestinal side effects of dry mouth and nausea, respectively. One subject in the 40 mg dosage group experienced chest and lower jaw pain that resolved after stopping PE.

[47] For more details, see Table 1 in (Meltzer et al. 2015).

FDA identified several limitations with the study. FDA considered the study to be a partially open-label design because placebo was similar to but not exactly matched with active drug. The lack of blinding could introduce a treatment group bias (i.e., a bias that favors finding a difference between active and control) which is a major concern when a difference between one of the active treatment groups (PE) and control (placebo) is found. While the addition of a partial dummying technique to the study could assist, it did not completely blind the study because subjects could count the number of different pills and infer meaning. For example, if a subject received four of one tablet and one of another, the subject could reasonably assume that they had been allocated to 10 mg and 40 mg of PE. However, the lack of any differences between the four active treatment groups and the placebo group despite the possibility of a blinding bias (which would be in favor of finding such a difference) lends support to the validity of the findings.

Another limitation is that the study did not include an active comparator arm, such as PSE. However, the fact that the study arms were similar in size with other allergic rhinitis studies using the same study evaluations and endpoints, and that the findings are replicated and virtually identical for all four active treatment groups lends credence to the results.

While FDA acknowledges these limitations with the study, the study is of sufficiently high quality that it accurately portrays the treatment effect of oral PE, including dosages up to 40 mg. The trial provides substantive evidence that oral PE at dosages of 10 mg to 40 mg are not effective as a nasal decongestant.

Table 8. Change From Baseline in Reflective Nasal Congestion Symptom Scores Over Entire Treatment Period, by Treatment, ITT Population, Merck Protocol #CL2010-06

Parameter	PE HCl 10 mg N=109	PE HCl 20 mg N=108	PE HCl 30 mg N=107	PE HCl 40 mg N=112	Placebo N=103
Baseline (SD)*	2.417 (0.4327)	2.517 (0.3995)	2.481 (0.4148)	2.492 (0.3887)	2.514 (0.4208)
Day 7 (SD)†	-0.460 (0.5374)	-0.499 (0.5042)	-0.508 (0.5618)	-0.461 (0.5308)	-0.4208 (0.5530)
p-value#	0.4912	0.4519	0.2186	0.5983	

Source: Aggregate data from (Meltzer et al. 2015) and results published at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT01330017).

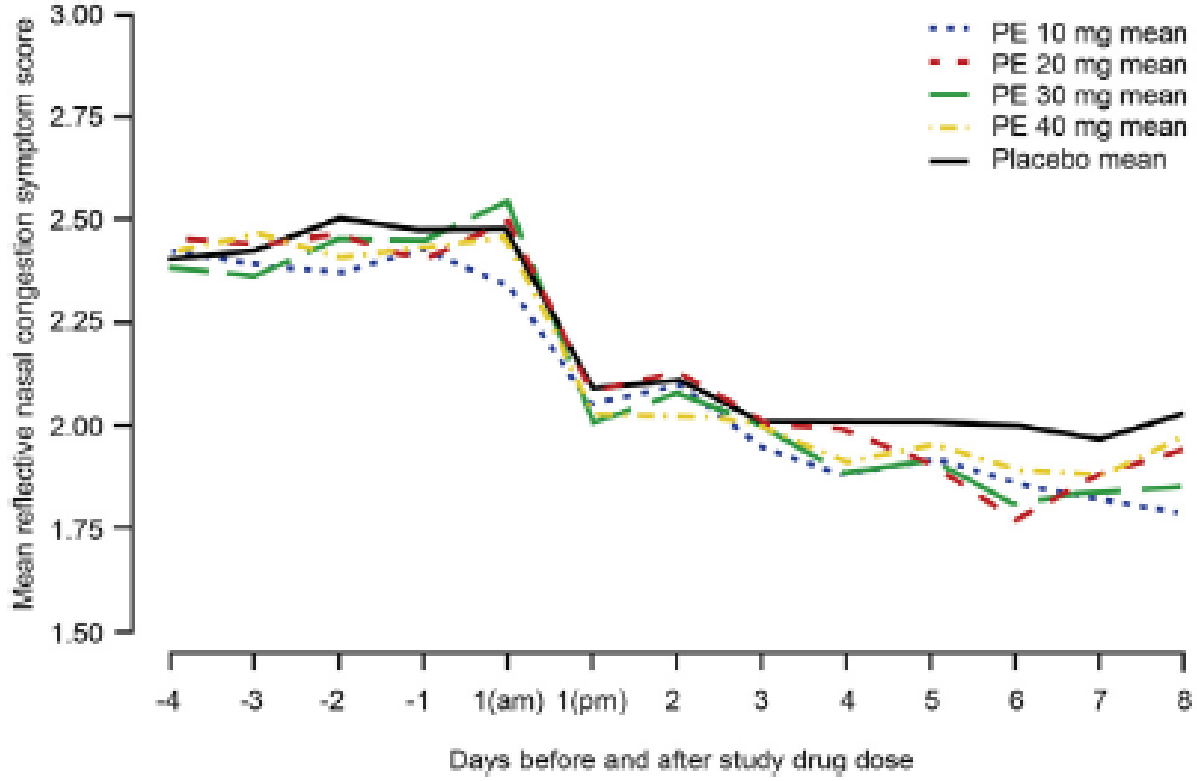
* Reflective nasal congestion symptom scores were captured in participant diaries just before the 8:00 a.m. dose and 12 hours later just before the 8:00 p.m. dose. Participants rated congestion on a four-point scale of severity from 0 (best) to 3 (worst), with 0 = absent symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. The daily reflective nasal congestion symptom score was defined as the average of the morning and evening reflective nasal congestion score for the entire treatment period. Baseline was defined as the average of the daily scores over the four consecutive 24-hour periods before randomization.

† Primary outcome measure reported with the ITT population defined as all randomized participants who received at least one dose of study drug.

An analysis of covariance model was used for analysis of the mean change from baseline versus placebo for all end points, with adjustments for the baseline score, investigative site, age, and sex. Multiple comparisons between each of the four active doses and placebo for the primary efficacy end point were performed as a closed family of tests, each at the 0.05 level of significance, and proceeded in sequence from the highest dose to the lowest dose to control the overall significance level of 0.05.

Abbreviations: ITT, intent-to-treat; PE, phenylephrine; HCl, phenylephrine hydrochloride.

Figure 12. Reflective Nasal Congestion Scores by Treatment and Study Day, ITT Population, Merck Protocol #CL2010-06



Source: (Meltzer et al. 2015).
Abbreviations: ITT, intent-to-treat; PE, phenylephrine.

ii. Study P08498 (NCT01413958)

Merck conducted a phase 3 trial to study the effects of extended-release (ER) oral PE on allergy-related nasal congestion. It was a multicenter, randomized, double-blind, placebo-controlled, two-arm, parallel-group trial that evaluated 30 mg of a modified-release formulation of PE HCl (PEH-MR) and placebo in 575 otherwise healthy adults with documented SAR caused by fall pollen allergens. The trial was conducted between August and October 2011, at 29 study sites. The study was funded by Merck, Kenilworth, New Jersey. The results were published in a peer-reviewed journal in 2016 (Meltzer et al. 2016) and posted at clinicaltrials.gov.[48]

FDA reviewed the results of the trial posted at clinical trials.gov and the publication.

Study visits included the following: screening (Days -41 to -8), baseline (Days -7 to -1), start of treatment (Day 1), end of treatment (Day 8) and follow-up (Days 22 to 31) visits. Consistent with FDA recommendations discussed in its guidance for industry,[49] subjects were washed out of any allergy drugs that might interfere with study evaluations. During study treatment, subjects were allowed rescue loratadine 10 mg oral tablets once-daily as needed for intolerable allergic-rhinitis symptoms. Subjects recorded nasal congestion symptom scores on a four-point, 0-to-3 scale (where 0 = none, 3 = severe) and AEs as diary entries starting approximately 7 days prior to start

[48] Available at https://clinicaltrials.gov/ct2/show/NCT01413958.

[49] See the guidance for industry (CDER 2018).

of study treatment and extending through the entire treatment period. During the treatment period, subjects continued to record assessments of nasal congestion, AEs, and time of study drug dosing twice daily in the diary, just before the AM and PM doses.

The primary endpoint was the mean change from baseline during the entire treatment period in daily reflective nasal congestion scores, which was calculated (average of AM and PM reflective nasal congestion scores for the entire treatment period) from data in the subjects' diary entries during the run-in and treatment periods. The baseline was defined as having a minimum self-rated symptom score of 1 (sign or symptom clearly present but minimal awareness; easily tolerated), equivalent to experiencing mild symptoms over four consecutive 24-hour periods before randomization. Reflective assessment was considered the symptom severity score during the preceding 12 hours; instantaneous assessment was considered the symptom severity at the moment of the assessment before the next dose. This primary endpoint is consistent with FDA recommendations discussed in its guidance for industry.[50]

Secondary efficacy measurements included the following:

- Mean change from baseline during the entire treatment period in:
  - AM and PM reflective symptom scores
  - Daily instantaneous symptom assessment scores
  - AM predose instantaneous nasal congestion symptom score (to assess 12-hour duration of action)
- Mean change from baseline for each day during the treatment period for:
  - Reflective symptom assessment score (to assess onset of action and durability of response)
  - AM and PM reflective and instantaneous symptom assessment scores (calculated and analyzed separately)
  - Instantaneous symptom assessment score (to assess onset of action and durability of the response)
- Time to maximal effect (defined as earliest time that mean change from baseline in reflective nasal congestion symptom score demonstrated greatest numerical difference from placebo)
- Duration of effect (end-of-dosing interval analysis measured as change from baseline for instantaneous symptom assessment score at Day 7)

Instantaneous assessment was performed and recorded at similar time points to the reflective assessment. Baseline for instantaneous symptom assessment scores was calculated similar to the reflective scores. Subjects self-administered the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) with standardized activities before and after receiving the study drug. If possible, the RQLQ also was administered before any discussion with trial personnel.

The study was powered, and a statistical analysis was completed. The trial was designed to have a power of 94 percent to detect a difference of at least 1 unit with respect to the change from baseline in nasal congestion symptom score on Day 8. Using a two-sided test with 5 percent

[50] See the guidance for industry (CDER 2018).

significance level assuming a standard deviation of 2 units, the study design required at least 500 subjects. An analysis of covariance model with adjustments for baseline value, investigative site, age, and sex, was used for analysis of the primary endpoint. Secondary analyses were carried out using an analysis of covariance with no adjustments for multiplicity.

A total of 575 subjects were enrolled and randomized, 288 to the PEH-MR 30 mg treatment group and 287 to placebo. 574 subjects (99.8 percent) completed the study.

Demographics and baseline characteristics of the treatment groups were similar.[51] Subjects were mostly female (61 percent) and White (82 percent), with a mean age of 40.1 years. Mean study compliance was 99.5 percent and there were no differences between study groups in rescue loratadine use.

The primary endpoint results are summarized numerically in Table 9 and graphically in Figure 13. They showed no statistically meaningful difference between the PEH-MR 30 mg and placebo treatment groups. Mean daily reflective scores at baseline and over the course of the 7 days of treatment (a secondary endpoint), shown graphically in Figure 14, demonstrate that PEH-MR was numerically no better than placebo at any timepoint in the trial. While the baseline score for placebo was numerically lower than the PEH-MR 30 mg treatment arm, the placebo arm also had numerically more mean improvement over the course of the study (see Table 9). Analyses of secondary endpoints for instantaneous and daily congestion scores showed similar results.

There were no clinically meaningful differences in AEs between the treatment groups in this trial. As in the dose-ranging trial, the system organ class with the most TEAEs was nervous system disorders (overall 4.0 percent [23/575]), and the most common TEAE was headache, occurring in 3.1 percent (9/288) and 2.8 percent (8/287) of the PEH-MR and placebo groups, respectively.

The study provides high-quality evidence that PE is not an effective nasal decongestant when administered orally in a 30 mg MR formulation. Further, the study provides substantive evidence that oral PE is not effective as a nasal decongestant within the dosage limits allowed under OTC Monograph M012, particularly because the study acknowledged that the outcome of their bioequivalence study indicated that systemic exposure would be higher for the oral PEH-MR 30 mg compared to oral PE 10-mg tablets dosed every 4 hours.[52]

Table 9. Change From Baseline in Reflective Nasal Congestion Scores Over Entire Treatment Period, ITT Population, Study P08498

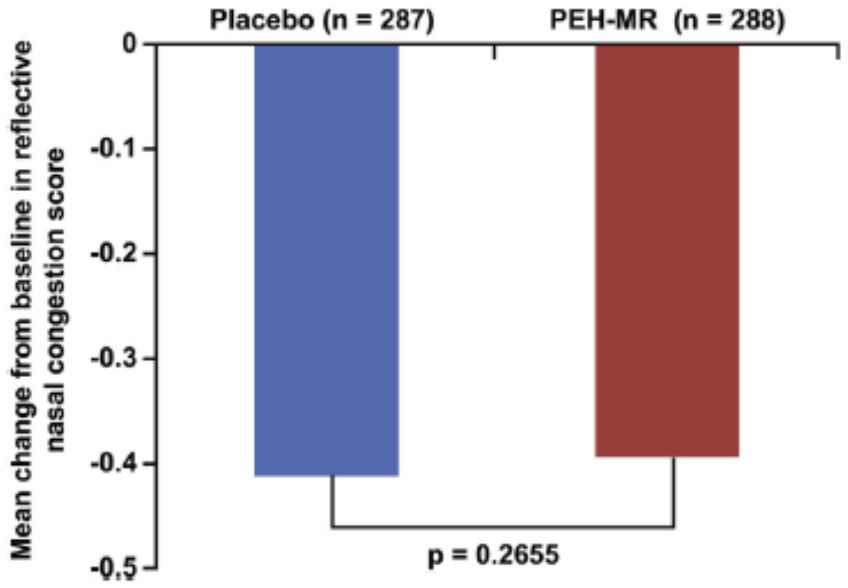
Parameter	PEH-MR 30 mg N=288	Placebo N=287
Baseline (SD)	2.357 (0.5203)	2.271 (0.5586)
Mean change over treatment period (SD)	-0.394 (0.4880)	-0.412 (0.5383)

Source: Results published at clinicaltrials.gov (Bayer 2015).
Abbreviations: ITT, intent-to-treat; PEH-MR, phenylephrine hydrochloride–modified-release; SD, standard deviation.

[51] For more details, see Table 1 in (Meltzer et al. 2016). Study results are available at https://clinicaltrials.gov/ct2/show/NCT01413958.

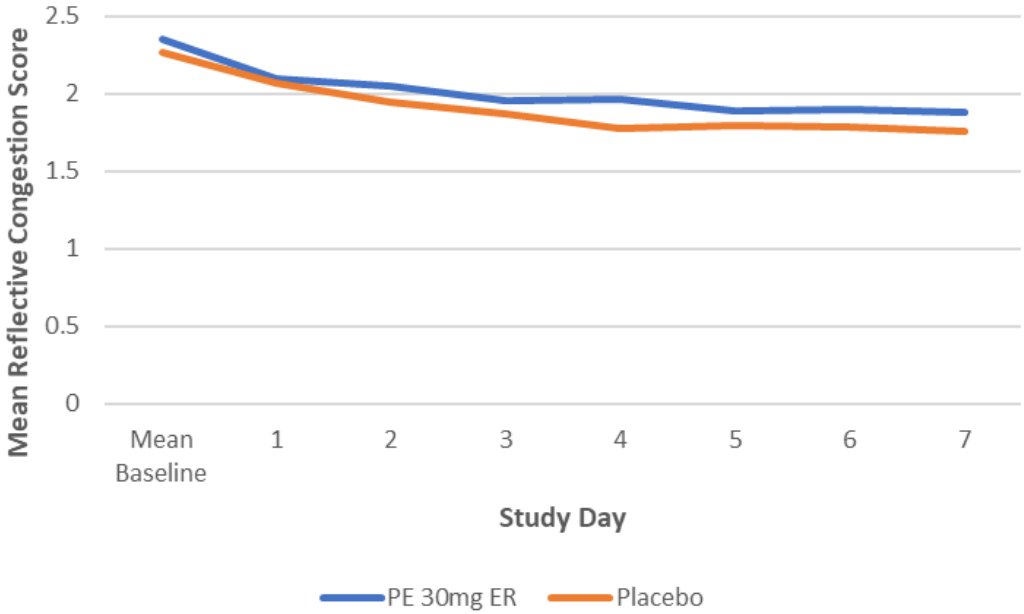
[52] See discussion section in (Meltzer et al. 2016) at page 70 of the article.

Figure 13. Mean Change From Baseline in Reflective Nasal Congestion Score Over Entire Treatment Period, ITT Population, Study P08498



Source: (Meltzer et al. 2016).
Abbreviations: ITT, intent-to-treat; PEH-MR, phenylephrine hydrochloride–modified-release.

Figure 14. Mean Daily Reflective Nasal Congestion Score at Baseline* and Per Day, ITT Population, Merck Protocol #CL2011-06



Source: Adapted from results published at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT01413958).
* Baseline was defined as the mean from four consecutive 24-hour periods in which a symptom score was ≥1, prior to randomization. The nasal congestion score was calculated from data captured twice daily (morning and evening) in the subject's diary during the run-in and treatment periods. Subjects rated congestion on a four-point scale of severity: 0 = absent symptoms (no sign/symptom evident), 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated), 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable), and 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping). The average of individual reflective nasal scores was reported as the daily reflective nasal congestion score over the entire treatment period.
Abbreviations: ER, extended-release; ITT, intent-to-treat; PE, phenylephrine.

iii. Johnson & Johnson Consumer, Inc. Phase 2 Study (NCT03339726)

J&J conducted a study of a new formulation of PE. The study was conducted in Canada during the 2017–18 common cold season. It was a randomized, double-blind, double-dummy, placebo-controlled, parallel-group study that evaluated the efficacy of an ER 30 mg PE oral tablet (30 mg PE-ER) compared with an IR 12 mg PE oral capsule (12 mg PE-IR) and placebo in subjects with nasal congestion due to the common cold. Information about the study was posted on clinicaltrials.gov ((J&JCI) 2019).[53]

FDA reviewed the results of the trial posted at clinicaltrials.gov. The posted information includes a redacted protocol and statistical analysis plan. As a result, certain data are not available, such as baseline values for each treatment group. Therefore, FDA cannot not provide a full analysis of this study.

The study enrolled subjects 18 years of age and older who were experiencing common cold symptoms for up to 72 hours (3 days) prior to entry, had at least a nasal congestion / stuffy nose score of ≥5 and at least a mild (score of ≥3) for sinus pressure / tenderness, and two or more of the following symptoms: runny nose, sore or scratchy throat, sneezing, headache, malaise, or cough.

Subjects were randomized to one of three treatment groups: (1) two doses of 30 mg PE-ER tablets taken 12 hours apart; (2) four doses of 12 mg PE-IR capsules taken 4 hours apart; and (3) four doses of placebo capsules taken 4 hours apart. The study included a double-dummy design and PE or placebo tablets were administered as follows:

- For the 30 mg PE-ER treatment group, one 30 mg PE-ER tablet plus one placebo IR capsule taken orally twice daily and one placebo ER tablet plus one placebo IR capsule taken orally twice daily
- For the 12 mg IR treatment group, one 12 mg PE-IR capsule plus one placebo ER tablet taken orally four times daily
- One placebo ER tablet plus one placebo IR capsule taken orally four times daily

Therefore, all subjects took both tablets and capsules four times a day. Subjects stayed on site for the first and second doses (at 0 and 4 hours, respectively). One-third of subjects were assigned to a pharmacokinetic (PK) cohort, with samples collected at the time of the first and second doses, although the results of this aspect of the study are not included in the information posted on clinicaltrials.gov.

The primary endpoint was mean change from baseline in reflective nasal congestion severity score (NCSS) over 0 to 12 hours after the first study dose, as measured on an eight-point scale where 0 = none and 7 = severe. Change from baseline in NCSS averaged over assessments at 2, 4, 6, 8, 10, and 12 hours. The primary endpoint was analyzed for the ITT population using an analysis of variance (ANOVA) model with treatment group, study center, and baseline nasal

[53] Available at https://clinicaltrials.gov/ct2/show/NCT03339726.

scores as factors. This primary endpoint is consistent with FDA's recommendations discussed in its guidance for industry.[54]

Secondary endpoints included the following:

- Average change from baseline in NCSS (time frame: 0 to 12 hours) (eight-point scale with 0 = none and 7 = severe)
- Average change from baseline in NCSS averaged over Hours 8 to 12
- Change from baseline in NCSS (time frames: 0 to 2, 0 to 4, 0 to 6, 0 to 10, 0 to 12, and 0 to 24 hours), and at 2, 4, 6, 8, 10, 12, and 24 hours
- Average change from baseline in sinus pressure / tenderness scores (time frame: 0 to 12 hours) (8-point scale with 0 = none and 7 = severe)
- Change from baseline in sinus pressure / tenderness scores averaged over assessments at 2, 4, 6, 8, 10, and 12 hours
- Change from baseline in sinus pressure / tenderness scores (time frames: 0 to 2, 0 to 4, 0 to 6, 0 to 8, 0 to 10, 0 to 12, and 0 to 24 hours), and at 2, 4, 6, 8, 10, 12, and 24 hours

The majority of subjects were female (63.2 percent) and either White (78.2 percent) or Asian (13.0 percent). The demographics were similar between the three treatment arms.

The study results are shown in Table 10, and graphically over the course of the study in Figure 15 and Figure 16. No benefit was seen for the primary endpoint. However, the results provided at clinicaltrials.gov do not state whether the mean changes from baseline of NCSS are listed as improvements or getting worse with treatment, (i.e., as absolute or relative congestion score changes). The results for all treatment arms trend in a similar direction, which suggests no beneficial effect of either PE treatment when compared with placebo.

b. Proposal Based on Review of Efficacy Studies

In three studies conducted after the 2007 meeting, oral PE failed to demonstrate any benefit over placebo. Therefore, FDA proposes that these studies demonstrate that oral PE is not effective as a nasal decongestant within the dosage limits and in the dosage forms allowed under OTC Monograph M012.

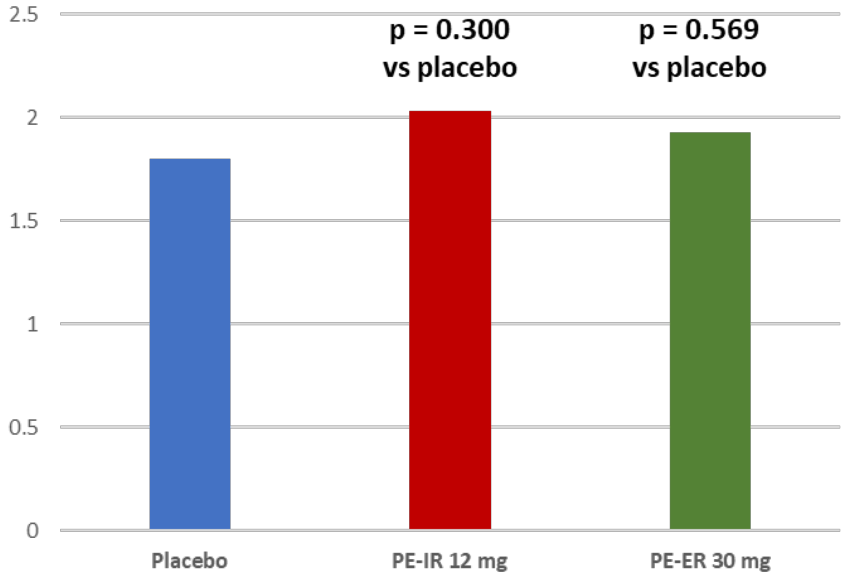
[54] See the guidance for industry (CDER 2018).

Table 10. Primary Endpoint of Mean Change From Baseline in Nasal Congestion Severity Score Over 12 Hours, J&J Study NCT03339726

Parameter	Placebo N=64	PE-IR 12 mg N=66	PE-ER 30 mg N=63
Baseline	NA	NA	NA
Mean change over 12 hours	1.80 (0.156)	2.03 (0.1540)	1.93 (0.158)
Mean difference vs. placebo (95% CI)		0.23 (-0.205 to 0.662)	0.13 (-0.311 to 0.564)
p-value vs. placebo		0.300	0.569

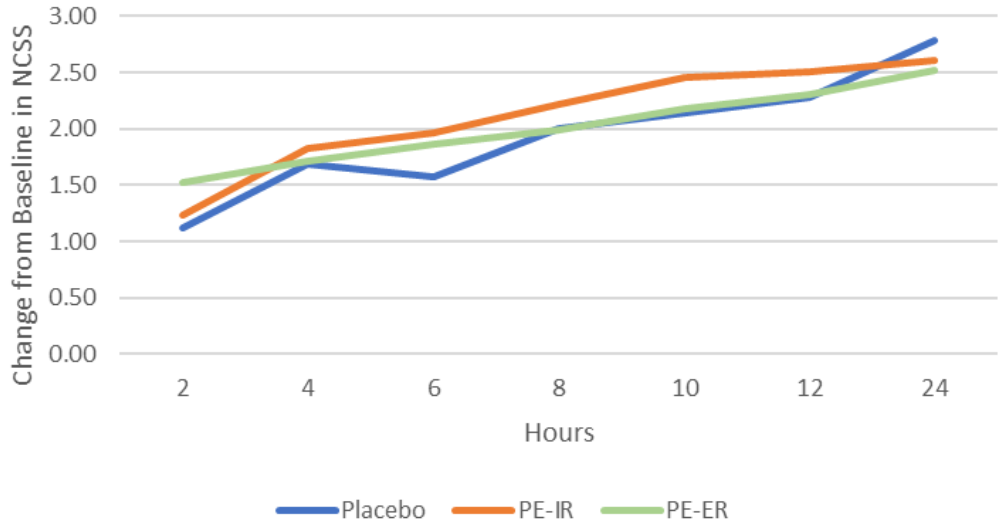
Source: https://clinicaltrials.gov/ct2/show/NCT03339726.
Abbreviations: CI, confidence interval; ER, extended-release; IR, immediate-release; J&J, Johnson & Johnson Consumer, Inc.; NA, not applicable; PE, phenylephrine.

Figure 15. Primary Endpoint of Mean Change From Baseline in NCSS Over 12 Hours, J&J Study NCT03339726



Source: Adapted from data available at https://clinicaltrials.gov/ct2/show/NCT03339726.
Abbreviations: ER, extended-release; IR, immediate-release; PE, phenylephrine; J&J, Johnson & Johnson Consumer, Inc.; NCSS, Nasal Congestion Severity Score.

Figure 16. Change From Baseline in NCSS Over 24 Hours, J&J Study NCT03339726



Source: Adapted from data available at https://clinicaltrials.gov/ct2/show/NCT03339726.
Abbreviations: ER, extended-release; IR, immediate-release; PE, phenylephrine; J&J, Johnson & Johnson Consumer, Inc.; NCSS, Nasal Congestion Severity Score.

C. Proposal Based on the Scientific Review of Efficacy Data

Based on FDA's comprehensive review of the clinical data,[55] FDA proposes that the data demonstrate that oral PE is not effective as a nasal decongestant within the dosage limits and in the dosage forms allowed under OTC Monograph M012.

III. Scientific Review of Pharmacology Data

FDA conducted a comprehensive review of the pharmacology data of oral PE as a nasal decongestant. As part of the clinical pharmacology review, FDA reviewed clinical pharmacology data that have become available on oral PE and its metabolites since FDA's original GRASE determination for oral PE as a nasal decongestant as reflected in the 1994 final rule.[56] The comprehensive review on the pharmacology of oral PE included:

- Review of clinical trials with pharmacokinetic and pharmacodynamic data
- Review of publicly available pharmacokinetic data in one new drug applications (NDAs) for drug products containing PE

[55] See 59 FR 43409 (Aug. 23, 1994). Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Nasal Decongestant Drug Products.

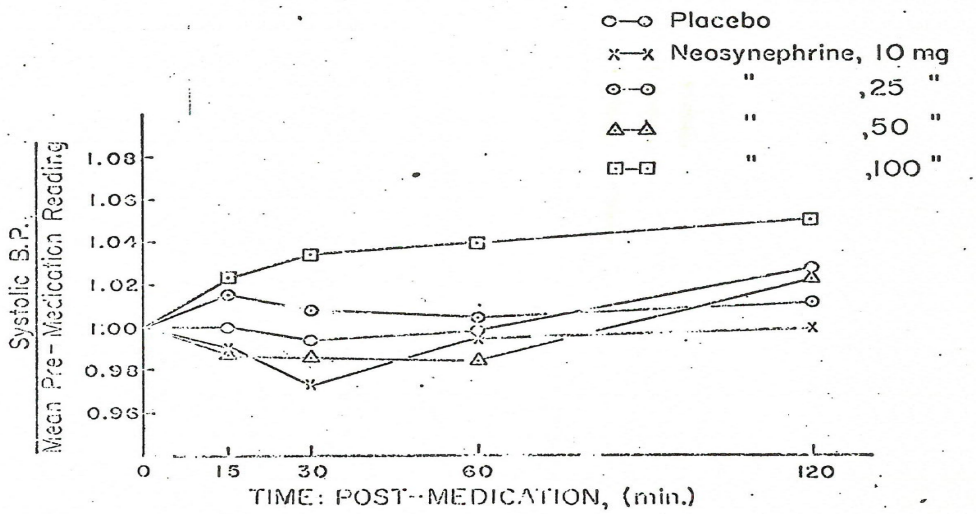
[56] See 59 FR 43409 (Aug. 23, 1994).

A. Background

1. Historical Rulemaking Pharmacodynamic Data

For FDA to understand pharmacology data within the context of the long history of oral PE use, FDA reviewed the historical data used to support FDA's GRASE determination for oral PE as a nasal decongestant in the 1994 final rule. The Panel reviewed the 17 studies for clinical safety and pharmacodynamic (PD) data of oral PE doses between 10 mg and 60 mg (see also Section IV.A Background). A number of the studies evaluated by the Panel produced inconsistent results as to the threshold dose necessary for PD effect of oral PE, particularly at lower doses.[57] For example, the Panel evaluated one study that reported that 40 to 60 mg of oral PE is required for PD effects, (i.e., potentially clinically meaningful effects on systolic BP (an increase of 5 to 10 mm Hg) and HR (a reduction of 4 to 8 beats/minute)).[58] The study also noted that 250 mg of oral PE produces a PD effect (HR decline from 67 to 46 beats/minute and BP rise from 112/71 to 143/96). The PD effect of 250 mg of oral PE is roughly equivalent to 5 mg of subcutaneous PE, a subcutaneous dose that consistently produces a measurable PD effect. However, the Panel evaluated a second study that suggested 100 mg or more of oral PE is needed to exert a meaningful PD effect on systolic BP (see Figure 17).[59]

Figure 17. Fractional Changes in Systolic Blood Pressure in Subjects Given Oral Placebo or 10, 25, 50, or 100 mg of Neo-Synephrine (PEH) (n=20)



Source: 41 FR 38312, Reference 3: Standler to Ludena. Analysis of blood pressure and pulse results for subjects given placebo and Neo-Synephrine orally. Unpublished report from Sterling-Winthrop Lab, dated January 6, 1967.
Abbreviations: BP, blood pressure; PEH, phenylephrine hydrochloride; FR, *Federal Register*; min, minute(s).

[57] See 41 FR 38312.

[58] 41 FR 38312 Reference 1: (Keys and Violante 1942).

[59] 41 FR 38312 Reference 3: Standler to Ludena. Analysis of blood pressure and pulse results for subjects given placebo and Neo-Synephrine orally. Unpublished report from Sterling-Winthrop Lab, dated January 6, 1967.

2. 2007 Meeting

At the 2007 meeting, Schering-Plough presented on the metabolism, PK, bioavailability, and activity of PE.[60,61] They presented that PE has α1-adrenergic pharmacologic activity, which is its presumed mechanism of action as an oral decongestant. Oral PE is known to undergo extensive presystemic metabolism, with a majority of the metabolism taking place within the gut wall. After oral administration, four main metabolites were excreted in urine, reported as percent of dose: PE-3-O-glucuronide (12%), PE-3-O-sulfate (47%), 3-hydroxymandelic acid (30%), and 3-hydroxyphenylglycol. Data from a small, single-dose oral bioavailability study conducted in 14 subjects showed that active parent PE represents less than 1 percent of the total PE (i.e., total PE includes parent PE and its conjugated metabolites (PE-3-O-glucuronide and PE-3-O-sulfate)) in the plasma after a single 10 mg oral dose of PE (Figure 18).

Schering-Plough presented that they had developed in vitro pharmacology data to make PK comparisons. Schering-Plough conducted studies to determine the affinity and functional activity of PE 3-O-sulfate, PE 3-O-glucuronide, and 3-hydroxymandelic acid, at the human recombinant α1-adrenoreceptors (α1a and α1b subtypes) and α2-adrenoreceptors (α2a, α2b and α2c subtypes). The calcium flux response assay demonstrated that the in vitro α1-adrenergic agonistic half maximal effective concentration (EC_{50}) values (2.3 and 16.9 ng/mL) of parent PE (Table 11) are higher than the in vivo parent PE maximum plasma concentration (C_{max}) value (~0.65 ng/mL) following administration of oral PE 10 mg (Figure 18). None of three major metabolites of PE had any detectable α1-adrenergic receptor agonistic activity as measured by calcium flux response assay. In addition, none of three major metabolites of PE had any detectable α2-adrenergic receptor binding activity as measured by GTPγS binding exchange assay.

Schering-Plough concluded that none of the conjugates tested demonstrated any activity. Schering-Plough explained that earlier bioavailability studies based on total PE concentration measurement had not accounted for the small composition of parent PE and the lack of activity of conjugated PE. The small composition of parent PE and the lack of activity of conjugated PE explains why oral PE 10 mg is not sufficient to provide efficacy, whereas even a lower than 1 mg dose PE by intravenous (IV) administration demonstrates systemic alpha-1-agonist activity.[62]

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[60] Schering-Plough Corporation Presentation Slides at NDAC Meeting (December 14, 2007) are available at https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm (accessed February 28, 2024).

[61] Schering-Plough Corporation Briefing Document for NDAC Meeting (December 14, 2007). Understanding Phenylephrine Metabolism, Pharmacokinetics, Bioavailability and Activity. Available at https://wayback.archive-it.org/7993/20170404050450/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-00-index.htm (accessed February 28, 2024).

[62] See (Martinsson et al. 1986).

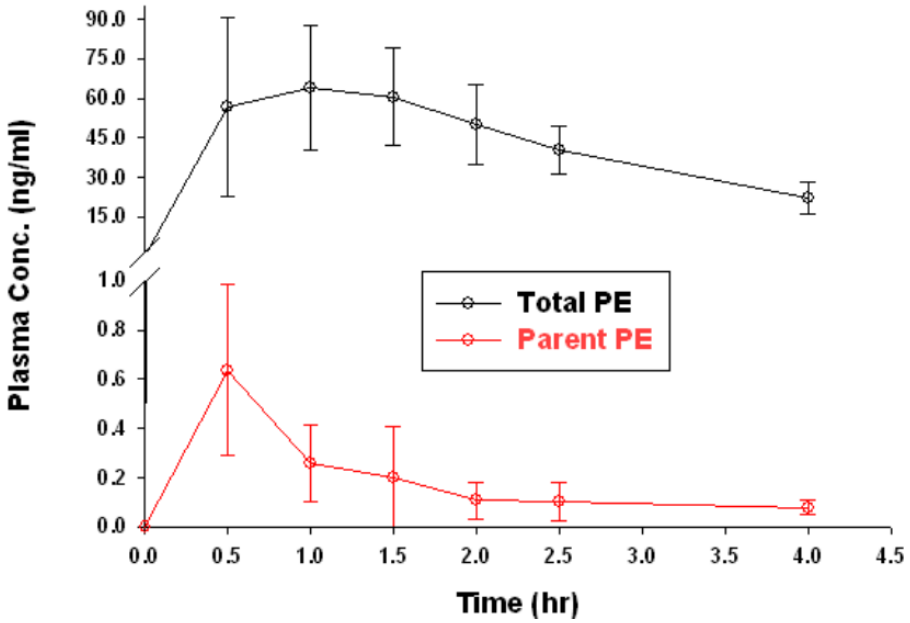
Table 11. In Vitro 50% Effective Concentration Values (ng/mL) of Alpha-Adrenergic Agonizing Activity of Phenylephrine and Its Metabolites

α Receptor	PE	PE-3-O-Sulfate	PE-3-O-Glucuronide	3-Hydroxy Mandelic Acid
α1a[1]	16.9	No activity	No activity	No activity
α1b[1]	2.3	No activity	No activity	No activity
α2a[2]	37.6	No activity	No activity	No activity
α2b[2]	390.3	No activity	No activity	No activity
α2c[2]	147.8	No activity	No activity	No activity

Source: Adapted from Schering-Plough Corporation Presentation Slides at NDAC Meeting (December 14, 2007) are available at https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm (accessed February 28, 2024).
[1] As measured by cell-based calcium flux response assay.
[2] As measured by [35S]-GTPγS binding exchange assay.
Abbreviations: NDAC, Nonprescription Drugs Advisory Committee; PE, phenylephrine.

Figure 18. Plasma Concentrations of Parent PE and Total PE vs. Time for a Single Oral Dose of a PE Tablet

Total phenylephrine (PE):
Parent PE (active)
PE-3-O-glucuronide (inactive)
PE-3-O-sulfate (inactive)



Source: Schering-Plough Study CL2005-07, 2005. Schering-Plough Merck Briefing Document for NDAC Meeting (December 14, 2007). The Effects of Phenylephrine on the Symptoms of Allergic Rhinitis. 2007-4335b1-02-Schering-Plough-Merck.pdf. Available at https://wayback.archive-it.org/7993/20170404050450/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-00-index.htm. Slides available at https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm.
Total PE consists of parent PE, PE-3-O-glucuronide (inactive), and PE-3-O-sulfate (inactive).
Black line represents total PE.
Red line represents parent PE.
Abbreviations: PE, phenylephrine; hr, hour(s); conc, concentration; NDAC, Nonprescription Drugs Advisory Committee.

B. Review of Clinical Pharmacology Data

FDA identified four relevant clinical trials with pharmacology data. Additionally, FDA identified two NDAs for drug products containing PE with pharmacology data.

1. Pharmacologic Activity of PE and Its Metabolites

On June 27, 2017, FDA approved NDA 204300 for Vazculep (phenylephrine) injection, 10 mg/mL.[63] The approved drug label for NDA 204300 states that "Phenylephrine hydrochloride is an α-1 adrenergic receptor agonist."[64] In addition, the label states that after IV administration of radiolabeled PE, "there are two major metabolites, with approximately 57 percent and 8 percent of the total dose excreted as m-hydroxymandelic acid and sulfate conjugates, respectively. The metabolites are considered not pharmacologically active." These statements are consistent with the data presented by Schering-Plough at the 2007 NDAC meeting (see Section III.A.2 2007 Meeting).[65]

2. Oral Bioavailability

a. Radiolabeled PE Bioavailability Study

A radiolabeled PE bioavailability study was conducted to examine the PK of PE (Hengstmann and Goronzy 1982). 7-^{3}H-phenylephrine was given via IV infusion to 15 volunteers. Analysis of serum free ^{3}H-phenylephrine and fractionation of urinary radioactivity was performed by ion-exchange and thin-layer chromatography. The study estimated that the absolute oral bioavailability (i.e., ratio of PE exposure following oral administration versus IV infusion) of parent PE was 38 percent.

The absolute oral bioavailability of 38 percent is an overestimate due to underestimating the PE exposure following the IV infusion. The PK samples were not collected during the IV infusion which lasted about 12.5 to 20 minutes. The parent PE systemic exposure during the IV infusion was expected to have significantly contributed to its overall systemic exposure given its short half-life (~5 minutes) following IV administration. The underestimate of the PE exposure following the IV infusion rendered the ratio of PE exposure following oral administration/PE exposure following IV infusion artificially relatively higher.

While this study was conducted in 1992, reliable nonradiolabeled high-performance liquid chromatography tandem mass spectrometry bioanalytical assay sufficiently sensitive to characterize the full PK profile of parent PE following the administration of oral PE did not become available until the 21st century.[66]

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[63] The drug approval package for NDA 204300 is available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204300Orig1s000TOC.cfm (accessed February 28, 2024).

[64] NDA 204300, Labeling. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204300Orig1s000LBL.pdf (accessed February 28, 2024).

[65] Schering-Plough Corporation Presentation Slides at NDAC Meeting (December 14, 2007) are available at https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm and Schering-Plough Corporation Briefing Document for NDAC Meeting (December 14, 2007). Understanding Phenylephrine Metabolism, Pharmacokinetics, Bioavailability and Activity. 2007-4335b1-01-Schering-Plough.pdf. Available at https://wayback.archive-it.org/7993/20170404050450/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-00-index.htm (accessed February 28, 2024).

[66] See (Feng et al. 2013).

b. Study P08340 (NCT01354418)

Prior to conducting a larger study, Merck conducted a relative bioavailability study of a single dose of oral PE-ER 30 mg and oral PE-IR tablets dosed every 4 hours.[67] No results are listed at clinicaltrials.gov for this study. Therefore, FDA could not evaluate the results.[68]

c. NDA 022565

On May 27, 2010, FDA approved NDA 022565 for Advil Sinus Congestion & Pain (ibuprofen 200 mg and phenylephrine HCl 20 mg) tablet.[69] As part of the review of NDA 022565, FDA reviewed a study that showed that the parent PE systemic exposure is <1 percent of the total PE (i.e., parent PE + conjugated PE) systemic exposure following oral administration of PE (Figure 19 and Table 12). Further, the study showed that both the effective and elimination half-lives of the parent PE are shorter than that of total PE.[70] This is consistent with the data presented by Schering-Plough at the 2007 NDAC meeting (see Section III.A.2 2007 Meeting).[71]

[67] See also Section II.B.2.b. Study P08498 (NCT01413958). The results of this trial are referred to in (Meltzer et al. 2015; Meltzer et al. 2016).

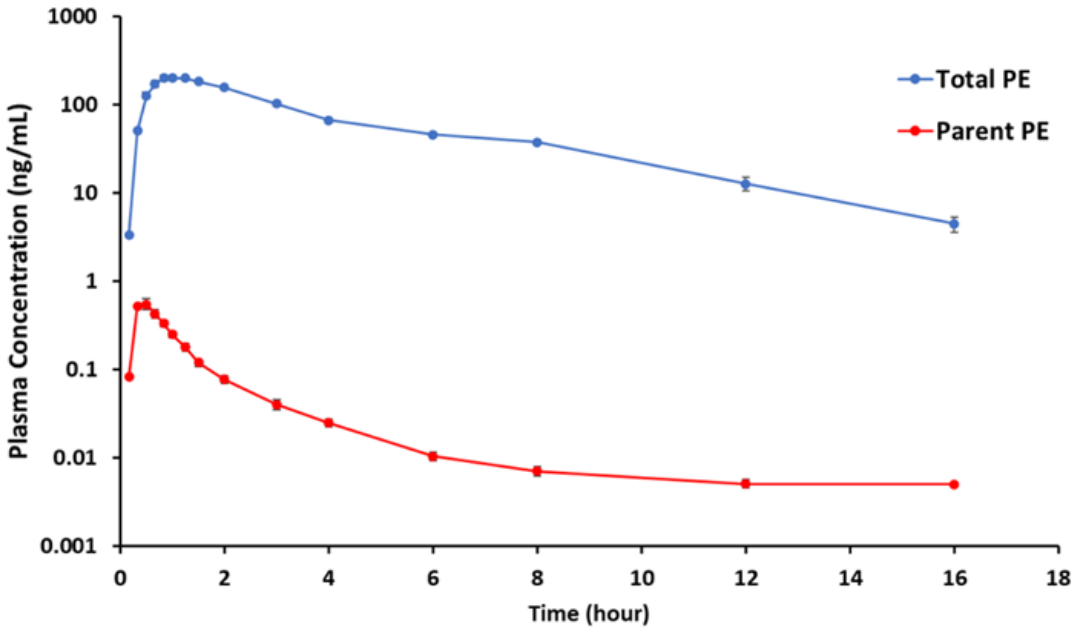
[68] See https://www.clinicaltrials.gov/study/NCT00874120.

[69] The drug approval package for NDA 022565 is available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022565s000TOC.cfm (accessed February 28, 2024).

[70] Study 0813 in NDA 022565.

[71] Schering-Plough Corporation Presentation Slides at NDAC Meeting (December 14, 2007) are available at https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm and Schering-Plough Corporation Briefing Document for NDAC Meeting (December 14, 2007). Understanding Phenylephrine Metabolism, Pharmacokinetics, Bioavailability and Activity. Available at https://wayback.archive-it.org/7993/20170404050450/https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4335b1-00-index.htm (accessed February 28, 2024).

Figure 19. Geometric Mean Parent and Total Phenylephrine Pharmacokinetic Profile (N=42) Following 10 mg Single Oral Dose of Sudafed PE®



Source: NDA 022565, Study 0813.
Abbreviations: NDA, new drug application; PE, phenylephrine.

Table 12. Systemic Exposure of Parent and Total PE Following 10 mg Single Oral Dose of Sudafed PE®

Parameter	Parent PE	Total PE	Mean Ratio (Parent/Total)
C_{max} (ng/mL)[1]	0.766 (49%)	225 (33%)	0.34%
AUC_{last} (ng×h/mL)[1]	0.692 (26%)	864 (22%)	0.08%
AUC_{inf} (ng×h/mL)[1]	0.730 (26%)	885 (22%)	0.08%
T_{max} (hour)[2]	0.33 (0.17, 0.83)	0.92 (0.5, 2)	N/A
$t_{1/2}$ (hour)[1]	1.55 (59%)	2.68 (21%)	N/A

Source: NDA 022565, Study 0813 (N=42) following single-dose administration of 10 mg oral phenylephrine (Sudafed®).
[1] Geometric mean (CV%).
[2] Median (minimum, maximum).
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; NDA, new drug application; PE, phenylephrine; T_{max}, time to maximum plasma concentration; N/A, not available.

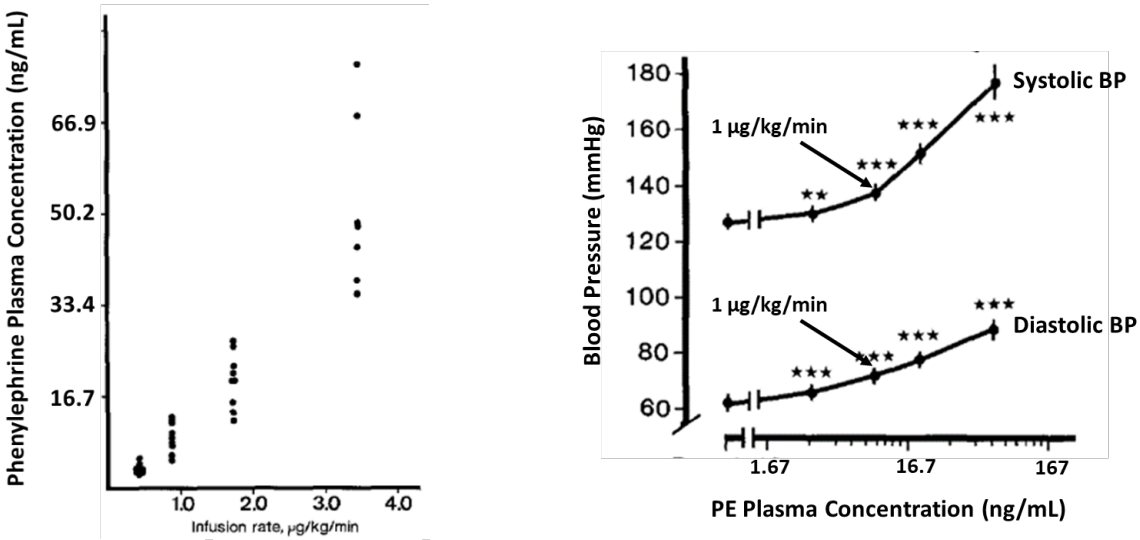
3. Pharmacokinetic/Pharmacodynamic Relationships

Based on the in vitro pharmacology results, PE is presumed to stimulate the local α -1 adrenergic receptors expressed on the blood vessels in nasal mucosa to exert its desired pharmacological effect, if the local concentration of parent PE reaches to certain levels (Johnson and Hricik 1993). However, there is a lack of data that directly measure the α -1 adrenergic activity in the nasal mucosa. Therefore, FDA conducted a review of the relationships between PE PK and systemic α -1 adrenergic PD response (systolic BP change from baseline) and compared those relationships between orally administered PE and IV administered PE.

a. Martinsson et al. Study

A study was conducted to analyze the concentration of PE in plasma (Martinsson et al. 1986). The study was a crossover clinical trial. The trial was conducted in nine healthy subjects. Subjects were given an IV infusion of PE 0.5, 1, 2 and 4 µg/kg/minute for 6 minutes at each dose level. It showed that following a lower-than-oral dose (1 µg/kg/minute, or a 6-minute total dose of a 0.42 mg infusion for a subject weighing 70 kg) continuous IV infusion of PE, a steady-state parent PE mean plasma concentration of ~10 ng/mL was reached within 6 minutes (Figure 20) (Martinsson et al. 1986). At this plasma concentration during the IV infusion, both systolic and diastolic BP elevated noticeably, about 10 mm Hg from baseline.

Figure 20. Plasma Concentrations of Parent PE (Left) and Systemic Blood Pressure Change (Right) During the 6-Minute Continuous IV Infusion of 0.5, 1.0, 2.0, and 4.0 µg/kg/Minute PE



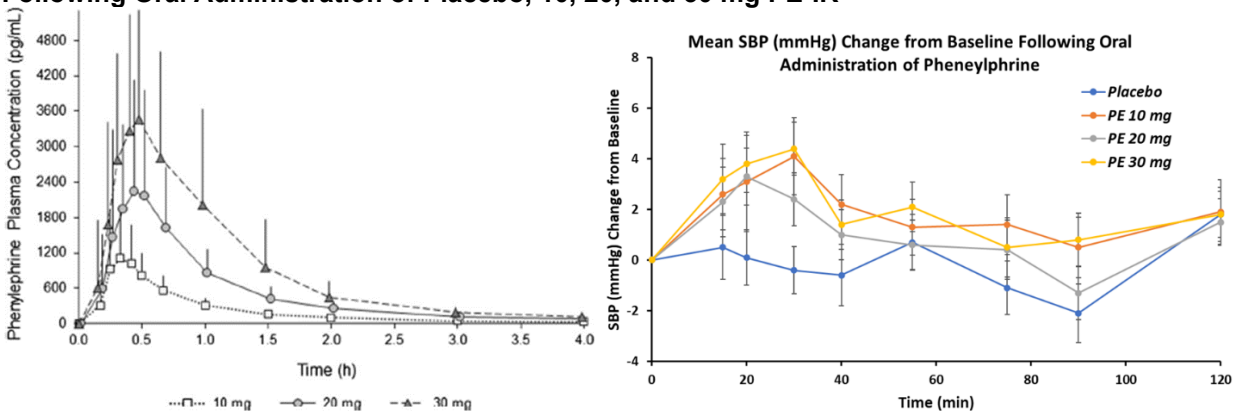
Source: Adapted from (Martinsson et al. 1986).
Abbreviations: BP, blood pressure; IV, intravenous; PE, phenylephrine.

b. McNeil Consumer Healthcare Study

In 2015, McNeil Consumer Healthcare (McNeil) published results from a phase 2 study, which characterized the PK, safety, and cardiovascular tolerability following a single dose of oral PE-IR (Gelotte and Zimmerman 2015). The study was a randomized, double-blind, placebo-controlled, single-dose, crossover design that compared four oral treatments: placebo, PE 10 mg, PE 20 mg, and PE 30 mg. Twenty-eight healthy subjects were randomized, with seven subjects receiving each of the four treatments during each of the four periods (four periods were conducted for four consecutive days). The PK results showed that parent PE peak plasma concentration was reached about 20 to 30 minutes post oral dose and the C_{max} values increased roughly dose-proportionally (Figure 21). The mean C_{max} value following PE 10 mg oral dose was 1.35 ng/mL. Meanwhile, the postdose mean systolic BP increased less than 5 mmHg from baseline and no dose-response relationship was observed (Figure 21). After adjustment by the placebo treatment, the maximal elevation of mean systolic BP from baseline within 2 hours postdose was 4.1, 3.3, and 4.4 mmHg for 10, 20, and 30 mg PE treatment, respectively. Although the relationship between systemic alpha-1 adrenergic activity and local alpha-1 adrenergic activity that is required for a nasal decongestion effect is unclear, the numerically small changes

of systolic BP following up to a 30 mg oral dose of PE are consistent with the lack of local decongestion effect of PE observed from efficacy trials (Meltzer et al. 2015; Meltzer et al. 2016). The results are also consistent with the studies reviewed by the Panel (see Section III.A.1 Historical Rulemaking Pharmacodynamic Data).

Figure 21. Plasma Concentrations of Parent PE (Left) and Systolic Blood Pressure Change (Right) Following Oral Administration of Placebo, 10, 20, and 30 mg PE-IR



Source: Adapted from (Gelotte and Zimmerman 2015) Gelotte, CK and BA Zimmerman, 2015, Pharmacokinetics, safety, and cardiovascular tolerability of phenylephrine HCl 10, 20, and 30 mg after a single oral administration in healthy volunteers, Clin Drug Investig, 35(9):547-558.
Abbreviations: IR, immediate-release; PE, phenylephrine; SPB, systolic blood pressure; h, hour(s); min, minute(s).

The cross-study comparison of the Martinsson et al. study and the McNeil study showed that, regardless of a relatively much lower dose of PE being administered, the steady state parent PE plasma concentration following 1 µg/kg/minute IV infusion was about 10-fold higher than the parent PE C_{max} value following the oral PE 10 mg oral dose. In addition, there was a clear dose-dependent increase of BP from baseline following continuous IV infusion with about 10 mm Hg elevation at a plasma concentration about 10 ng/mL achieved by infusion rate of 1 µg/kg/minute. However, the mean systolic BP increased less than 5 mm Hg following up to a 30 mg oral PE dose (three times the dose allowed under OTC Monograph M012 (see § M012.80(d)(1) of OTC Monograph M012), and no clear dose-response relationship of vital sign change from baseline was observed following oral PE doses of 10 to 30 mg. Based on the results from the 2015 McNeil study and the IV infusion study (Martinsson et al. 1986), FDA estimates that an approximately 50 mg oral dose of PE may be needed to achieve a 5 mmHg increase of systolic BP from baseline. This estimate is consistent with the estimation from a clinical trial reviewed by the Panel that a threshold dosage of at least 40 to 60 mg oral PE is needed to result in a meaningful elevation of systolic BP.[72] In addition, FDA estimates that an approximately 100 mg oral dose of PE would be needed to match the steady-state concentration (~10 ng/mL) following 1 µg/kg/minute IV infusion of PE that resulted in 10 mmHg elevation of systolic BP (Martinsson et al. 1986).

Although an effective oral dose of PE that results in a sufficient local α -1 adrenergic activity for nasal decongestive effect is unknown, a much higher oral dose than the 10 mg PE (the dose

[72] See (Keys and Violante 1942).

allowed under OTC Monograph M012) is expected based on the currently available in vivo PK and PD results of parent PE.[73]

C. Proposal Based on Pharmacology of Oral PE

We propose that the actual oral bioavailability of PE is less than 1 percent, which explains the lack of efficacy of oral PE. While literature often cites the oral bioavailability of PE of 38 percent, that value is an overestimate and based on outdated technology. The low oral bioavailability of PE is due to the high first-pass metabolism effect. In comparison, systemic exposure of PE is relatively higher when a much lower dose than 10 mg is administered via IV infusion due to the lack of first-pass metabolism.

Based on FDA's review of the pharmacology data, FDA proposes that oral PE has very low systemic exposure with little systemic pharmacologic effect within the dosage limits and dosage forms allowed under OTC Monograph M012, which further explains the lack of efficacy data.

IV. Scientific Review of Safety Data

FDA conducted a comprehensive review of data regarding the safety of orally administered PE as a nasal decongestant. While the efficacy and pharmacology studies provide general information on the safety of oral PE, as part of the safety review, FDA reviewed the safety data that have become available since its GRASE determination for oral PE as a nasal decongestant.[74] This comprehensive review included:

- Review of clinical safety study of oral PE
- Review of safety reports

A. Background

For FDA to understand safety data within the context of the long history of oral PE use, FDA reviewed the historical data used to support FDA's GRASE determination for oral PE as a nasal decongestant in the 1994 final rule. The Panel reviewed 17 studies for clinical safety and PD data of oral PE doses between 10 mg and 60 mg (see also Section III.A.1 Historical Rulemaking Pharmacodynamic Data). Most of the 17 studies evaluated for safety were single-dose studies. The Panel concluded that oral PE was safe in the dosages used as a nasal decongestant. Perceived side effects of 10 mg of oral PE approximated the incidence and pattern of placebo response. The Panel concluded that 15 to 25-mg doses of oral PE are associated with an increasing incidence of symptoms related to mild central nervous system stimulation.[75]

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[73] The lowest concentration of PE solution for intranasal use allowed under OTC Monograph M012 is 0.125 percent, or 1.25 mg/mL (see § M012.80 (d)(2) of OTC Monograph M012), equals 1,250,000 ng/mL. That is about one million-fold higher than the mean parent PE Cmax value following a 10 mg oral dose of PE.

[74] See 59 FR 43409 (Aug. 23, 1994).

[75] See 41 FR 38312 at 38399.

B. Review of Safety Data

FDA identified one relevant clinical trial that was specifically a safety study of oral PE. Additionally, FDA reviewed safety reports.

1. Study P07529 (NCT0874120)

Merck conducted a safety study comparing oral PE-ER 30-mg tablets and placebo. The study was a randomized, double-blind, placebo-controlled, multiple-dose crossover ambulatory BP safety study conducted in 2009.[76] The results were posted on clinicaltrials.gov.[77]

The study compared 7 days of treatment with oral PE-ER 30 mg and placebo, with a 6 to 8-day washout between treatment arms. A total of 116 subjects were randomized, 58 per arm, and a total of 106 completed the study. Mean (SD) age was 29 (10.5) years, and 52.6 percent were males. The primary outcome was average systolic BP readings for a 5-hour range around the time of maximal concentration. No meaningful differences in mean systolic BP (SD) were noted between the two treatment arms: 118.3 (9.24) and 118.6 (9.38) for the 30 mg oral PE-ER 30 mg and placebo arms, respectively.

2. Safety Reports

To evaluate whether there is a safety signal (i.e., potential safety issue) for oral PE, FDA evaluated safety reports in the FDA Adverse Event Reporting System (FAERS),[78] America's Poison Centers-National Poison Data System (APC-NPDS), and medical literature.

FDA reviewed adverse events (AEs) associated with single-ingredient oral PE products labeled for use as a nasal decongestant, in the absence of concomitant medications. FDA focused on cardiovascular (CV) and neurologic AEs given the sympathomimetic action of the drug. The data FDA reviewed from FAERS, APC-NPDS, and the medical literature suggest that PE is associated with CV and neurologic AEs, which is expected and addressed by the current labeling for oral PE drug products. Despite widespread use, FDA identified very few cases reporting severe AEs.

Analysis of FAERS data also indicated that consumers used oral PE products at higher doses, or at more frequent dosing intervals, or for longer durations of therapy than specified on the label, which might reflect PE's poor oral bioavailability and lack of effectiveness.

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[76] Merck conducted two preliminary studies using PE-ER 30 mg, Study P07529 (NCT00874120) and Study P08340 (NCT01354418), prior to conducting a larger trial, Study P08498 (NCT01413958). See also Section II.B.2.a.ii Study P08498 (NCT01413958)).

[77] Study results available at https://clinicaltrials.gov/ct2/show/NCT00874120.

[78] FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. For more information, see Questions and Answers on FAERS available at https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers (accessed March 1, 2024).

C. Proposal Based on the Scientific Review of Safety Data

Based on the available data FDA reviewed specifically focused on the safety of oral PE, in addition to the efficacy and pharmacology studies that provided additional information on safety, FDA proposes that no safety signal was identified for oral PE within the dosage limits and in the dosage forms allowed under OTC Monograph M012.

V. Proposal Based on Scientific Review

Based on our comprehensive scientific review of available data, FDA proposes that oral phenylephrine—in the salt forms of phenylephrine hydrochloride and phenylephrine bitartrate—is not GRASE under section 201(p)(1) of the FD&C Act because it is not effective as a nasal decongestant within the dosage limits and in the dosage forms allowed under OTC Monograph M012. Furthermore, there are no clinical data demonstrating that oral PE is effective as a nasal decongestant at any dosage. Rather, data demonstrates that oral PE is not effective within the dosage limits and in the dosage forms allowed under in OTC Monograph M012.

FDA conducted a careful and thorough review of all available efficacy, pharmacology, and safety data for oral phenylephrine. FDA reviewed significant data on oral phenylephrine which was not available at the time of the FDA's initial generally recognized as safe and effective determination for oral phenylephrine in the 1994 final rule, specifically new efficacy and pharmacology data. The clinical data on phenylephrine that have become available since the 1994 final rule demonstrate that oral phenylephrine is not effective as a nasal decongestant. In addition, due to significant issues with study design, methodology, disease context, conduct, and statistical analysis, the historical studies cannot be relied upon to provide evidence of efficacy of oral phenylephrine as a nasal decongestant. The lack of efficacy for oral phenylephrine can be explained with clinical pharmacology data demonstrating that oral phenylephrine has no meaningful systemic exposure within the dosage limits and in the dosage forms set forth in OTC Monograph M012. While FDA identified no safety signal for oral phenylephrine within the dosage limits and in the dosage forms under OTC Monograph M012, available data suggests that a much higher dose of phenylephrine would be needed to achieve a clinically meaningful outcome which would raise significant questions about safety.

Therefore, FDA is proposing to amend OTC Monograph M012 to remove oral phenylephrine hydrochloride and phenylephrine bitartrate as nasal decongestant active ingredients. If finalized, OTC drug products containing oral phenylephrine hydrochloride and phenylephrine bitartrate will be deemed new drugs under section 201(p) of the FD&C Act and subject to the requirements for an approved new drug application under section 505 of the FD&C Act.

VI. References

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Links to Important Resources

Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for OTC Human Use Monograph

The CCABA OTC Monograph (including all amendments) was deemed a final order (OTC Monograph M012, order number OTC000026, posted on the FDA web portal on October 14, 2022) under the CARES Act: https://www.govinfo.gov/content/pkg/COMPS-15754/pdf/COMPS-15754.pdf). M012 is available at https://dps.fda.gov/omuf/monographsearch/monograph_m012.

2007 Phenylephrine Citizen Petition

Hendeles L, Hatton RA, Winterstein AG. Citizen Petition – Phenylephrine. Docket ID: FDA-2007-P-108 (formerly FDA-2007-P-0047/CP1), available at https://www.regulations.gov/docket/FDA-2007-P-0108.

2007 Nonprescription Drugs Advisory Committee Meeting

NDAC meeting held on December 14, 2007. Information available at https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs.

2007 Joint Nonprescription Drugs and Pediatric Advisory Committee Meeting

Meeting held on October 18 and 19, 2007. Information available at https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs.

2015 Phenylephrine Citizen Petition

Hendeles L, Hatton RA. Citizen Petition – Phenylephrine. Docket ID: FDA-2015-P-4131, available at https://www.regulations.gov/docket/FDA-2015-P-4131.

Appendix A

Table 13. Oral PE Efficacy Studies Reviewed by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Product (1976)

Study/Site Info/ Docket Number	Drugs/ Doses	N	Study Design and Results
Sterling-Winthrop (Lands to Ludena 5-23-59) Reference 5	PE 10 PE 25 PE 50 PE 75 PPA 50 PPA 75 Placebo	15	This was an early, preparatory study for the 10 studies from Sterling-Winthrop, including 5 Elizabeth, 3 Cintest, and 2 Huntingdon studies. 10, 25, 50 and 75 mg of PEH (Neo-Synephrine) were compared with 25 and 50 mg of PPA (Propadrine) in 15 subjects in a double-blind, placebo-controlled, crossover design. NAR methodology: Sternstein, HJ and MO Schur, 1936, Quantitative study of nasal obstruction: A new method, Arch Otolaryng, 23:475. Only minor changes SBP were noted at 1 and 2 hours postdosing after PE, and no significant effects on NAR readings were noted for any dose of PE, whereas significant effects were noted for PPA at 1 hour postdosing. The findings were said to suggest that 50 mg of PPA and 75 mg of PE are the threshold oral doses for these drugs.

Study/Site Info/ Docket Number	Drugs/ Doses	N	Study Design and Results
Elizabeth 1 (Hulme to Suter 6-28-67) Reference 6	PE 25 Eph 8 Placebo	12 13 25	Conducted at Elizabeth Biochemical Labs, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY. Two-way crossover in 25 patients with colds. Two sets of treatment groups: PE 25 mg vs. placebo (n=12), or ephedrine 8 mg vs. placebo (n=13). Evaluations 24 hours apart. Testing to 120 minutes. Endpoints: airway resistance and symptoms. NAR methodology: not described. Both actives were effective vs. placebo.
Elizabeth 2 (Hulme to Wessinger 1-12-68) Reference 7	PE 10 PE 15 PE 25 Eph 50 Placebo	16 10 6 6 38	Conducted at Elizabeth Biochemical Labs, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY. Two-way crossover in 38 subjects with demonstrable congestion (cause not stated): PE 10 mg vs. placebo (n=16), PE 15 mg vs. placebo (n=10), PE 25 mg vs. placebo (n=6), Eph 50 mg vs. placebo (n=6). Evaluations 24 hours apart. Testing to 120 minutes. Endpoints: airway resistance and symptoms. There was a highly significant difference among patient responses over the 0-, 15-, and 30-minute predosing time periods, with a consistent trend toward increased NAR as related to time of observation, and the last observation was used as baseline. There also were differences between the right and left nostrils on the first day of testing. While less on the second day, there was significant variation between patients. Used an average of repeated measurements from both nostrils to deal with this variability. All actives were reported as effective vs. placebo.
Elizabeth 3 (Hulme to Blackmore 6-2-69) Reference 8	PE 5 PE 15 PE 25 PPA 50 Placebo	16 10 10 10 46	Conducted at Elizabeth Biochemical Labs, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY. Two-way blinded crossover in 46 subjects with colds: PE 5 mg vs. placebo (n=16), PE 15 mg vs. placebo (n=10), PE 25 mg vs. placebo (n=10), phenylpropanolamine (PPA) 50 mg vs. placebo (n=10). Evaluations 24 hours apart. Testing to 240 minutes. Endpoints: airway resistance, symptoms, pulse, BP. NAR methodology: modified Butler-Ivy procedure. All actives were effective vs. placebo, although no differences in symptoms at 5 mg vs. placebo, no dose-response relationship noted, and PPA was more effective than any dose of PE. Variable results with pulse and BP, with no clinically relevant differences in SBP or DBP vs. placebo at the 25 mg PE dose.
Elizabeth 4 (Hulme to Blackmore 8-11-69) Reference 9	PE 15 PE 20 PE 25 Placebo	6 5 9 25	Conducted at Elizabeth Biochemical Labs, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY. Two-way double-blinded crossover in 20 subjects with colds: PE 15 mg vs. placebo (n=6), PE 20 mg vs. placebo (n=5), PE 25 mg vs. placebo (n=9). However, not completed as envisioned due to lack of subjects. Evaluations 24 hours apart. Testing to 240 minutes. Endpoints: airway resistance, symptoms, pulse, BP. NAR methodology: modified Butler-Ivy procedure. All actives were effective vs. placebo for NAR results but no difference for symptoms at 25 mg. No clinically relevant differences in pulse, SBP, or DBP vs. placebo.

Study/Site Info/ Docket Number	Drugs/ Doses	N	Study Design and Results
Elizabeth 5 (Hulme to Blackmore 5-27-70) Reference 10	PE 10 PE 15 PE 25 Placebo	10 6 9 25	Conducted at Elizabeth Biochemical Labs, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY. Two-way double-blinded crossover in 25 subjects with colds: PE 10 mg vs. placebo (n=10), PE 15 mg vs. placebo (n=6), PE 25 mg vs. placebo (n=9). Planned 46, but only enrolled 25 subjects. NAR methodology: modified Butler-Ivy procedure. All actives were effective vs. placebo for NAR results with dose ordering. No clinically relevant differences in pulse, SBP, or DBP vs. placebo.
Blanchard et al. 1964 Reference 19	NA	NA	This is a publication that the ANPR cited to support effectiveness of oral PE. It is stated to have been conducted over a 3-year period in hundreds of patients at the University of Maryland. However, it cannot be used to support the effectiveness of oral PE because the actual products and dosing are not stated, *and* where it describes use of an oral decongestant is only in combination with antihistamine and an analgesic in a commercially available product or as part of extended-release medication that includes two vasoconstrictors, an antihistamine and an analgesic. Therefore, this study is of no value despite the fact that the ANPR cited it as such.
Huntingdon 1 (Hulme to Blackmore 5-13-69) Reference 20	PE 10 PE 25 PPA 50 Placebo	16 16 16 48	Conducted at Huntingdon Research Center, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY, with the express interest to confirm data from previous Elizabeth studies. Design the same as Cintest 1 study. No significant differences between PE 10 or PE 25 mg and placebo at 45 or 60 minutes, whereas PPA 50 mg vs. placebo was significant (although the magnitude of differences was not as great as expected). Missing data so no subjective scoring. Large variability in results and different or inexperienced technicians blamed for lack of positive results.
Huntingdon 2 (Hulme to Blackmore 6-26-69) Reference 21	PE 10 PE 20 Placebo	25 25 50	Conducted at Huntingdon Research Center, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY, with the express interest to confirm data from previous Elizabeth studies. Two-way double-blinded crossover in 50 subjects with colds: PE 10 mg vs. placebo (n=25), PE 20 mg vs. placebo (n=25). Evaluations 24 hours apart. Testing to 240 minutes. Endpoints: airway resistance, symptoms, pulse, BP. No significant difference between 10 mg vs. placebo, and only significant timepoint for 20 mg vs. placebo was at 45 minutes. Subjective comparisons not attempted due to lack of positive NAR findings. No significant pulse or BP findings. Different or inexperienced technicians blamed for lack of positive results.
Cintest 1 (Hulme to Blackmore 4-10-69) Reference 22	PE 10 PE 25 PPA 50 Placebo	16 16 16 48	Conducted at Cintest Division of Hill Top Laboratories, Cincinnati, OH, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY. Two-way double-blinded crossover in 48 subjects with colds: PE 10 mg vs. placebo (n=16), PE 20 mg vs. placebo (n=16), PPA 50 mg vs. placebo (n=16). Evaluations 24 hours apart. Testing to 240 minutes. Endpoints: airway resistance, symptoms, pulse, BP. Limited periods of differences noted: 90-180 minutes for PE 10 mg vs. placebo, 120-240 minutes for PE 25 mg vs. placebo, and 60-120 minutes for PPA 50 mg vs. placebo. No difference in symptoms at PE 25 mg vs. placebo. Large variability in results, operator technique blamed for lack of positive findings.

Study/Site Info/ Docket Number	Drugs/ Doses	N	Study Design and Results
Cintest 2 (Hulme to Blackmore 1-23-70) Reference 23	PE 10 PE 15 PE 20 Placebo	16 16 16 48	Conducted at Cintest Division of Hill Top Laboratories, Cincinnati, OH, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY. Two-way double-blinded crossover in 48 subjects with colds: PE 10 mg vs. placebo (n=16), PE 15 mg vs. placebo (n=16), PE 20 mg vs. placebo (n=16). Evaluations 24 hours apart. Testing to 240 minutes. Endpoints: airway resistance, symptoms, pulse, BP. Failed study: No significant difference between any PE treatment group and placebo for NAR, symptom scores, pulse, or BP. No reason why—same instrument and technicians. Discussed technique with Elizabeth Biochemical and observed technician giving the testing—no obvious problem found.
Cintest 3 (Hulme to Blackmore 5-18-70) Reference 24	PE 10 PE 15 PE 25 Placebo	16 16 16 48	Conducted at Cintest Division of Hill Top Laboratories, Cincinnati, OH, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY. Two-way double-blinded crossover in 48 subjects with colds: PE 10 mg vs. placebo (n=16), PE 15 mg vs. placebo (n=16), PE 25 mg vs. placebo (n=16). Evaluations 24 hours apart. Testing to 120 minutes. Endpoints: airway resistance, symptoms, pulse, BP. Indistinguishable results between PE 10 mg vs. placebo. Minimal differences between PE 15 or PE 25 mg vs. placebo. No differences in subjective findings.
(Rogers 1973) Reference 25	NA	NA	Physiologic and Pharmacologic Studies on Nasal Airway Resistance. Abstract presented at the American Society for Clinical Pharmacology and Therapeutics, March 22, 1973. Evaluated 5 topical and 10 oral nasal decongestants at varying dose levels in a double-blind crossover design in subjects with “reversible chronic, nonatopic nasal congestion,” but the drugs and doses were not stated. Primary endpoint was nasal airflow and trans-oro-nasal pressures. Because it is an abstract, no treatment arms are stated, nor are the number of subjects noted. However, FDA believes that what was cited as reference 25 in the ANPR was information based on an earlier publication by Bickerman in 1971. (See next row.)
(Bickerman 1971)	PE 10 PSE 60 PPA 40 Placebo	57	These were studies in 47 healthy volunteers and 57 patients who had a history of chronic rhinitis which was for the most part nonatopic. Day-to-day and in-day variations were noted, after which pharmacologic studies were done in a double-blind, crossover fashion in the patients with chronic nonseasonal rhinitis. NAR evaluations included the following treatment arms: intranasal placebo and oxymetazoline sprays; oral placebo, PSE 60 mg, PPA 4 mg, and PEH 10 mg. PSE results were highly significant starting at 0.5 hour and continuing through 4 hours. PPA results were significant at 0.5 hour up to 3 hours, and PE was only significant (p=0.3 level) at 3 hours.

Study/Site Info/ Docket Number	Drugs/ Doses	N	Study Design and Results
BEI 1025 (Cohen 6-1975) Reference 26	PE 10 mg q4h ×3 doses Placebo	100 100	Conducted for Whitehall Laboratories; the location and objective methodology used in the study were not included in the report. Double-blind, placebo-controlled study in 200 subjects with colds, who were treated with four doses of PE 10 mg or placebo every 4 hours and evaluated over 12.5 hours post first dose. Fifty subjects (PE 10 mg, n=25; placebo, n=25) who were evaluated with NAR testing over the first 120 minutes and subjective symptom scores for stuffy nose (i.e., congestion), runny nose, sneezing, itching (eyes and nose), coughing, muscle ache over the full treatment period. 150 subjects (PE 10 mg, n=75; placebo, n=75) were evaluated only with congestion symptom scores. The results were then pooled. Protocol not fully described in the summary report. Symptom scores at various timepoints postdosing. Results were significant for both objective and subjective symptom scores when compared with placebo.
(McLaurin et al. 1961) Reference 11	PE 10 PSE 60 Eph 25 PPA 25 Placebo	88	This study is included in the ANPR to support the safety but not the effectiveness of oral PE. It is included for completeness. Randomized, double-blind, placebo-controlled five-way crossover study in 88 subjects with various reasons for congestion. Subjects were asked to take two doses of medication, the first dose in center and the second dose at home 5 to 6 hours later 60 minutes before bed. Airway resistance was measured predose and 60 minutes postdose. Symptoms were measured at 60 minutes, reflectively 1 hour after taking the second dose the next morning, and reflectively 1 hour before going to sleep that evening. Of the 130 subjects enrolled in the study, 88 completed all five treatments. Unfortunately, the data tables do not convey the numbers in each treatment group, making interpretation of the results problematic. Specifically with regard to systolic BP, 11, 7, 1, 14, and 5 subjects experienced a 20 mm or more increase in systolic BP (presumably at the 60-minute time point) after placebo, PSE, PE, PPA, and ephedrine, respectively. As a result, the BP findings were not helpful (since a significant number of placebo subjects responded). Similar findings were noted for HR. Subjective “airway” changes showed PE to be the least effective, although placebo had about as much improvement as the other treatment groups. With regard to change in rhinometric evaluations, the slopes of the regression lines were not significant for any of the treatments except ephedrine. Therefore, this could be considered to have been a failed study.

Abbreviations: ANPR, advance notice of proposed rulemaking; BP, blood pressure; DBP, diastolic BP; Eph, ephedrine; HR, heart rate; NAR, nasal airway resistance; PE, phenylephrine; PEH, phenylephrine hydrochloride; PPA, phenylpropanolamine; PSE, pseudoephedrine; q4h, every 4 hours; SBP, systolic BP; NA, not available; OTC, over-the-counter.

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