FDA Briefing Document

Efficacy of Oral Phenylephrine as a Nasal Decongestant

Nonprescription Drug Advisory Committee Meeting
September 11 and 12, 2023

Division of Nonprescription Drugs 1 (DNPD1)
Office of Nonprescription Drugs (ONPD)

Division of Inflammation and Immune Pharmacology (DIIP)
Office of Clinical Pharmacology (OCP)

Division of Epidemiology II (DEPI-II)
Office of Surveillance and Epidemiology (OSE)

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Glossary

AC	Advisory Committee
AE	adverse event
ANPR	Advanced Notice of Proposed Rulemaking
CARES Act	Coronavirus Aid, Relief, and Economic Security Act of 2020
CCABA Monograph	Cough, Cold, Allergy, Bronchodilator, and Antiasthma OTC Monograph
CHPA	Consumer Healthcare Products Association
CMEA	Combat Methamphetamine Epidemic Act of 2005 (signed into law in 2006)
CP	Citizen Petition
BP	blood pressure
EEU	environmental exposure units
ER	extended-release
FDA	Food and Drug Administration
FM	final monograph
GRASE	Generally Recognized as Safe and Effective
HR	heart rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
IR	immediate-release
ITT	intent-to-treat
IV	intravenous
L/M	loratadine-montelukast
NAR	nasal airway resistance
NDA	new drug application
NDAC	Nonprescription Drugs Advisory Committee
OTC	over-the-counter
PAR	perennial allergic rhinitis
PD	pharmacodynamic
PE	phenylephrine
PEH	phenylephrine hydrochloride salt
PEB	phenylephrine bitartrate salt
PK	pharmacokinetic
PNIF	peak nasal inspiratory flow
PPA	phenylpropanolamine
PSE	pseudoephedrine
SAP	statistical analysis plan
SAR	seasonal allergic rhinitis
SD	standard deviation
TFM	Tentative Final Monographs

1 Introduction and Background

1.1 Introduction and Charge to the Advisory Committee

Thank you for participating in the Nonprescription Drugs Advisory Committee (NDAC) meeting to be held on September 11 and 12, 2023.

The Food and Drug Administration (FDA or *the Agency*) is convening this Advisory Committee (AC) to discuss the adequacy of efficacy data available for orally administered phenylephrine (PE) as a nasal decongestant and whether the oral nasal decongestants phenylephrine hydrochloride and phenylephrine bitartrate should be reclassified as not Generally Recognized as Safe and Effective (GRASE) due to lack of efficacy.

The Agency has been evaluating data with regard to the efficacy of oral PE since the NDAC meeting held in December of 2007,[1] which had been prompted by data submitted to the Agency by Leslie Hendeles, PharmD, Randy Hatton, PharmD, and Almut Winterstein, PhD, in a 2007 Citizen Petition earlier that year (2007 CP).[2] The CP requested that the Agency amend the dosage(s) of both oral PE salts by increasing the maximum dosage for patients ≥12 years of age, and "withdraw approval for use" (i.e., reclassify as not GRASE) in children <12 years of age. At that meeting, several meta-analyses of the original studies that supported the decision to include PE in the monograph were presented and discussed. Additionally, several industry speakers presented new bioavailability data that show that <1% of an oral PE dose is systemically available in an active form as well as clinical information from two environmental exposure unit (EEU) studies that suggest that PE is not more effective than placebo. The NDAC provided feedback that more clinical data would be needed in order to make a final decision regarding the effectiveness of oral PE (for patients 12 years of age and older).[3]

Since the 2007 NDAC meeting, three large clinical trials have been conducted, two of which are cited in a second CP submitted by Drs. Hendeles and Hatton on November 4, 2015 (2015 CP) requesting that both oral phenylephrine salts be reclassified as Not GRASE due to lack of efficacy (i.e., to remove oral PE from the Final Monograph).[4]

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[1] 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.

[2] 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. Note: The 2007 Citizen Petition was withdrawn by the petitioners on June 19, 2023, citing the fact that new information is available showing that doses up to 40 mg are not effective and that they have since submitted a second CP (2015 CP) requesting the Agency reclassify the status of oral PE as not GRASE. See Footnote 4.

[3] Note that the NDAC did not discuss the petitioner's second request to withdraw use in children less than 12 years of age. Pediatric use of cough and cold medicines (including phenylephrine) in the CCABA OTC Monograph was discussed at a joint Nonprescription Drugs and Pediatric Advisory Committee meeting held on October 18 and 19 of 2007. Information available at: https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs.

[4] Hendeles L, Hatton RA. Citizen Petition – Phenylephrine. Docket ID: FDA-2015-P-4131, available at: https://www.regulations.gov/docket/FDA-2015-P-4131. The petitioners recently published a summary of their findings (Hatton and Hendeles 2022) and submitted additional information to the CP docket in May 2022. Additionally, the American Association of Colleges of Pharmacy (AACP) submitted a letter to the docket in July of 2022, in support of the petitioner's request.

Since the 2007 NDAC meeting the Agency has continued to re-evaluate the scientific support for use of oral PE as a nasal decongestant, and we have now completed a thorough review of all those data. Our review includes all of the available clinical pharmacology and clinical data, which include significant new data that were not available at the time that the original GRASE decision was made (to include oral PE in the monograph), as well as a detailed evaluation of each of the original studies that supported that decision. As such, throughout this document, the term "new" (when referring to data, studies, or trials) refers to any data that was generated or has become available since the publication of that nasal decongestant FM Federal Register notice on August 23, 1994 (59 FR 43386).

In accordance with the effectiveness standard for determining that a category of over-the-counter (OTC) drugs is generally recognized as safe and effective that is set forth in 21 CFR § 330.10(a)(4)(ii), which defines effectiveness as: "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", we have now come to the initial conclusion that orally administered PE is not effective as a nasal decongestant at the monographed dosage (10 mg of PE hydrochloride every 4 hours) as well as at doses up to 40 mg (dosed every 4 hours). We will present the scientific data that support our conclusions and seek concurrence from the AC on the strength of that evidence. Because this would represent a major change in the Agency's position, we believe that presenting this information in an open public forum, along with a full discussion and vote from the AC, will be extremely helpful.

During our review, the Agency has not identified any safety issues with orally administered PE products, and none are planned to be discussed at the meeting. However, we are concerned about avoiding potential unintended consequences with regard to changing the GRASE status of oral PE. We anticipate that any action taken by the Agency in this regard will have significant downstream effects, including effects on both industry and consumers, because the only other oral decongestant listed in the CCABA Monograph is pseudoephedrine (PSE), which is now regulated as a 'behind-the-counter' product under the Combat Methamphetamine Epidemic Act of 2005 (CMEA).[5] Subsequently, and in response to the CMEA, most OTC products were reformulated away from inclusion of PSE to PE. As a result, consumers will require education to make the appropriate choices for alternative treatments. We recognize that many of these educational components will require input and coordination with communication specialists within the Agency, professional organizations that can aid in focusing and amplifying the messaging, and industry.

That stated, there are a number of potential benefits that would be derived by changing the GRASE status of oral PE. These include but are not limited to avoiding the unnecessary costs and delay in care of taking a drug that has no benefit, avoiding the risks of potential allergic reactions or other side effects related to use of phenylephrine in combination products, avoiding the inherent risks (especially for combination therapies) of taking more in order to seek some benefit, avoiding the risks of medication use in children, lowering of overall healthcare costs, and avoiding missed opportunities for use of more effective treatments (including seeing a doctor if needed).

Should the Agency take an action regarding the GRASE status of oral phenylephrine, we also understand that a significant impact on industry would be inevitable. Manufacturers, warehousers, and pharmacies all have a significant supply chain investment in stocks of PE, either as a precursor chemical, ingredient

[5] Combat Methamphetamine Epidemic Act of 2005, signed into law on March 9, 2006.

itself, or in a finished product. There will also be significant retooling costs. In addition to OTC products, prescription products and drug development programs will be affected (because acceptability of PE in the formulation was/is based on the GRASE status of PE). However, other than providing historical use data to frame the discussion regarding potential impacts, the Agency does not intend to present or discuss impacts on industry at the meeting. Instead, we will ask you to focus on two issues: 1) the scientific merits of our findings regarding the lack of efficacy of oral PE, and 2) the risk management/communication/educational issues that would arise if the Agency makes the decision to remove oral PE from the OTC monograph (i.e., change its status to not GRASE), including the unintended consequences that may result from substitution and use of alternative treatments such as safety issues related to the use of drugs that contain other active ingredients, prolonged use of topical intranasal decongestant products that may result in rebound congestion (rhinitis medicamentosa, a condition that is difficult to treat), and safety issues related to the off-label use of other products or ingredients. We will also ask you to focus on the education of consumers regarding alternatives to phenylephrine (including both oral and intranasal products), how to obtain PSE from behind-the-counter, and education of consumers with a preference for PE regarding why it is being removed from the market.

Specifically, we will ask you, as a member of the Advisory Committee, to address the following points for consideration:

1. Do the scientific data support that the monographed dosage of orally administered PE (for adults and children 12 years of age and older, 10 mg of PEH every 4 hours, not to exceed 60 mg in 24 hours) is effective as a nasal decongestant?
2. Do the scientific data support that doses of orally administered PE up to 40 mg are effective as a nasal decongestant?
3. Discuss the potential consequences, unintended consequences, and risk mitigation/communication strategies if a decision were made to remove oral PE from the Monograph due to lack of efficacy.

Note that, when not otherwise specified in this document, all doses and dosages are for the adult/adolescent dosage of the hydrochloride salt (PEH). However, the voting and discussion apply to all age groups as well as both salts, because inclusion in the monograph of doses for lower age groups was based on extrapolation from older age groups, and inclusion of the bitartrate salt (PEB) was based solely on bioavailability data (see Section 1.3, Background on Phenylephrine, for details).

1.2 Background on the CCABA Monograph

The CCABA monograph is complex and wide-ranging, including antihistamine (oral), nasal decongestant (oral and topical), expectorant (oral), antitussive (oral and topical), and bronchodilator (oral and inhaled) ingredients (Table 16). It provides a listing of permitted ingredients along with required labeling and dosing (Table 17 for oral ingredients, Table 18 for topical and inhaled ingredients), as well as permitted combinations of ingredients, including with ingredients in several other OTC monographs (Table 19). Several ingredients are listed in multiple sections. For example, diphenhydramine (hydrochloride and citrate salts) is listed as both an antihistamine and as an antitussive (as well as in several other OTC monographs), and ephedrine is included as both an oral bronchodilator (ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride) and as a topical nasal decongestant (ephedrine, ephedrine hydrochloride, and ephedrine sulfate as nasal drops, nasal spray, or nasal jelly). Additionally, the monograph includes professional (i.e., prescription) labeling and dosing for certain oral

ingredients in children down to 2 years of age, and in one instance (triprolidine hydrochloride) down to 4 months of age (Table 17).[6]

Inclusion of ingredients in the CCABA Monograph was based on recommendations made by an Advisory Review Panel on Over-the-Counter Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products (hereafter referred to as 'the Panel' or the 'Cough-Cold Panel'). The Panel was convened by the National Academy of Sciences / National Research Council (NAS/NRC) on behalf of the FDA, to review and provide recommendations to the Agency regarding the safety and efficacy of therapeutic groups of these products.[7] The Agency published the Cough-Cold Panel's recommendations as a Proposed Rule (ANPR) in 1976[8] and issued Tentative Final Monographs (TFM) in segments by drug class between 1982 and 1988: anticholinergics and expectorants (1982), bronchodilators (1982), antitussives (1983), antihistamines (1985), nasal decongestants (1985), and permitted combinations (1988).[9] Respectively, each TFM established the conditions under which an ingredient within a drug class, or permitted combination of ingredients or drug classes, would be considered to be Category I, 'generally recognized as safe and effective' (GRAS/GRAE, also referred to as GRASE). Final Monographs (FM) for each of the drug classes in the CCABA monograph were subsequently published in segments: anticholinergics (1985), bronchodilators (1986), antitussives (1987), expectorants (1989), antihistamines (1992), nasal

[6] Professional labeling is theoretically available only to physicians and only by prescription, and is specific to oral ingredients, including: all antihistamines (diphenhydramine is listed twice, as both an antihistamine and as an antitussive), ephedrine, chlophedianol, and codeine. Guaifenesin is also listed, but only with specific labeling for use as a single-ingredient product for "stable chronic bronchitis."

[7] In 1972, in response to the Kefauver-Harris Amendment [AKA the "Drug Efficacy Amendment", signed into law by President Kennedy on October 10, 1962] to the Food, Drug, and Cosmetic Act, which required drug manufacturers to provide proof of the effectiveness [as well as safety] of their drugs before approval, the Agency implemented an administrative process of reviewing OTC drugs through rulemaking by therapeutic classes (e.g., antacids, antiperspirants, cold remedies). This process [usually referred to as "DESI" for Drug Efficacy Study Implementation] involved convening an Advisory Panel for each therapeutic class to review data relating to claims and active ingredients. The Panel reports and comments were then published in the Federal Register as Advanced Notice(s) of Proposed Rulemaking (ANPR) and after FDA review, a Tentative Final Monograph (TFM) for each therapeutic class of drugs was published. The final step was the publication of a Final Monograph (FM) for each class, which sets forth the allowable claims, labeling, and active ingredients for OTC drugs in each class. Drugs marketed in accordance with a FM are considered to be generally recognized as safe and effective (GRAS/GRAE or GRASE) and do not require FDA approval of a marketing application.

[8] Cough-cold ANPR, ANPR: 41 FR 38312 (September 9, 1976).

[9] Tentative Final Monographs: Anticholinergic and expectorant: 47 FR 30002 (July 9, 1982); Bronchodilator: 47 FR 47520 (October 26, 1982); Antitussive: 48 FR 48576 (October 19, 1983); Antihistamine: 50 FR 2200 (January 15, 1985), with corrections in 50 FR 6199 (February 14, 1985) and 50 FR 9040 (March 6, 1985), and with an amendment in 52 FR 31892 (August 24, 1987); Decongestant: 50 FR 2220 (January 15, 1985); Permitted combinations: 53 FR 30522 (August 12, 1988).

decongestants (1994), and permitted combinations (2002).[10] FMs are/were included in the Code of Federal Regulations.[11,12]

Of note, on the basis of the Panel's recommendations, the ANPR included three oral decongestant ingredients: phenylpropanolamine (PPA), pseudoephedrine (PSE), and phenylephrine hydrochloride. However, PPA was excluded from the listing of ingredients included as GRASE in the 1985 Tentative Final and the 1994 Final Decongestant Monographs because of potential safety issues, and was removed from OTC use in 2005 after a large safety analysis showed that it was associated with hemorrhagic stroke in women of childbearing age.[13] This left only PEH and PSE as GRASE oral nasal decongestants (PEB was added in 2006). However, after passage of the CMEA in 2006, PSE became regulated as 'behind-the-counter', limiting its use in the OTC setting and leaving PE as the only remaining OTC oral decongestant.

Over the years, multiple amendments to the CCABA monograph have been contemplated by the Agency, but while some amendments have been made, no major overhaul of the monograph has been carried out, and almost no amendments have been made in the last 15 years. Additionally, the Agency has received multiple CPs, several of which are outlined in this review, requesting to amend various aspects of the monograph. Changes contemplated by the Agency were primarily delayed by the time and resources needed to fully review the issues. That stated, the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), signed into law on March 27, 2020, does provide an updated pathway to issue, revise, or amend OTC monographs by replacing rulemaking with an administrative order process, which will simplify the process of making any contemplated changes to the monograph.[14] In addition to

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[10] Final Monographs: Anticholinergic: 50 FR 46582 (November 8, 1985); Bronchodilator: 51 FR 35326 (October 2, 1986); Antitussive: 52 FR 30042 (August 12, 1987); Expectorant: 54 FR 8494 (February 28, 1989); Antihistamine: 57 FR 58356 (December 9, 1992); Nasal decongestant: 59 FR 43386 (August 23, 1994); Permitted Combinations: 67 FR 78158 (December 23, 2002).

[11] The FM for nasal decongestants was issued in 59 FR 43386 on August 23, 1994. The nasal decongestant monograph previously resided as 21 CFR § 341.20(a) within the CCABA OTC Monograph, 21 CFR § 341 (eCFR :: 21 CFR Part 341 -- Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use). The CCABA OTC Monograph (including all amendments) was deemed to be a Final Order (OTC Monograph M012, Order Number OTC000026, posted on the FDA web portal on October 14, 2022) under the CARES Act (Coronavirus Aid, Relief, and Economic Security Act, signed into law on March 27, 2020: https://www.govinfo.gov/content/pkg/COMPS-15754/pdf/COMPS-15754.pdf). M012 is available at: https://dps.fda.gov/omuf/monographsearch/monograph_m012.

[12] Additional rulemaking history is available at: Rulemaking History for OTC Nasal Decongestant Drug Products | FDA. This page represents that status of OTC rulemakings prior to the enactment of the CARES Act (e.g., before March 27, 2020). This rulemaking history site is intended as a research aid and is not an official FDA record.

[13] Data from the Yale Hemorrhagic Stroke Project study, discussed at an NDAC meeting held on October 19, 2000. A proposed rule, reclassifying PPA from Category 1 to Category 2 for OTC use in both nasal decongestant and weight control products, was published in 70 FR 75988 (December 22, 2005). See https://www.fda.gov/drugs/historical-status-otc-rulemakings/rulemaking-history-otc-weight-control-drug-products#PPA and https://www.fda.gov/drugs/information-drug-class/phenylpropanolamine-ppa-information-page.

[14] The CARES Act (Public Law No. 116-136, 134 Stat. 281, 457), which added section 505G to the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355g), includes provisions that govern the way certain OTC drugs are regulated in the United States. Section 505G reforms and modernizes the OTC drug review process. For information about OTC

reaffirming and giving FDA specific authority to add, remove, or change the GRASE conditions for an OTC monograph, the CARES Act also requires the Agency to report to Congress yearly on the status of certain planned revisions to the CCABA monograph, and specifically on pediatric dosing issues. Since all of the GRASE determinations for the CCABA drugs, including phenylephrine, were made based on extrapolation of efficacy and dosing from adult data, one must address these pediatric issues by addressing the adult data under the pediatric extrapolation principles set forth in the Agency's draft guidance on the General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products[15] and in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E11A.[16] For this reason, any recommendations made regarding the efficacy of oral PE in adults would apply to its use in adolescents and children. As noted previously, the CCABA OTC Monograph conditions previously set forth in 21 CFR § 341 were deemed to be a final order by the CARES Act and can now be found in OTC Monograph M012, meaning that the CCABA monograph may now be amended via the new administrative order process established under Section 505G of the Food, Drug, and Cosmetic Act.[11]

1.3 Background on Phenylephrine

Phenylephrine is a specific alpha-1 adrenergic receptor agonist that works by temporarily constricting blood vessels. By contrast, pseudoephedrine is a relatively less selective agonist that acts on both alpha- and beta-adrenergic receptors. The literature reports that PSE is more lipophilic than PE and thus is more accessible to the central nervous system by crossing the blood-brain barrier (Gheorghiev et al. 2018). The vasoconstriction effect of PSE is likely contributed to by an indirect action via release of norepinephrine in synaptic nerve terminals (Gorodetsky 2014).

The FM for OTC nasal decongestant drug products, issued in 1994, classified the PEH as a GRASE nasal decongestant when administered orally (immediate-release [IR] formulations) or intranasally (M012.80, previously 21 CFR 341.80). The PEB, an IR effervescent tablet for oral administration, was added to the monograph in 2006, based on pharmacokinetic (PK) data demonstrating that it has similar bioavailability to PEH.[17]

The monograph provides oral dosages of PEH down to 2 years of age, and dosages of PEB down to 6 years of age (see Table 1). It should be noted that inclusion in the monograph of doses for ages less than 12 years was based entirely on historical use and not on data in those age groups. It should further be noted that a convention for determining pediatric dosing was used for all oral ingredients included in

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Monograph reform under the CARES Act see: Over-the-Counter (OTC) Drug Review | OTC Monograph Reform in the CARES Act | FDA.

[15] Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-including-biological-products.

[16] ICH E11A Draft Guidance on Pediatric Extrapolation, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11a-pediatric-extrapolation.

[17] See rulemaking history at: Rulemaking History for OTC Nasal Decongestant Drug Products | FDA. In 2004, in response to a Citizen Petition from a manufacturer, FDA issued a Proposed Rule to add phenylephrine bitartrate (an immediate-release [IR] effervescent tablet dosage form) as a GRASE oral nasal decongestant when used as an IR effervescent tablet (69 FR 63482 [November 2, 2004]). The manufacturer submitted data from in vitro and in vivo studies to support the request. After considering safety information from U.S. databases and marketing experience, FDA determined that the data demonstrated acceptable comparability of PEB with PEH and issued a Final Rule adding PE bitartrate to the monograph in 2006 (Amended Final Monograph: 71 FR 43358 [Aug. 1, 2006]).

the CCABA monograph, and later supported by several AC meetings in the 1990s, namely that doses for children 6 to 11 years of age should be half the adult/adolescent dose, and doses for children 2 to 5 years of age of one quarter of the adult/adolescent dose.

PEH is also approved for other OTC (rectal[18] and ophthalmic[19]) uses, as well as by prescription for intravenous (IV) administration. The recommendations in this document do not apply to such use, nor do they apply to intranasal use of phenylephrine as a nasal decongestant.

Table 1. Monographed Dosages 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	

Source: CCABA OTC Monograph M012. See Footnote 11.

1.4 Introduction to the Agency's Reviews

With the availability of new studies since FDA last evaluated oral phenylephrine under the CCABA OTC Monograph, the Agency undertook a careful and thorough review of all of the available data. The new data appear compelling that the monographed dosage of oral PE results in no meaningful systemic exposure or evidence of efficacy. Furthermore, the review suggests that higher doses (of PEH), which have been tested clinically up to 40 mg every 4 hours, have also not shown efficacy. These findings are supported by in vitro and in vivo clinical pharmacology data showing that orally administered phenylephrine undergoes high first-pass metabolism resulting in less than 1% bioavailability for the active parent PE. The clinical pharmacology data also suggest that the monographed every-4-hour dosing interval is likely not adequate (i.e., not sufficiently frequent to cover the full dosing period), meaning that in addition to lack of an efficacious dose, an appropriate dosing interval for oral PE has not been established. Finally, pharmacodynamic/clinical safety data suggest that doses of 80 to 90 mg result in potentially clinically meaningful systemic increases in blood pressure (BP), a physiologic finding expected of an alpha-1 adrenergic receptor agonist. As a result, these data support that 40 mg (half the dose associated with clinically significant changes in BP) is the highest oral dose that should be considered for the treatment of nasal congestion, and that studying higher doses will not be a viable option.

In order to understand how the new data fit within the context of the long history of oral phenylephrine use, we reviewed all of the available data, including the original data that supported the Agency's GRASE determination. What follows is a summary of all the pertinent history and data, starting with the original efficacy and safety materials reviewed as part of the Agency's initial GRASE determination and progressing through the 2007 AC meeting, subsequent studies and clinical trials, and the Agency's detailed reviews of all of the available data. Finally, we discuss the potential impacts should a decision be made to remove oral phenylephrine from the CCABA OTC monograph.

[18] M015 (previously 21 CFR 346): Anorectal Drug Products for Over-the-Counter Human Use.

[19] M018 (previously 21 CFR 349): Ophthalmic Drug Products for Over-the-Counter Human Use.

2 Detailed Background

2.1 Original Cough-Cold Advisory Panel Recommendations

Phenylephrine HCl was evaluated for OTC use as an (oral and intranasal) nasal decongestant in 1976 by the Advisory Review Panel on OTC CCABA Products, which provided recommendations to the Agency regarding the safety and efficacy of these products. The Agency published the Panel's summary findings (without Agency review or comment) in the Federal Register as part of the Advanced Notice of Proposed Rulemaking (ANPR) in 1976.[20] This section summarizes and discusses those findings, as presented in the 1976 ANPR. The Final Oral Decongestant Monograph, which represents the information that was subsequently reviewed by the Agency (including the ANPR and public comments), was published in 1994.

2.1.1 Safety/Pharmacodynamics

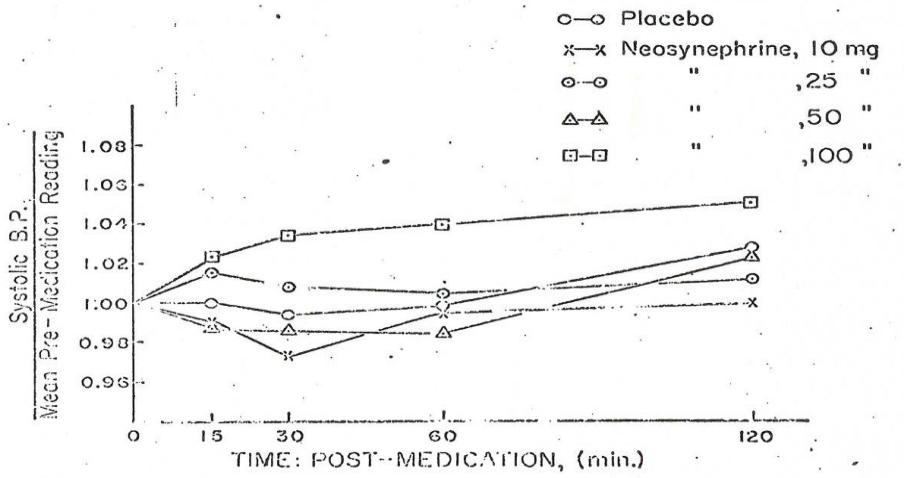
The Panel reviewed the clinical safety data of orally administered PEH doses between 10 mg and 60 mg and concluded that at the 10 mg dose level the cardiovascular side effects (i.e., pharmacodynamic or PD effects) were similar to that of a placebo, with mild central nervous system stimulation noted only at doses of 25 mg and higher. Most of the 17 studies evaluated for safety were single-dose studies, and the ANPR notes that a number of the studies produced inconsistent results, particularly at lower doses. One study submitted to the docket (and referenced in the ANPR) noted that the threshold for PD effects, i.e., clinically meaningful effects on systolic BP (an increase of 5 to 10 mm Hg) and heart rate (HR) (a reduction of 4 to 8 beats/minute) is 40 to 60 mg.[21] That said, the same study also noted that oral dose of 250 mg produces a PD effect (pulse rate decline from 67 to 46 and BP rise from 112/71 to 143/96) that is roughly equivalent to a subcutaneous dose of 5 mg, a subcutaneous dose that consistently produces a measurable PD effect. A second study submitted to the docket (but not specifically written up in the ANPR) suggested that a dose of 100 mg or more is needed to exert a meaningful PD effect on systolic BP, with no effect noted after a 50 mg dose (see Figure 1).[22]

[20] Cough-cold ANPR, 41 FR 38312 (September 9, 1976) at 38399-383100.

[21] Cough-cold ANPR, 41 FR 38312 (September 9, 1976) at 38400, reference 1: Keys and Violante (1942).

[22] Cough-cold ANPR, 41 FR 38312 (September 9, 1976) at 38400, 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.

Figure 1. Fractional Changes in Systolic Blood Pressure (BP) in Subjects Given Oral Placebo or 10, 25, 50, or 100 mg of Neo-Synephrine (PEH) (n=20)[22]



Source: 41 FR 38312 (September 9, 1976) at 38400, reference 3.

Another study tested single oral doses of 10, 25, 50, and 75 mg of PEH and compared them with 25 and 50 mg of PPA in a double-blind fashion in 14 or 15 subjects.[23] BP, pulse rate, and nasal airway resistance (NAR) were evaluated prior to and at 1, 2, and 5 hours after drug administration. Only minor changes were noted in BP at 1 and 2 hours post-treatment even after 75 mg of PEH, a "small but significant" change in BP was noted after 50 mg of PPA, and no significant changes were noted in NAR. The discussion section of that reference (reference 5) is also interesting in that it notes that a previous study from 1933, which may or may not have been reviewed but was not discussed by the Panel in the ANPR, had calculated that the minimal pressor dose (i.e., PD effect on blood pressure) of oral PEH is 70 mg, and found that the minimally effective dose is approximately 120 mg (Tainter and Stockton 1933).

A final study submitted to the docket is of interest, but primarily with respect to the metabolism of PE. It noted that concurrent use of 10 mg oral dose of PE with a monoamine oxidase inhibitor produced a substantial rise in blood pressure that required intervention by phentolamine antagonism,[24] which both suggests that monoamine oxidase is involved in the metabolism of orally administered PE and provides a clue to an eventual more comprehensive understanding of PE metabolism that is discussed below.

It should also be noted that the safety findings from the original studies are consistent with subsequent safety/PD studies that will be discussed in the Agency Reviews section, which found potentially clinically meaningful changes in systolic BP at oral PEH doses of 80 to 90 mg.

[23] Cough-cold ANPR, 41 FR 38312 (September 9, 1976) at 38399, 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.

[24] Cough-cold ANPR, 41 FR 38312 (September 9, 1976) at 38400, reference 12: Elis et al. (1967).

2.1.2 Effectiveness

2.1.2.1 Preliminary Comments

The Panel reviewed clinical effectiveness data for oral doses between 5 mg and 40 mg. A total of 14 studies were reviewed, of which 7 reported positive measurable efficacy results.[25] The 14 studies are summarized in Table 2 and Table 3, with a more complete breakdown in Appendix Table 15. Note that in this section, which presents the studies that the Panel reviewed, the Panel had access to the study reports which had figures and tables, but none of those figures were shown in the ANPR, only a summary description of what the Panel felt was important. This section includes those figures and tables.

A word about the endpoint used in these studies is also in order. All of the studies used measurements of airflow and air pressure in the nasal passage to calculate NAR as an indirect measure of the level of nasal congestion. NAR was the principal methodology used to assess the effectiveness of oral PE in all of the studies, with nasal congestion symptoms evaluated as a secondary measure, and the ANPR cites onset of action, duration of effect, and maximal response based on NAR methodology. However, the science has evolved since the time of the Panel, and NAR is no longer used as a primary endpoint to evaluate congestion in pivotal trials. The Agency now recommends use of nasal congestion symptom scores to evaluate congestion as part of evaluation of other symptoms related to allergic rhinitis.[26] Please see further discussion of this endpoint in the Clinical Review, Original Panel Studies, Methodological and Statistical Issues section, which discusses the significant issues with the methodology employed in all of the original studies.

2.1.2.2 Outline of the Effectiveness Studies

Of the 14 studies submitted to support effectiveness, only 12 provided evaluable efficacy information. Eleven of the 14 were from a single sponsor, Sterling-Winthrop Research Institute on behalf of Sterling-Winthrop Labs, the manufacturer of Neo-Synephrine (references 5 to 10 and 20 to 24) [27], of which one was a preliminary descriptive study that focused primarily on safety and not efficacy (reference 5) and therefore provides no useful efficacy information.[23] One study conducted at the University of Maryland failed to adequately identify the ingredients and doses studied (Blanchard, reference 19), and therefore also provided no evaluable information.[32] See the "Effectiveness" Studies With No Useful Efficacy Information section below for details on these two studies.

Of the remaining 12, 10 were conducted for Sterling-Winthrop (see Sterling-Winthrop Studies), one was conducted by Whitehall Laboratories (BEI 1025, reference 26)[29] (see Whitehall Labs (BEI 1025)), and one was conducted at Columbia University (see Columbia University Study (Rogers / Bickerman publications)). The Whitehall Laboratories study (BEI 1025) was considered in the ANPR to be a 'positive' study (meaning that it was considered to have demonstrated the effectiveness of oral PE), whereas the Columbia University study was considered a 'negative' study (did not demonstrate effectiveness).

The 10 Sterling-Winthrop studies (Table 3) include 6 studies that were considered positive and 4 that were considered negative. All were of similar design, and because they comprise 6 of the 7 positive

[25] Cough-cold ANPR, 41 FR 38312 (September 9, 1976) at 38400, references 5 to 10 and 19 to 26.

[26] See Guidance for Industry; Allergic Rhinitis: Developing Drug Products for Treatment (FDA 2018).

[27] Note that the ANPR mistakenly cites reference 19 as having been one of those studies when it was not.

studies, they appear to have formed a large part of the basis for the original Panel's recommendations. The 4 non-Sterling-Winthrop studies, including the 2 that did not provide any evaluable efficacy data, are shown in shown in Table 2, whereas the 10 Sterling-Winthrop studies are shown in Table 3. Studies in red font were considered to have been supportive of the effectiveness determination.

Table 2. Doses (mg) and Numbers of Subjects in the Four Non-Sterling-Winthrop Oral PE Effectiveness Studies

Site	Ref #	Year	Phenylephrine (n)				PSE	PPA		Ephedrine	
			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
Blanchard*	19	1964	NA								
Rogers**	25	1973									
Bickerman**		1971	57				57	40 mg n=57			
BEI 1025	26	1975	25/75								

Source: Adapted from oral PE studies submitted to the docket. Reference numbers refer to the docket reference numbers (not the reference numbers in the ANPR text).
Notes: All studies used placebo arms (not shown). BEI 1025 was a parallel-group study; all others were of a crossover design. 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) only for symptoms (total of 200 subjects, n=100 PEH, n=100 placebo), as shown in the table above. Red font indicates arms that were considered positive with regard to NAR results. Black font indicates arms that were considered negative with regard to NAR results. The studies are presented in order of the date of the study report.
* Blanchard (ANPR reference 19) is included 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. Further, the study does not support the effectiveness of oral PE for a number of reasons, including that the product and dose is not stated and the decongestant was administered as a commercial combination product. The fifth Elizabeth study is actually in ANPR reference 10, not 19.
** We believe that ANPR Reference 25 (Rogers 1973), which is an abstract, is based on a previous publication by the same authors (Bickerman et al. 1971). See the Columbia University Study (Rogers / Bickerman publications) section for details.
Abbreviations: ANPR, Advanced Notice of Proposed Rulemaking; NAR, nasal airway resistance; PE, phenylephrine; PEH, phenylephrine hydrochloride salt; ref, reference

2.1.2.3 Sterling-Winthrop Studies

As noted in the introductory section above, 11 of the 14 studies came from the same sponsor (Sterling-Winthrop Research Institute on behalf of Winthrop Labs, the manufacturer of Neo-Synephrine), of which 1 was a preliminary descriptive study that only secondarily included NAR evaluations (see "Effectiveness" Studies With No Useful Efficacy Information section below), and 10 were virtually identical using a single-dose, double-blind, placebo-controlled, two-way crossover design in subjects with the common cold. Various doses of oral PE were evaluated (see Table 3), and three of the studies included an active comparator (PPA or ephedrine).[28]

Critically, among these 10 studies were 6 of the 7 studies that were considered to have demonstrated the effectiveness of oral PE, 5 of which were performed in a single laboratory, Elizabeth Biochemical. Whereas the ANPR does not go into much depth about these studies, as part of our re-assessment of the data, a full discussion of these studies may be found in the Clinical Review, Original Panel Studies section.

[28] Cough-cold ANPR, 41 FR 38312 (September 9, 1976) at 38399, references 5 to 9, and 19.

Table 3. Doses (mg) and Numbers of Subjects in the 10 Sterling-Winthrop Oral PE Effectiveness Studies (Shown in Order of Study Date)

Site	Ref #	Study Date	Phenylephrine (n)					PPA	Ephedrine	
			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 docket reference numbers (not the reference numbers in the ANPR text).
Bolded studies (Elizabeth 2 and Cintest 1) were considered the most 'positive' studies.
* Red font denotes significance reported for NAR results for specific doses by the FDA Statistician, Dr. Lin, in his 2007 statistical review. Note that studies considered to be 'positive' studies, i.e., studies reporting positive findings, are also highlighted in red font.
^ Denotes that active control was not effective (even though it would be expected to have been).
** Elizabeth studies 4 and 5 did not enroll the expected number of subjects, either because the cold season had ended (Elizabeth 4) or because they were unable to recruit sufficient numbers of subjects (Elizabeth 5).
Abbreviations: ANPR, Advanced Notice of Proposed Rulemaking; NAR, nasal airway resistance; PE, phenylephrine; PPA, phenylpropanolamine; ref, reference

2.1.2.4 Whitehall Labs (BEI 1025) Study

The twelfth study, and the seventh positive study, was a relatively large, double-blind, placebo-controlled, parallel-group study (BEI 1025 and 1025a) that had been conducted for Whitehall Laboratories in 200 adults with nasal congestion associated with the "common cold" (100 per group) who were administered four doses of either PEH 10 mg or placebo at 4-hour intervals over 12 hours.[29] Because of the way it is described in the ANPR (as a full paragraph that is last in the efficacy section), it is likely that this particular study pushed the Panel in favor of a positive recommendation for oral PE. Subjects were followed for 12.5 hours (30 minutes beyond the fourth dose). However, the primary endpoint of rhinometry evaluations over 2 hours post the first dose (at 15, 30, 60, and 120 minutes), were only evaluated/performed in 50 subjects (25 per arm). Subjective subject and investigator evaluations of the symptoms of stuffy nose (i.e., congestion), runny nose, sneezing, itching (eyes and nose), coughing, and muscle ache were evaluated for all 200 subjects at various time points over the treatment period.

NAR results (Table 4 and Figure 2) are said to have "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." Note, however, that percent change tends to exaggerate any differences, whereas the absolute change in NAR (Figure 2) was far more modest. Likewise, the "phenylephrine treatment group experienced relief of nasal congestion, runny nose and sneezing throughout the 12-hour observation period" is said to have differed from placebo. However, no differences were noted between active versus placebo groups in systolic or diastolic BP (Figure 3).

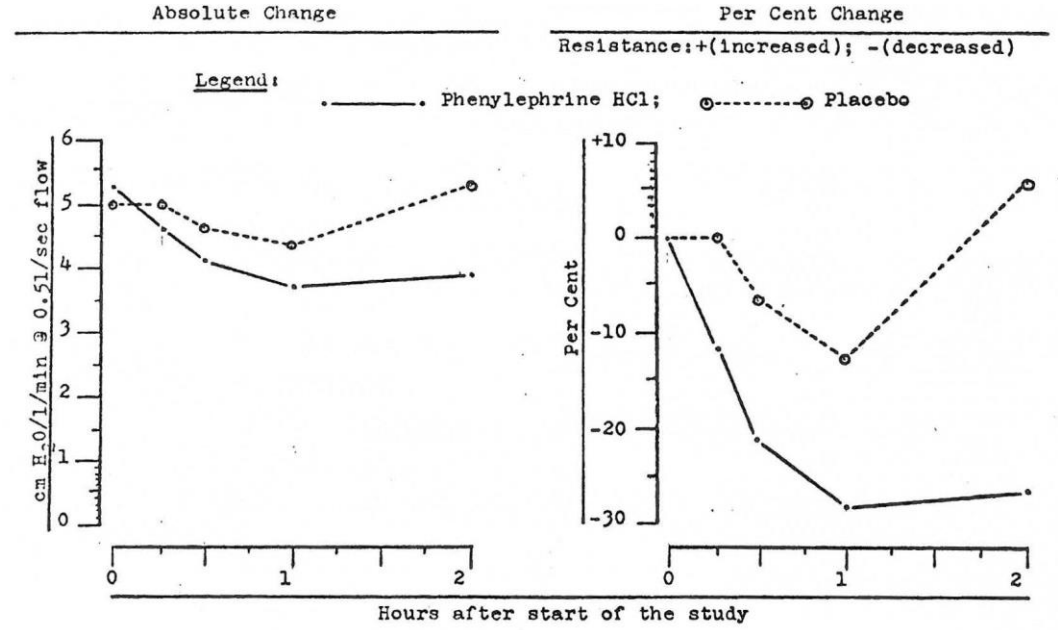
[29] Cough-cold ANPR, 41 FR 38312 (September 9, 1976) at 38399, reference 26: Study report from Burton Cohen at Bio-Evaluation, Inc., for Study BEI 1025 and 1025a, conducted for Whitehall Laboratories, June 1975.

Table 4. Study BEI 1025. Percentage Change in Nasal Airway Resistance Over 2 Hours[29]

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

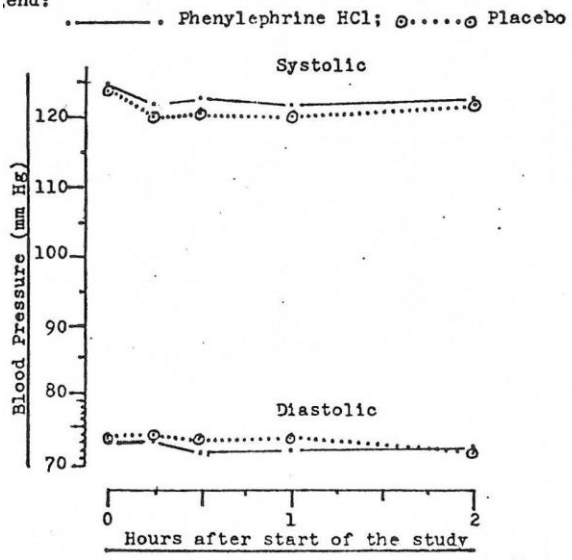
Source: Study BEI 1025.
Abbreviation: PEH, phenylephrine hydrochloride

Figure 2. Study BEI 1025a. Absolute and Percentage Changes in Nasal Airway Resistance Over 2 Hours[29]



Source: Study BEI 1025a.

Figure 3. Study BEI 1025. Results for Systolic and Diastolic BP Following PEH 5 mg or Placebo[29]



Source: Study BEI 1025.
Abbreviations: BP, blood pressure; PEH, phenylephrine hydrochloride

2.1.2.5 Columbia University Study (Rogers / Bickerman publications)

One of the 14 studies cited in the ANPR was specifically stated to have been a negative study that did not support the effectiveness of oral PE. This study is stated to have evaluated 10, 20, 30, and 40 mg in 20 subjects with chronic rhinitis in a double-blind, crossover fashion. All doses were negative, whereas both PPA 40 mg and PSE 60 mg were positive.[30] However, the ANPR citation for the Columbia University study pointed to an abstract with no dosing information (Rogers 1973, reference 25)[31], whereas the ANPR discusses the negative results from the study in a manner that matches a previous 1971 publication by one of the same authors (Bickerman 1971), which is likely the source of the data in the ANPR.

Of note, the Bickerman publication actually refers to 57 rather than 20 subjects with chronic rhinitis who had been followed at Columbia University over an extended period of time, and those 57 subjects provide valuable efficacy information with regard to oral PE. Data from this study were presented (by the petitioners) at the 2007 Advisory Committee meeting (see Presentations by Drs Hendeles, Hatton, and Schuster (2007 CP) and Figure 6). We also reviewed the study in depth, and our analysis is presented in the Columbia University Study (Rogers / Bickerman publications) section (3.3.3.5.1) of our review. Rather than presenting this information in multiple sections of this document, please refer to those sections for further details.

2.1.2.6 "Effectiveness" Studies With No Useful Efficacy Information

As noted above, two of the studies considered for effectiveness (as well as safety) provided no useful efficacy information.

One study was in the form of an unpublished report of a descriptive preliminary study that preceded the series of 10 small crossover studies conducted for Sterling Winthrop Research Institute and which comprise some of the key effectiveness evidence evaluated by the Panel (reference 5).[23] This preliminary study evaluated blood pressure and heart rate, as well as NAR, after either various intranasal or oral PEH treatments. After intranasal administration, PEH 0.5% and PPA HCl 1.0% both produced what they termed as pronounced reduction in NAR within 15 minutes, which lasted more than 60 minutes and less than 180 minutes. Oral doses included 10, 25, 50 and 75 mg of PEH (Neo-Synephrine) as well as 25 and 50 mg of PPA (Propadrine) in 14 or 15 subjects in a double-blind, placebo-controlled, crossover design. NAR was measured using Sterntein and Schur methodology (Sternstein and Schur 1936) at 1, 2, and 5 hours after drug administration. Only minor changes in systolic BP 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.

One other study (Blanchard et al. (1964)) included in the listing is of no value.[32] It was submitted in the form of a publication of a study that had been conducted at the University of Maryland in hundreds of

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[30] Cough-cold ANPR, 41 FR 38312 (September 9, 1976) at 38399, reference 25.

[31] Cough-Cold ANPR, 41 FR 38312 (September 9, 1976) at 38399, reference 25: Rogers et al. (1973).

[32] Cough-cold ANPR, 41 FR 38312 (September 9, 1976) at 38400, 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. The fifth Elizabeth study is actually in ANPR reference 10, not 19.

subjects with colds or hay fever over a 3-year period. However, the study does not support the effectiveness of oral PE for a number of reasons, including that the product and dose is not stated and the decongestant that was administered was a commercial combination product and not a single-ingredient oral PE product.

2.1.3 The Panel's Findings

While the Panel specifically noted that the data were "not strongly indicative of efficacy", in the absence of a safety concern, they recommended that the Agency categorize oral PE (immediate release hydrochloride salt) as safe and effective for use as an orally administered nasal decongestant at an adult/adolescent dosage of 10 mg administered every 4 hours.[33]

With regard to pediatric use, the original Panel acknowledged that data on use of most drugs in children was negligible or nonexistent even though cough-cold products, including PE, were widely used in pediatric populations.[34] They suggested that pediatric studies be done to support dosing, but given that such studies would be difficult to perform, they convened a Special Panel on Pediatric Dosage and made recommendations regarding the dosage of the various CCABA active ingredients.[35] In addition, pediatric dosing was the subject of at least two Advisory Committee meetings that explored what was known about the physiology of different age and weight groupings and evaluated which ages could be grouped to simplify pediatric dosing regimens for OTC drugs. It was eventually decided that adolescents 12 years of age and older were sufficiently similar to adults that they could be grouped with adults (from efficacy, safety, and dosage perspectives) and receive an adult dosage. For children 6 to less than 12 years of age, the recommendation was to halve the adult dose, and for children 2 to less than 6 years of age the recommendation was to quarter the dose. These dosing regimen decisions were the same as what had been recommended by the original Panel and were applied to almost all of the orally administered ingredients included in the CCABA monograph, including PE.

The ANPR requested public comment, and comments submitted to the docket were discussed in the TFM (proposed rule), published in the Federal Register on January 15, 1985. Two comments discussed in the TFM are directly relevant to this review. The first comment, TFM Comment 10, questioned the studies used by the Panel to substantiate the effectiveness of PEH as an oral nasal decongestant. The comment argued that the Panel had based its decision on numerous unpublished studies which "split evenly between mild successes and total failures" and noted that, in one study published in a peer-reviewed journal, no efficacy was seen even with doses greater than 10 mg.[36] TFM Comment 10 also included two references that questioned the oral bioavailability of PEH. A second comment, Comment 11, noted that the Panel had cited a study that did not contain the information referenced in the text. The Agency agreed that it was unable to resolve that discrepancy, although after careful review we believe that we have resolved that discrepancy, and our findings are presented in detail in Section 6.1. Having reviewed the information cited in the comments, the Panel's recommendations, and all of the supporting data, the Agency stated that it had concluded that "based on the studies cited by

[33] Decongestant TFM, 50 FR 2220, January 1, 1985, at 2226.

[34] Cough-cold ANPR, 41 FR 38312, September 9, 1976, at 38333; and 53 FR 23180, June 20, 1988.

[35] Cough-cold ANPR, 41 FR 38312 (September 9, 1976) at 38333.

[36] Decongestant TFM, 50 FR 2220, January 15, 1985, at 2226, Comment 10 (also Comment 11, which referred to possibly incorrect reference citations in the 1976 ANPR).

the Panel, information on clinical use and marketing experience, and the Panel's expertise in evaluating the clinical and marketing experience of this ingredient, there is sufficient basis to determine the phenylephrine hydrochloride is generally recognized as effective for OTC use as an oral nasal decongestant."[37]

Comment: We performed a comprehensive review of all the studies and publications submitted to the docket, and that review may be found within the Clinical Review subsection in the Agency Reviews section.

2.2 2007 Meeting of the Nonprescription Drug Advisory Committee

The Agency held a Nonprescription Drugs Advisory Committee (NDAC) meeting on December 14, 2007,[1] to discuss the scientific data raised by a CP submitted on February 1, 2007[2] (2007 CP), that requested that the Agency amend the dosage(s) of both oral phenylephrine salts (as nasal decongestants) in the FM by increasing the maximum dosage for patients 12 years of age and older and to withdraw approval for use in children younger than 12 years of age.[3,38] The petitioners had obtained (under the Freedom of Information Act) the original Cough-Cold Advisory Panel data from the Agency, evaluated each of the studies, performed additional literature searches, and performed a meta-analysis of the data. Their meta-analysis resulted in a different conclusion than that of the original Cough-Cold Advisory Panel, namely that orally administered PE is not effective at the monographed dosages (Hatton et al. 2007).

In addition to the petitioners, who presented their findings, a group from industry represented by the Consumer Healthcare Products Association (CHPA)[39] presented a second meta-analysis that they believed support the findings of the original Panel. Data that supported the original decision about inclusion of PE in the monograph as well as both sets of meta-analyses were reviewed and discussed by an FDA statistician. Finally, several industry speakers, notably from Schering-Plough and Schering-Plough Merck, provided previously unpublished data that support the petitioners' second CP to withdraw PE from the monograph. What follows below is summary of the information presented and discussed at the 2007 NDAC meeting.

2.2.1 Presentations by Drs Hendeles, Hatton, and Schuster (2007 CP)

Leslie Hendeles, PharmD, Randy C. Hatton, PharmD, and Jonathan J. Schuster, PharmD,[40] presented their meta-analysis of the studies submitted to and reviewed by the original Panel. Specifically, they noted that the data from one company, Elizabeth Biochemical, appeared to drive the majority of the positive results, and therefore the Panel's recommendations (see Elizabeth Biochemical Nos. 2 and 5 in Figure 4). They noted that not only had most of studies from other laboratories not found a difference between PE

[37] Decongestant TFM, 50 FR 2220, January 15, 1985, at 2226.

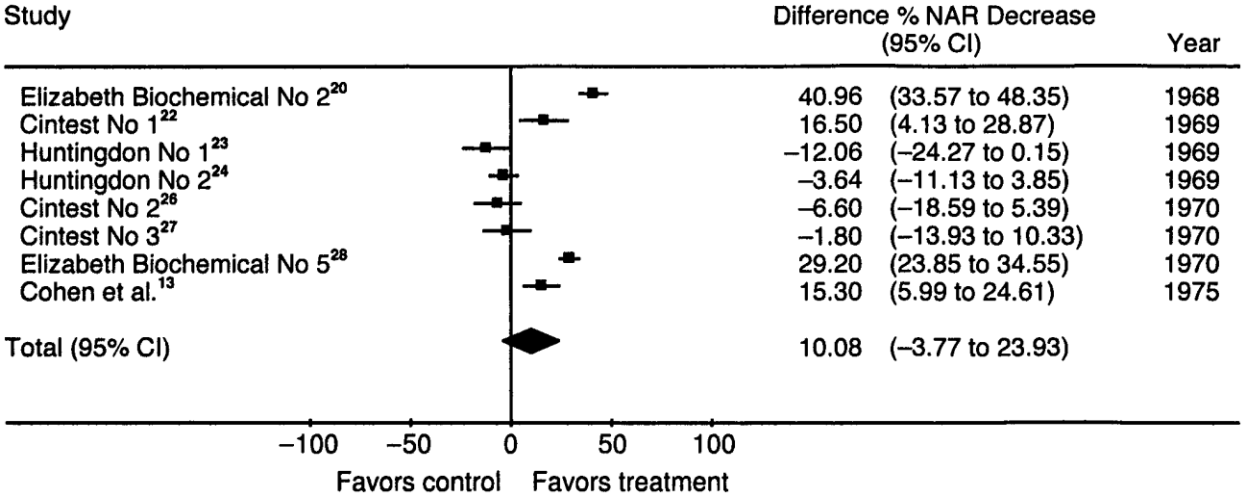
[38] Note that two of the 2007 petitioners, Drs Hendeles and Hatton, submitted a second CP on November 4, 2015, requesting that both oral phenylephrine salts be reclassified as Not GRASE due to lack of efficacy (i.e., to remove oral PE from the Final Monograph). See Footnote 4.

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

[40] Dr. Schuster was not one of the 2007 petitioners. He was a Research Biostatistician and Professor in the Division of Biostatistics in the Department of Epidemiology and Health Policy at the University of Florida College of Medicine.

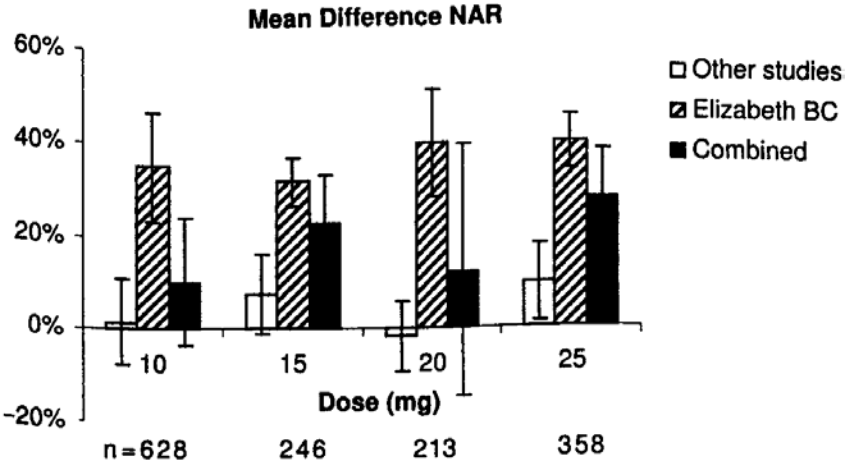
and placebo, when they did find a difference the magnitude of effect was much smaller than that reported by Elizabeth Biochemical (Figure 5), which suggested a reporting bias.

Figure 4. Pooled Random Effects Mean Maximum Difference in Percentage NAR Decrease Over 120 Minutes Between Phenylephrine and Placebo



Source: Hatton et al. (2007).
Abbreviations: CI, confidence interval; NAR, nasal airway resistance

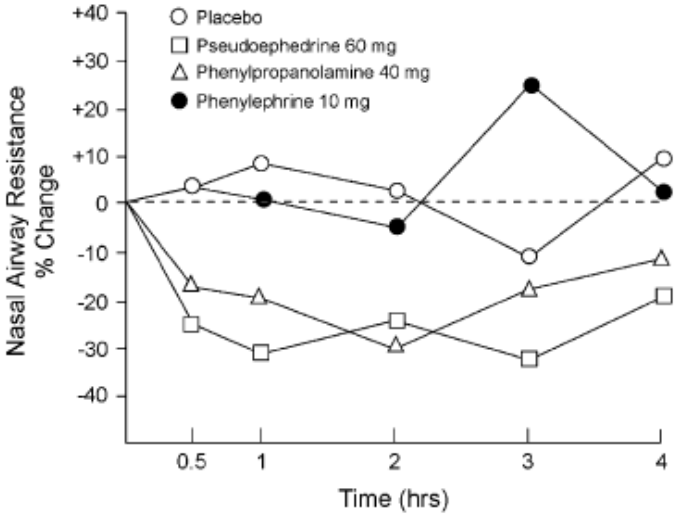
Figure 5. Difference in Mean Maximum NAR Decrease Within 120 Minutes Between Phenylephrine and Placebo by Dose: Combined Results and Stratification by Study Site



Source: Hatton et al. (2007).
Abbreviations: BC, biochemical; NAR, nasal airway resistance

They also reviewed the literature and a Cochrane review and noted several negative studies, including one negative study (that the Panel had noted but otherwise did not comment upon in favor of the positive evidence), which tried to overcome some of the complex methodological issues with NAR measurement (see Columbia University Study (Rogers / Bickerman publications) in the Clinical Review section) (Bickerman 1971). The study compared 10 mg of PE, 60 mg of PSE, 40 mg of PPA and placebo in subjects with nonatopic chronic nasal congestion who had previously been shown to respond to decongestant treatment. In this study, oral PE demonstrated no effect on NAR measurements, whereas both PPA and PSE showed changes that persisted over a 4-hour postdosing period (Table 11 and Figure 6). *Note*: The table was not presented at the AC meeting, only the figure.

Figure 6. Effects of Phenylephrine, Phenylpropanolamine, and Pseudoephedrine on Nasal Airway Resistance Over 4 Hours[41]



Source: Adapted from Bickerman (1971).

Finally, they presented data showing that an oral PE 10 mg dose resulted in no change in systolic or diastolic BP, or increased HR, whereas 50 mg of PPA did (Thomas et al. 1991). They noted that a dose of only 120 mg of PSE (twice the recommended maximum dose) was required to significantly increase BP in normotensive subjects whereas 120 mg of oral PE (12-fold the monographed dose) was required to produce a similar effect (Chua and Benrimoj 1988). As a result, they suggested that raising the monographed dose would be safe.

Of note, while the petitioners recommended increasing the monographed dose of PE, they did not present data suggesting that higher oral PE doses are effective.

The petitioners also noted that none of the studies reviewed by the Cough-Cold Panel included children less than 12 years of age, resulting in their recommendation to limit use to patients 12 years of age and older.

2.2.2 Industry Presentations

There were three sets of industry presentations at the AC meeting, which are discussed below. But, before discussing the presentations, it is helpful to provide some background. Of major interest were two presentations from Schering-Plough and Schering-Plough Merck, because these companies presented data that, counterintuitively, supported the petitioners CP that the monographed dose of oral PE is not effective and higher doses would be needed. The AC recommended that more clinical data would be needed to support higher doses of oral PE.

Note: Over the subsequent 5 to 7 years, Schering-Plough/Merck proceeded to perform studies that [based on publicly available information, we believe they hoped] would support these new higher dose products, including a higher strength of IR oral PE and an extended-release formulation. We believe that the information they presented at the NDAC meeting were the early results that supported development of these products by providing preliminary support that the monographed dose is not

[41] Adapted into a figure from Bickerman (1971). Figure published by Hendeles (1993) and Hendeles and Hatton (2006).

effective. Information from subsequent publications makes it clear that this was followed by safety studies, after which they conducted two large clinical trials. The data that Schering-Plough and Merck developed during these programs form the primary source of the evidence that oral PE is not effective at both the monographed dosage and at doses up to four-fold the monographed dose, a dose that (based on the safety /PD studies that they performed) was the highest dose that they felt could be safely marketed. See the Agency Reviews, Preface to Merck's Two Clinical Trials section (3.3.2.1) for further details.[42]

2.2.2.1 Industry Meta-Analysis

CHPA, on behalf of industry, presented a second meta-analysis, which also used the original data supplied to the Advisory Panel (see the CHPA column in Table 6 for studies included in the industry meta-analysis). This meta-analysis, which reported findings congruent with the original Panel, was performed by GlaxoSmithKline Consumer Healthcare and the CHPA in response to the CP, and was later published (Kollar et al. 2007).

2.2.2.2 Schering-Plough Presentation

John O'Mullane, PhD, Group Vice-President of Consumer Healthcare Research and Development at Schering-Plough Corporation, reviewed what is now known about the metabolism, pharmacokinetics, bioavailability, and pharmacologic activity of PE, and discussed what had changed in the interim since the original Cough-Cold Panel reviewed the studies that supported the current monographed doses. He noted that PE administered orally is known to undergo extensive first-pass metabolism (conjugation and oxidation) in the gut wall to (inactive) PE-3-O-glucuronide, (inactive) PE-3-O-sulfate, and (inactive) 3-hydroxymandelic acid as three major metabolites. These PE metabolites are the predominant molecules in the systemic circulation. He presented data from a small, single-dose oral bioavailability study conducted in 14 subjects who revealed that active parent PE represents less than 1% 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 (Figure 7).[43,44]

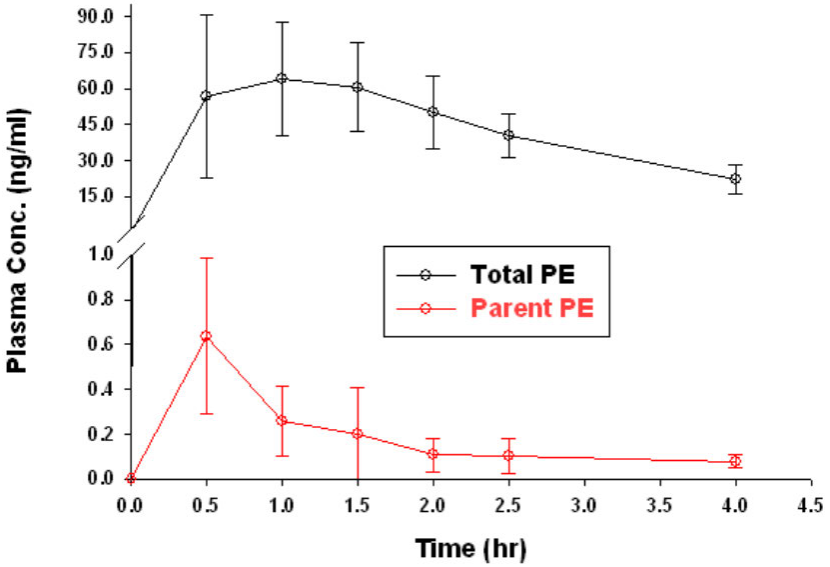
[42] Note that an additional source is a separate trial conducted by Johnson and Johnson for an ER oral PE product (see Johnson and Johnson Phase 2 Study (CO-170302131230-URCT; NCT03339726).

[43] Schering-Plough Corporation Presentation Slides at NDAC Meeting (December 14, 2007) Phenylephrine 10 mg. Available at: https://wayback.archive-it.org/7993/20170404050454/https://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4335s1-00-index.htm.

[44] 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.

Figure 7. Plasma Concentrations of Parent PE and Total PE Versus Time for a Single Oral Dose of a PE Tablet[44]

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



Source: Schering-Plough Study CL2005-07, 2005.

Further, Dr. O'Mullane compared the in vitro pharmacology data (developed by Schering-Plough) between the parent PE and its three major metabolites.[43,44] The calcium flux response assay demonstrated that the in vitro α1-adrenergic agonistic EC_{50} value (2.3 and 16.9 ng/mL) of parent PE (Table 5) is higher than the in vivo parent PE C_{max} value (~0.65 ng/mL) following 10 mg oral dose (Figure 7). None of three major metabolites of PE had any detectable α1-adrenergic receptor binding affinity and α1-adrenergic agonistic activity as measured by GTPγS binding exchange assay and calcium flux response.[43] Dr. O'Mullane noted 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, such that a 10 mg oral dose is not sufficient to provide efficacy, whereas even a less than 1 mg dose administered intravenously clearly demonstrates systemic alpha-1-agonist activity (Martinsson et al. 1986).

Table 5. In Vitro 50% Effective Concentration Values (ng/mL) of Alpha-Adrenergic Agonizing Activity of Phenylephrine (PE) 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 the NDAC Meeting on December 14, 2007.
[1] As measured by cell-based calcium flux response assay.
[2] As measured by [35S]-GTPγS binding exchange assay.

2.2.2.3 Schering-Plough Merck Presentation

Melvin Danzig, PhD, Director of Clinical Research at Schering-Plough Merck, reviewed the findings from two allergen challenge chamber (environmental exposure unit or EEU) studies that compared monographed doses of PE with placebo and either PSE 60 mg (active comparator) or a combination of loratadine/montelukast 10/10 mg (test combination).[45] While the EEU is an artificial setting, it is well documented and accepted as providing a reasonable assessment of the pharmacodynamic 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). 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. The results of both studies were subsequently published in 2009 (Day et al. 2009; Horak et al. 2009). In one study (Study P04579; Horak et al. (2009)), PE (12 mg, the EU-approved dosage form) was compared with placebo and a known effective oral decongestant (PSE 60 mg – the monographed dose for adults and adolescents 12 years of age and older), and in the other study (Day et al. 2009) PE (10 mg) was used as the "active" comparator to evaluate a different "test" drug (a combination of loratadine 10 mg and montelukast 10 mg) versus placebo. In both studies, PE failed to provide any benefit over placebo, while 60 mg of PSE provided good relief of congestion symptoms as well as a clear effect on nasal rhinometry and peak nasal inspiratory flow measures. (For a detailed review of the studies, see Section 3.3.3.5, in Section 3.3, Clinical Review, below.)

2.2.3 FDA Statistical Presentation

In preparation for the meeting, Dr. Stan Lin from the Division of Biometrics in the FDA Office of Translational Sciences reviewed all the original data, both sets of meta-analyses, and four previously unpublished studies conducted by Wyeth Consumer Healthcare or Schering-Plough.

Dr. Lin noted that all of original studies evaluated by the Panel (and used in both meta-analyses) used a measure of resistance to nasal inspiration (nasal airway resistance or NAR) as the primary clinical measure, and [Dr Lin noted that] that this measure is sufficiently problematic that the Agency no longer accepts it as a clinical endpoint. He noted that the petitioners' meta-analysis used maximal reduction in NAR measured periodically during the first 2 hours after study drug administration, whereas the industry (CHPA) meta-analysis used reduction in NAR in 0 to 60 minutes. While noting that the statistical design of the primary endpoints in each of the studies was not well defined, he considered the endpoints used in the two meta-analyses to be new endpoints, which is problematic because they were not the basis for the original design or analysis of the studies reviewed by the panel and their use might obscure differences throughout dosing intervals. Further, the CHPA meta-analysis only used the crossover studies, whereas the petitioners also included at least one parallel-group study. Therefore, the meta-analyses could not be easily compared. He went on to state that neither meta-analysis was conclusive, quoting the Agency's Senior Scientific Advisor, Dr. Robert Temple, who is quoted at an FDA

[45] 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.

Regulatory Briefing in March of 2007, as having stated that "All meta-analysis is post facto. You only do it if you know you're going to win."

Dr. Lin also presented a summary of his findings for each of the individual studies (see Table 6 and Figure 8). He noted that all of the Elizabeth studies showed relatively stronger efficacy regardless of dose and that the two most positive studies came from that site (Elizabeth), concluding that the lack of replication at other sites, the lack of multicenter representation, and the small sample size of the studies "limits the generalizability of these results." He pointed out that "evidence exists for treatment by study interaction at the different time points where NAR was measured," which indicates "study and/or outcome heterogeneity and limits the poolability of data." While Dr Lin did not go so far as to state that the data do not support efficacy, he noted that "averaging these studies with other studies would mask a finding of no effect from the other studies."

Table 6. FDA Statistical Evaluation of Effectiveness Demonstrated in the Original Studies

Effectiveness of Phenylephrine (Hydrochloride Salt) at 10 and 25 mg Doses

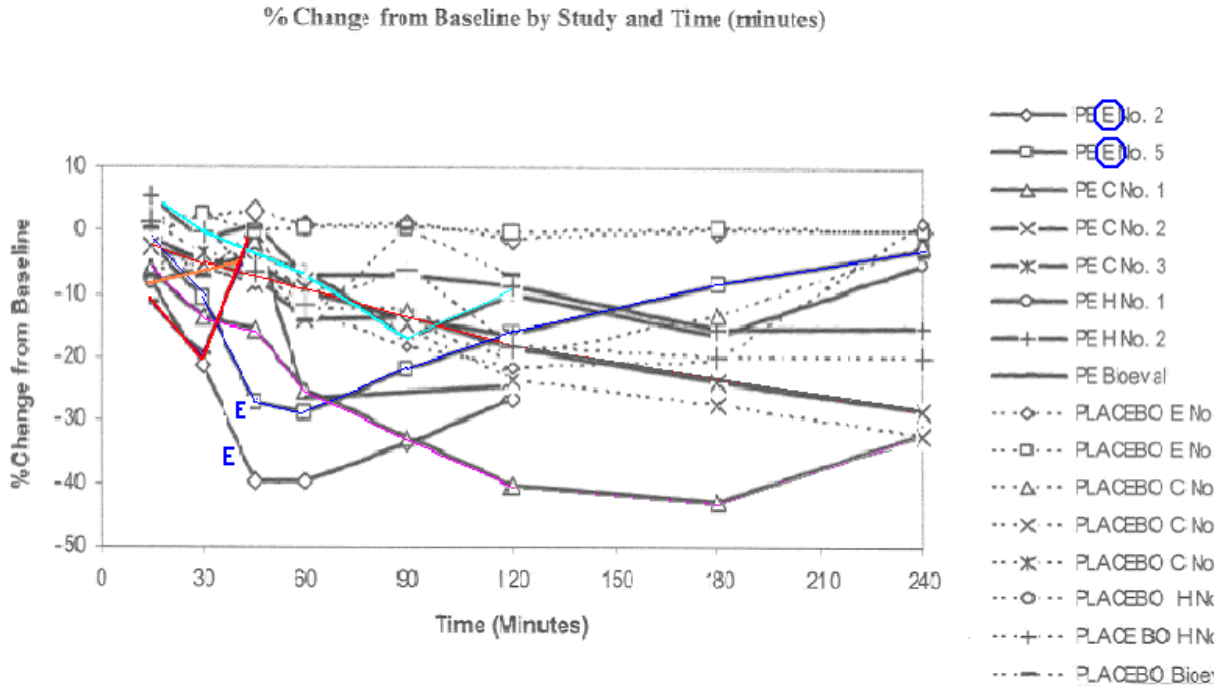
Study	ANPR	CP	CHPA	Patient Condition	Effectiveness			
					↓Nasal Airway Resistance		Symptom Relief	
					10 mg	25 mg	10 mg	25 mg
Sterling-Winthrop	■			Healthy	■	■		
Eliz1	■			Cold		■*		■*
Eliz2	■	■	■	Cold	■*	■*	■*	■
Eliz3	■			Cold		■*		■
Eliz4	■			Cold		■*		■
Eliz5	■	■	■	Cold	■*	■*	■	■*
McLaurin et al	■			Various[5]	■		■	
Blanchard et al[1]	■							
Hunt1	■	■	■	Cold	■	■		
Hunt2	■	■	■	Cold	■			
Cin1	■	■	■	Cold	■*	■*	■*	■
Cin2	■	■	■	Cold	■		■	
Cin3	■	■	■	Cold	■	■	■	■
Rodgers et al[2]	■							
BEI (Cohen, 1975)	■	■		Cold	■*		■*	
Bickerman[3]								
Cohen				Cold	■*	■*	■*	■*
Wyeth GIA				URTI	■		■	
Wyeth 4010-3				URTI	■*		■	
Wyeth 7032				Allergy	■			
S-P P04579[4]				SAR			■	
S-P/Merck P04822				SAR			■	

Excluded Studies
[1] Combination product – no data specifically for PEH
[2] Abstract only – insufficient data
[3] One table in a review article – insufficient data
4 12 mg dose of PEH
5 Congestion due to acute coryza, acute and chronic sinusitis, allergic or vasomotor rhinitis, hypothyroidism

* Statistically significant effect

Source: Presentation by Stan Lin, PhD, FDA Division of Biometrics 4/OB/OTS, at the December 14, 2007 NDAC meeting.
Abbreviations: ANPR, Advanced Notice of Proposed Rulemaking; CHPA, Consumer Healthcare Products Association; CP, citizen petition; PEH, phenylephrine HCl; SAR, serious adverse reaction; URTI, upper respiratory tract infection

Figure 8. FDA Statistical Evaluation of the Change From Baseline in NAR Results Over Time for Active and Placebo in Each of the Original Studies



Source: FDA.
Abbreviations: NAR, nasal airway responsiveness; PE, phenylephrine

In summary, Dr. Lin noted that the small size, the lack of multicenter representation, the lack of reproducibility, and the problematic nature of the methodology used by the original studies evaluated by the Panel suggests that the data underlying the original recommendation made by the Cough-Cold Panel are not conclusive.

2.2.4 NDAC Recommendations

The committee noted the inconsistency of results across studies, but concluded that available evidence is "suggestive of efficacy" (Votes: 11 Yes, 1 No, 0 Abstain).[46] This was based on the NAR data from the seven original studies that had supported the inclusion of PE in the monograph, as well as a meta-analysis of the original data presented by industry that supported the original Panel's findings (Kollar et al. 2007). Nevertheless, due to the limitations of the data, 9 of the 12 committee members voted to recommend that additional clinical data would be necessary, including new studies that should evaluate the decongestant effect of higher doses of oral PE. Based on the Agency's recommendation, the NDAC suggested that the future studies evaluate subjective symptom scores rather than use objective measurement of NAR as the primary endpoint. The NDAC further recommended that future trials include the following design elements:

- Multicenter, parallel, randomized, double-blind, placebo-controlled trials, preferably with an active control such as pseudoephedrine, to evaluate nasal congestion scores and symptom relief.

[46] Summary Minutes of the NDAC meeting, December 14, 2007. Available at: https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4335m1-Final.pdf.

- Sufficient sample size to evaluate efficacy and safety according to key characteristics such as age, gender, race, and severity of symptoms.
- Characterization of the PE dose response and the effect of dosing interval, formulation, type of delivery system, and potentially, genetic factors, on safety and efficacy endpoints.
- Comparison of the pharmacokinetics of single-ingredient products versus multiple-ingredient products.
- Safety evaluation of the effects of PE on blood pressure and cardiovasculature and use of PE in patients with important comorbidities such as benign prostatic hyperplasia, hypertension, or diabetes.

3 Agency Reviews

3.1 Summary of Findings

The presentations by Schering-Plough and Schering-Plough Merck at the 2007 NDAC meeting were remarkable in that they changed the way the Agency considered the clinical pharmacology of orally administered PE. It should be noted that those clinical pharmacology data had not been available to the original Panel when it made its recommendations >30 years previously. Even though the efficacy data were borderline, the Cough-Cold Panel considered that PE is effective when administered intranasally, and it is likely that they took that into consideration when they made their recommendation for the orally administered ingredient. They made this recommendation despite evidence that clinically relevant pharmacodynamic effects on BP do not occur until one reaches an oral PEH dose close to 100 mg, and that studies as far back as 1933 had suggested that it would take 120 mg or more of oral PE to be an efficacious dose (Tainter and Stockton 1933).

In response to the clinical pharmacology and clinical data presented at the 2007 NDAC meeting, the Clinical and Clinical Pharmacology teams reviewed all “new” the clinical pharmacology and clinical data that has become available since that time. By “new” data, we mean all of the data that has become available since the Agency made the GRASE determination regarding the efficacy of orally administered phenylephrine (i.e., publication of the Final Oral Decongestant Monograph) in 1994.

Contrary to what is often cited in the literature as the oral bioavailability of phenylephrine, i.e., 38%, which is based on outdated technology, the Agency’s Clinical Pharmacology team has confirmed that the actual oral bioavailability of PE is less than 1%. This is due to the high first-pass metabolism effect when PE is administered orally, whereas PE is effective when administered intranasally and has systemic effects when much smaller doses are administered intravenously. The Clinical Pharmacology team also confirmed that the half-life of the parent PE is much shorter than that of total PE, suggesting that the duration of action for active parent PE is far shorter than the monographed dosing interval of every 4 hours, and is therefore open to question.

Finally, the Clinical Pharmacology team confirmed that clinically relevant pharmacodynamic changes, such as an increase in systolic and diastolic BP, do not occur until oral PE doses of around 80 to 100 mg. The consistent finding across multiple studies that it takes around 80 to 100 mg of oral PEH to result in a clinically relevant effect on BP also suggests (unless there is a significant dichotomy between the systemic BP and intranasal decongestant effects, which we believe from an animal pharmacology study (Aviado et al. 1959) is not the case) that monographed doses are too low to result in efficacy. These PD data are therefore consistent with the bioavailability data.

All of the PD and PK data are also consistent with the two well-designed, placebo-controlled EEU studies, the results of which were presented at the 2007 NDAC meeting and subsequently published. The EEU studies were performed at well-recognized environmental exposure unit study sites and used accepted congestion symptom score scoring and endpoints in subjects with allergic rhinitis, a far more stable platform (i.e., less variability in patient symptoms over time) than subjects with colds. Such studies, while mechanistic and unacceptable as Phase 3 studies, are nevertheless acceptable when used for early Phase 2 proof-of-concept and dose-finding for drugs to treat allergic rhinitis, although the results must be corroborated in larger Phase 2 studies and in pivotal Phase 3 studies. These studies demonstrated no efficacy for PEH at monographed or slightly higher doses (one used 12 mg instead of 10 mg of PEH), whereas positive controls were clearly positive. Therefore, while these results were highly suggestive of an efficacy issue, they are not confirmative.

Data from three large, adequately controlled clinical trials conducted subsequent to the 2007 NDAC meeting are now available, and those data are consistent with the PK, PD, and EEU data. They demonstrate a lack of efficacy with oral IR doses up to 40 mg as well as ER doses of 30 mg. Merck (formerly Schering Plough) conducted two trials in subjects with allergic rhinitis to evaluate (and presumably potentially market) both higher than monographed doses of IR product and a 30 mg product, and Johnson and Johnson conducted a trial in subjects with colds to evaluate (and presumably potentially market) a 30 mg ER oral PE product. All used clinically acceptable designs and nasal congestion symptom scores as primary endpoints. These three trials represent by far the largest and most carefully constructed trials that have ever been performed to evaluate the decongestant effect of oral PE. While we were unable to review the actual datasets for any of the three trials (none were submitted to the Agency), we did review the results published at clinicaltrials.gov as well as any publications that resulted from these trials. Importantly, none of the three demonstrated any significant difference between monographed doses of oral PE, doses of up to 40 mg of oral IR PEH (four-fold higher than the monographed dose) (Table 8) (one trial), or two different 30 mg ER formulations (two trials), compared with placebo. We believe that these new clinical pharmacology and clinical data are consistent, substantial, and believable, and they confirm that orally administered PE is not effective at any dose that can be developed and still provide a reasonable margin of safety (see Section 3.3.2, New Clinical Trials).

In light of the results from these “new” data sources, and to understand how the new data fit with the previously available efficacy data, we also reviewed all of the data that supported the original GRASE determination. We noted significant methodological and statistical issues with the design and conduct of the original studies submitted to and evaluated by the Panel. All used a mechanistic endpoint (NAR) that is no longer accepted by the Agency because it is highly variable and unreliable as a measure of congestion. All but one study evaluated subjects with the common cold, a platform that is highly variable and difficult to study. All but one evaluated extremely small sample sizes, none adequately controlled for bias, none adequately controlled for multiplicity, and none performed appropriate sample size calculations. Ten of the studies (all from one sponsor) were small, single-center crossover studies that had significant issues but were nonetheless a major support for a GRASE recommendation.

In addition to the multiple methodological and statistical issues, we also noted that two studies from one site (Elizabeth Biochemical Labs) were not only the most positive studies, but they also produced near textbook perfect results that could not be duplicated in other similarly designed studies that used the same methodology but were conducted at two other centers by the same sponsor. This raises suspicion regarding potential bias and data integrity issues at the Elizabeth site, which contributed five

of the seven positive original studies. While we discuss those potential issues in our review, we consider them unsubstantiated, whereas the methodological and statistical issues with all of the original studies are both substantial and substantive.

It should also be noted that all of the original and subsequent clinical studies/trials used the PEH salt, and that a GRASE determination for the PEB salt was based entirely on matching the systemic exposure of total PE between the two salts. Given that less than 1% of PE is systemically available in an active form (parent PE), we now know retrospectively that this was a problematic approach. Therefore, a finding of lack of efficacy for PEH automatically carries over to a similar finding for PEB.

As a result of our evaluation, we believe that the new efficacy data far outweigh the data provided to the Agency as part of the original Panel review. These results suggest that: 1) oral PE at monographed dosages is not effective as a decongestant (i.e., in the face of the new data, the original data are likely not sufficient to support a GRASE determination), 2) oral doses up to 40 mg would also not be effective, 3) finding an effective oral dose that is also safe is not feasible (meaning that doses higher than 40 mg would need to be explored but would also not be safe to study due to effects on blood pressure), and 4) an appropriate dosing interval for oral PE has not been established (meaning that, based on the PK data, an every-4-hour dosing interval is likely too long). Therefore, in addition to lack of efficacy, there may be no path to evaluating higher doses of oral PE as a nasal decongestant.

3.2 Clinical Pharmacology Review

To confirm the α1-adrenergic pharmacologic activity results of PE and its metabolites that were presented by Schering-Plough at the 2007 NDAC Meeting, the Clinical Pharmacology team reviewed the literature and revisited the clinical pharmacology reviews of phenylephrine NDAs to compare with the PK and relative bioavailability results that were presented by Schering-Plough at the 2007 NDAC Meeting. As discussed below, we were able to confirm all of this information.

3.2.1 Pharmacologic Activity of PE and Its Metabolites

The approved drug label of New Drug Application (NDA) 204300, VAZCULEP (phenylephrine hydrochloride Injection) states that "*Phenylephrine hydrochloride is an α-1 adrenergic receptor agonist*."[47] In addition, the label states that after intravenous administration of radiolabeled phenylephrine, "*there are two major metabolites, with approximately 57 and 8% 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 α1-adrenergic pharmacology results of PE and its metabolites that were presented by Schering-Plough at the 2007 NDAC Meeting.

3.2.2 Oral Bioavailability

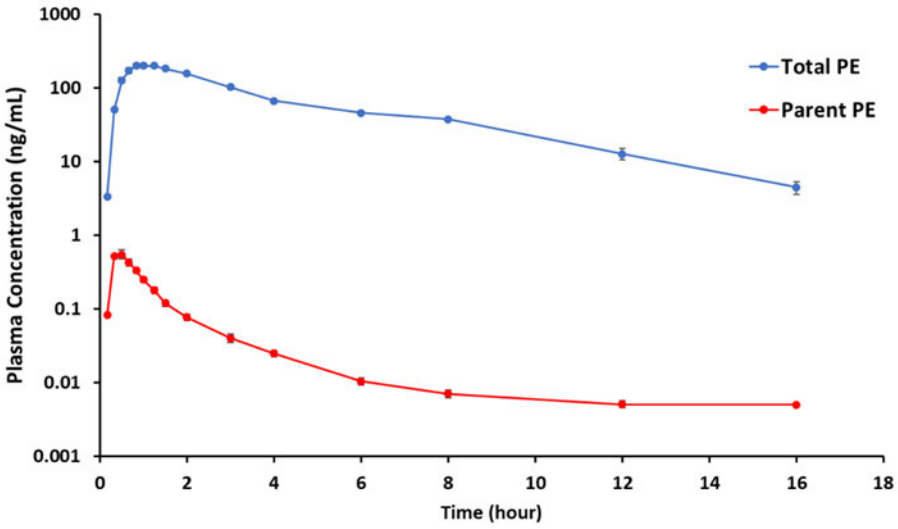
The VAZCULEP® (NDA 204300) clinical pharmacology reviewer acknowledged that a radiolabeled PE bioavailability study had estimated that the absolute oral bioavailability (i.e., ratio of PE exposure following oral administration versus IV infusion) of parent PE was 38% (Hengstmann and Goronzy 1982). However, the value of 38% is an overestimate due to the underestimate of the PE exposure following the IV infusion, as the PK samples were not collected during the IV infusion which lasted about 12.5 to

[47] NDA 204300, for Vazculep (phenylephrine hydrocholoride) Injection for intravenous use from Éclat Pharmaceuticals, approved June 27, 2014.

20 minutes and 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.[55] The underestimate of the PE exposure following the IV infusion rendered PE exposure following oral administration artificially relatively higher. The reviewer also acknowledged that a reliable non-radiolabeled high-performance liquid chromatography tandem mass spectrometry bioanalytical assay sufficiently sensitive to characterize the full PK profile of parent PE following the monographed 10 mg oral dose did not become available until the 21st century (Feng et al. 2013).

Consistent with the PK results presented by Schering-Plough at the 2007 NDAC Meeting, the clinical pharmacology program for NDA 022565, Advil Sinus Congestion & Pain (ibuprofen 200 mg and phenylephrine HCl 20 mg tablet)[48] confirmed that the parent PE systemic exposure is <1% of the total PE (i.e., parent PE + conjugated PE) systemic exposure following oral administration (Figure 9 and Table 7). Further, both the effective and elimination half-lives of the parent PE are much shorter than that of total PE, suggesting that the monographed dosing interval of every 4 hours needs to be further evaluated.

Figure 9. Geometric Mean Parent and Total Phenylephrine (PE) Pharmacokinetic Profile (N=42) Following 10 mg Single Oral Dose of Sudafed PE®



Source: NDA 022565, Study 0813.

[48] NDA 022565, for Advil Congestion Relief Tablets from GlaxoSmithKline Consumer Healthcare Holdings US LLC, containing ibuprofen 200 mg and phenylephrine HCl 10 mg, approved May 27, 2010.

Table 7. Systemic Exposure of Parent and Total PE Following 10 mg Single Oral Dose of Sudafed PE®

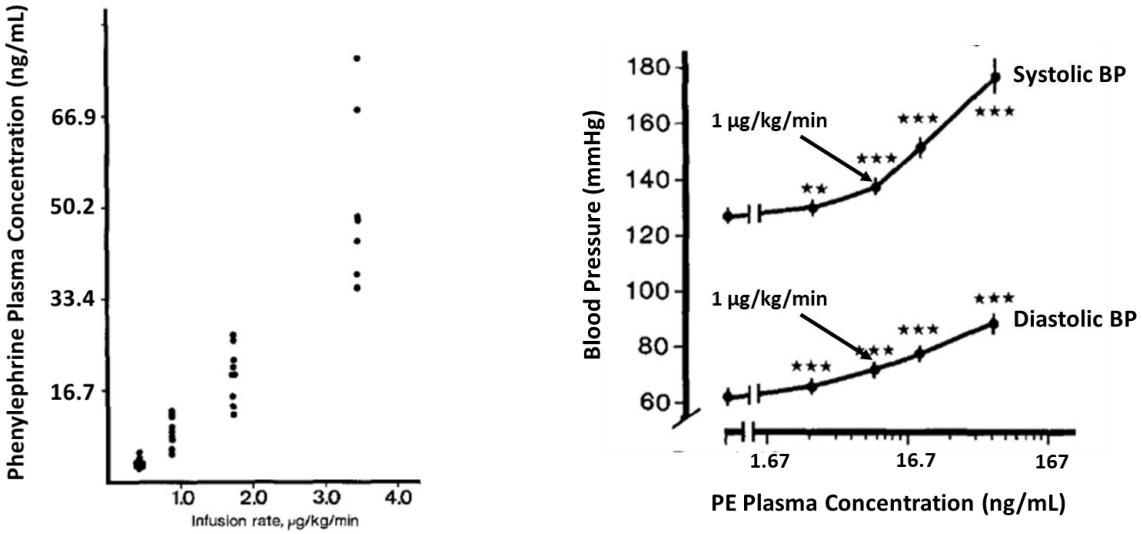
Parameter	Parent PE	Total PE	Mean Ratio (Parent/Total)
C_{max} (ng/mL)[1]	0.766 (49%)	225 (33%)	0.34%
AUC_{last} (ng×h/mL)[1]	0.692 (26%)	864 (22%)	0.08%
AUC_{inf} (ng×h/mL)[1]	0.730 (26%)	885 (22%)	0.08%
T_{max} (hour)[2]	0.33 (0.17, 0.83)	0.92 (0.5, 2)	N/A
$t_{1/2}$ (hour)[1]	1.55 (59%)	2.68 (21%)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

3.2.3 PK/PD Relationships

Based on the in vitro pharmacology results, PE is supposed to stimulate the local alpha-1 adrenergic receptors expressed on the blood vessels in nasal mucosa to exert its direct pharmacologic effect (Johnson and Hricik 1993), if the local concentration of parent PE reaches to certain levels. However, there is a lack of data that directly measure the alpha-1 adrenergic activity in the nasal mucosa. Instead, the Clinical Pharmacology team conducted a review of PE PK and systemic alpha-1 adrenergic PD response (systolic BP change from baseline) relationships, comparing those relationships between orally administered PE (Gelotte and Zimmerman 2015) and IV administered PE (Martinsson et al. 1986). A crossover clinical trial in nine healthy subjects 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, a steady-state parent PE mean plasma concentration of ~10 ng/mL was reached within 6 minutes (Figure 10) (Martinsson et al. 1986). At this concentration during the infusion, both systolic and diastolic BP elevated noticeably, about 10 mm Hg from baseline.

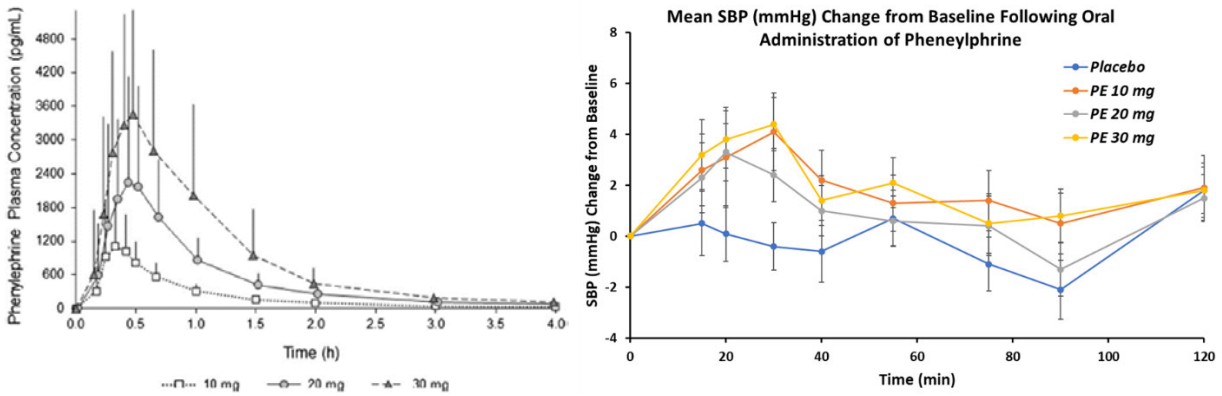
Figure 10. Plasma Concentrations of Parent PE (Left Panel) and Systemic Blood Pressure Change (Right Panel) During the 6-Minute Continuous IV Infusion of 0.5, 1.0, 2.0, and 4.0 µg/kg/Minute PE



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

In 2015, McNeil Consumer Healthcare published results from a Phase 2 study, which characterized the PK, safety, and cardiovascular tolerability following a single dose of oral IR PE HCl (Gelotte and Zimmerman 2015). The study was a randomized, double-blind, placebo-controlled, single-dose, crossover design that compared four treatments: placebo and phenylephrine hydrochloride 10, 20, and 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 11). The mean C_{max} value following the monographed 10 mg oral dose was 1.35 ng/mL. Meanwhile, the post-dose mean systolic BP increased <5 mmHg from baseline and no dose-response relationship was observed (Figure 11). 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 mm Hg 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 30 mg PE oral dose are consistent with the lack of local decongestion effect of PE observed from clinical efficacy trials (Meltzer et al. 2015; Meltzer et al. 2016). The results are also consistent with the previous PD safety data available to the Original Panel (see Section 2.1.1, Safety/Pharmacodynamics) as well as other data referred to in Meltzer's 2015 article cited above, which studied the efficacy and safety of doses up to 40 mg in a large Phase 2 trial (see Section 3.3.2.2, Dose-Ranging Trial (Merck Protocol #CL2010-06; NCT01330017)).

Figure 11. Plasma Concentrations of Parent PE (Left Panel) and Systolic Blood Pressure Change (Right Panel) Following Oral Administration of Placebo, 10, 20, and 30 mg IR PE



Source: Adapted from Gelotte and Zimmerman (2015).
Abbreviations: IR, immediate release; PE, phenylephrine

In sum, cross-study comparison showed that, after the dose adjustment, steady state parent PE plasma concentration following 1 µg/kg/minute IV infusion is about 200-fold higher than the parent PE C_{max} value following the monographed 10 mg oral dose. In addition, there is 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, mean systolic BP increased <5 mm Hg following up to a 30 mg oral PE dose (3× the monographed dose), and no dose-response relationship of vital sign change from baseline was observed following oral PE doses of 10 to 30 mg. The results from the McNeil trial are consistent with the estimation from a previous clinical

trial that a minimum of 40 to 60 mg oral PE is needed to result in an elevation of systolic BP of approximately 5 to 10 mm Hg. The clinical pharmacology reviewer estimates that 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 that resulted in 10 mmHg elevation of systolic BP. Although an effective oral dose of phenylephrine that results in a sufficient local alpha-1 adrenergic activity for nasal decongestive effect is unknown, a much higher oral dose than the monographed dose is expected based on the currently available in vivo PK and PD results of parent PE. As a reference, the concentration of monographed PE solution for intranasal use is 0.125%, or 1.25 mg/mL (previously 21 CFR 341.80). That is about one-million-fold the parent PE C_{max} value following a 10 mg oral dose.

3.3 Clinical Review

The Clinical team reviewed all of the "new" clinical data available, meaning all of the data that has become available since the Agency made the GRASE determination regarding the efficacy of orally administered phenylephrine (i.e., publication of the Final Oral Decongestant Monograph) in 1994. We started with the EEU studies and other data presented at the 2007 NDAC meeting, followed by the new clinical trials.

In light of those findings, we reviewed each of the studies submitted to and reviewed by the original Panel that supported the original finding of GRASE status for orally administered PE as a nasal decongestant. In so doing, we reviewed all the clinical data presented by the petitioners, industry, and the Agency at the 2007 NDAC meeting. We did so both for completeness and because we wanted to understand how the old data stood up against the new data.

What follows is our summary of our findings. That stated, please see the Agency Reviews: Summary of Findings section above for our tentative conclusions.

3.3.1 EEU Studies (2007 NDAC)

We reviewed the results for the two EEU studies presented (and subsequently published) at the 2007 NDAC meeting (see the Schering-Plough Merck Presentation section, above).[49] In both studies, PE failed to provide any benefit over placebo, while PSE provided good relief of congestion symptoms in one of the studies. The two studies are described in further detail below.

While the EEU setting is an artificial setting, it is well documented as providing a reasonable assessment of the pharmacodynamic properties of a drug, including onset of action and duration of effect. That said, EEU studies are at best considered as late Phase 1 or early Phase 2 proof-of-concept studies, although 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 the Agency as part of other drug development programs for pulmonary-allergy products. Further, the two studies were performed at well-known EEU study centers. And finally, we are aware of drug development programs that were terminated because such studies did not support the dose and dosing interval of a drug, particularly when the studied dose was the highest dose that would be considered acceptable for human use based on the preclinical and Phase 1 tolerability data (note that we have left out specifics

[49] Neither of these studies were conducted in the United States. There are two major sites for EEU studies, one in Vienna, Austria, and one in Ontario, Canada.

because the information is proprietary). The bottom line is that, while the results of these studies are not definitive, the findings are strongly supportive that the monographed dosage of oral PE is not effective.

3.3.1.1 Study P04579 (Horak et al. 2009) (NCT00276016)

This was a single-center, randomized, investigator-blind, active- and placebo-controlled, three-way crossover, single-dose study that evaluated the efficacy of PE, PSE, and placebo in 39 grass-sensitive patients exposed to grass pollen in the EEU setting. It was conducted at the University of Vienna, Vienna, Austria, and funded by Schering-Plough Research Institute, Kenilworth, New Jersey.[50]

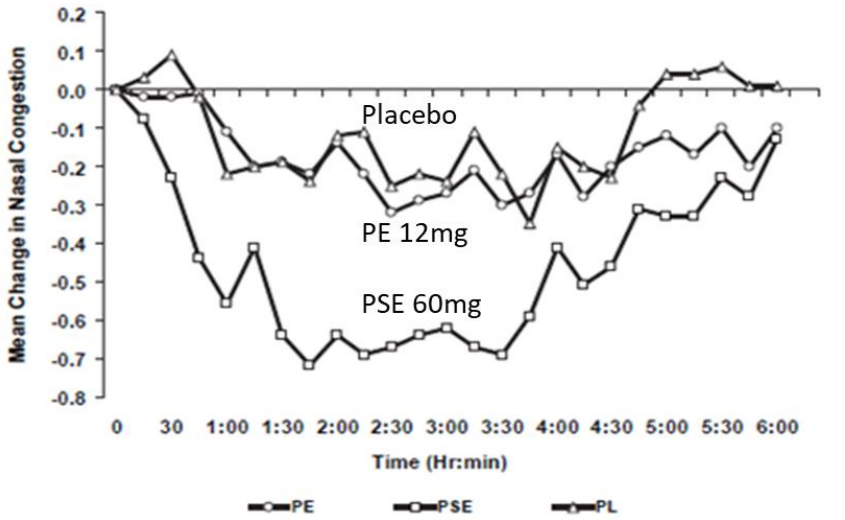
Subjects who met minimum symptom scores during a 120 minutes predose challenge were treated with IR formulations of PE 12 mg (European Union-approved product), PSE 60 mg, or placebo, and continued to monitor and record symptoms every 15 minutes over 6 hours. Measurements of rhinomanometry, peak nasal inspiratory flow (PNIF), and nasal secretions for weight were collected at 30-minute intervals over the 6-hour study period, although the publication does not explain the methodology used for the NAR and PNIF measurements. The primary efficacy assessment was change from baseline in average nasal congestion score over 6 hours.

A total of 39 subjects were randomized; and 38 subjects completed treatment. Subjects were predominantly white (97%), and female (59%), 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 rhinometry/PNIF measurements over the course of the EEU exposure after treatment are shown in Figure 12 and Figure 13, 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%. The results of rhinomanometry and PNIF measurements were consistent with the nasal symptom scores. No adverse events (AEs) were reported in the study.

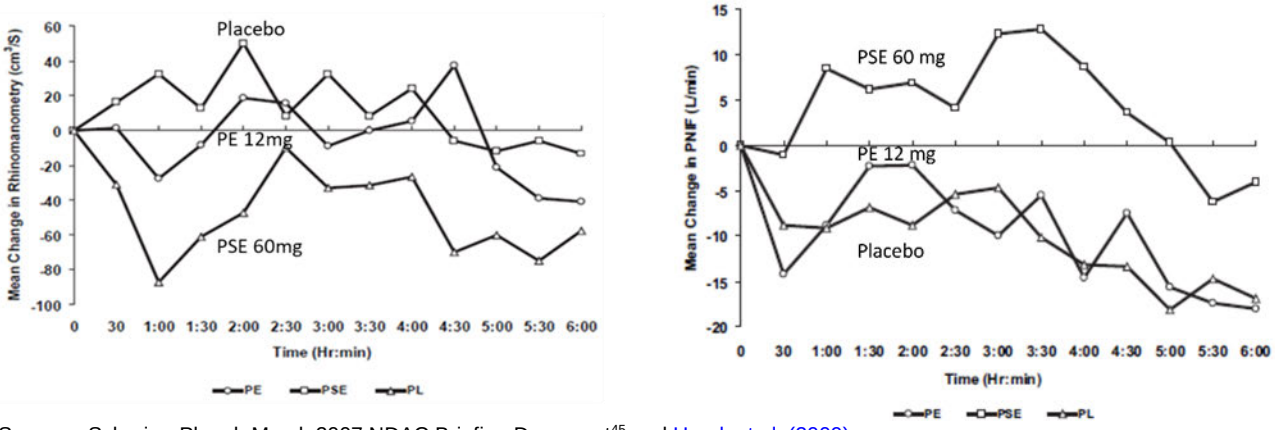
[50] The study results were presented at the 2007 NDAC meeting, were published by Horak et al. 2009, and are also available at: https://clinicaltrials.gov/ct2/show/NCT00276016.

Figure 12. EEU Study P04579. Mean Change in Subjective Nasal Congestion Scores at 15-Minute Intervals After Drug Administration



Sources: Schering-Plough Merck 2007 NDAC Briefing Document[45] and Horak et al. (2009).
Abbreviations: EEU, environmental exposure units; NDAC, Nonprescription Drugs Advisory Committee; PE, phenylephrine; PSE, pseudoephedrine

Figure 13. EEU Study P04579. Mean Change in Nasal Rhinometry (Left) and Peak Nasal Inspiratory Flow (Right) at 30-Minute Intervals After Drug Administration



Sources: Schering-Plough Merck 2007 NDAC Briefing Document[45] and Horak et al. (2009).
Abbreviations: EEU, environmental exposure units; NDAC, Nonprescription Drugs Advisory Committee; PE, phenylephrine; PSE, pseudoephedrine; PL, placebo

3.3.1.2 Study P04822 (Day et al. 2009)

This was a single-center, randomized, double-blind, double-dummy, placebo-controlled, three-arm parallel-group single-dose study that compared the efficacy of a loratadine-montelukast (L/M) combination, PE, and placebo in patients with adult seasonal allergic rhinitis (SAR) who were exposed to ragweed pollen in the EEU setting. It was conducted at Kingston General Hospital, Kingston, Ontario, Canada, and funded by Schering-Plough/Merck Pharmaceuticals, Kenilworth, New Jersey.

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

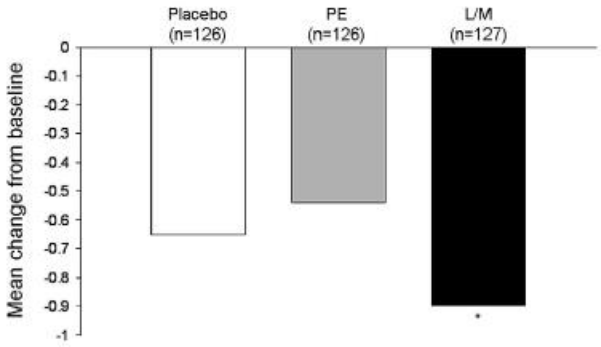
(itching/burning eyes, tearing/watery eyes, and itching of ears/palate) using a 0 to 3 severity scale (0=none, 1=mild, 2=moderate, and 3=severe) at 30-minute intervals.

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 study drug was administered at 120 minutes. Treatments included IR L/M 10 mg/10 mg tablets, IR PE 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 the L/M combination 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%), white (94 to 100%), nonasthmatic (83 to 89%), and ~33 years of age. While the L/M results were favorable to placebo, the PE results were not, both in mean change from baseline and at most timepoints starting at 1 hour posttreatment (Figure 14). Similar results were seen for PNIF (Figure 15).

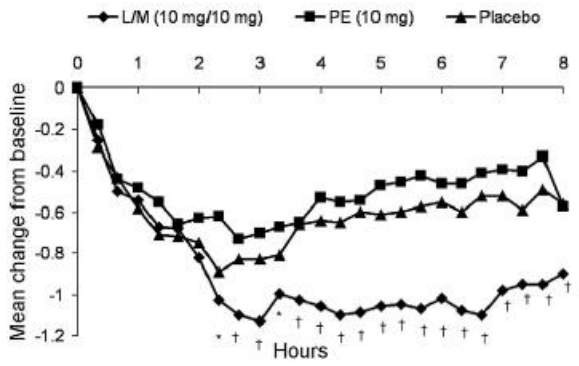
Figure 14. Study P04822. Mean Change From Baseline During the First 6 Hours After Treatment (A) and Across Time (B) in Nasal Congestion Scores for the Loratadine-Montelukast (L/M), Phenylephrine (PE), and Placebo Groups

A.



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

B.

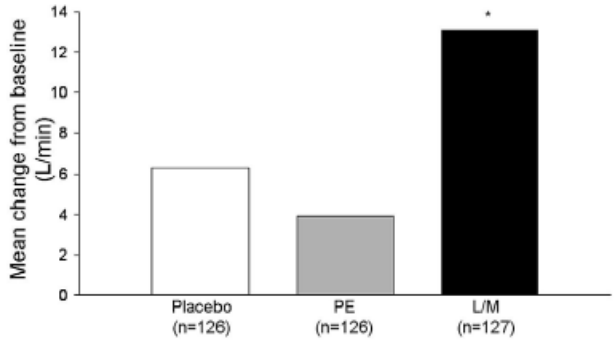


*P<0.01 L/M vs PE. †P<0.01 L/M vs PE and placebo.

Source: Day et al. (2009).

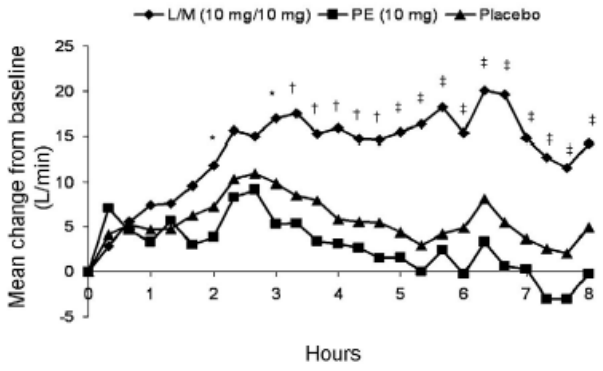
Figure 15. Study P04822. Mean Change From Baseline During the First 6 Hours After Treatment (a) and Across Time (B) in Peak Nasal Inspiratory Flow for the Loratadine/Montelukast (L/M), Phenylephrine (PE), and Placebo Groups

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).

3.3.2 New Clinical Trials

3.3.2.1 Preface to Merck's Two Clinical Trials

Before presenting the information in the following sections, it is helpful to review the publicly available data information with respect to understanding why Merck (under MSD Consumer Care) conducted these two large clinical trials. These trials and their results are listed at clinicaltrials.gov, and the results were published in peer-reviewed journals (see references and links below)[51], and all the information in these sections is from open sources.

Readers of this document will recall that the same sponsor(s), Schering-Plough and Schering-Plough Merck, presented at the 2007 NDAC meeting. Schering-Plough presented clinical pharmacology data

[51] Note: The name was changed Care from Schering-Plough Healthcare Products to MSD Consumer in 2011, so all of the studies were conducted by the same company.

showing that orally administered PE is metabolized during absorption such that less than 1% of the parent is bioavailable, and receptor affinity data showing that only the parent is active. Schering-Plough Merck conducted two EEU studies showing no effect from monographed doses of oral PE, and presented their results at the 2007 NDAC meeting. [redacted] What is missing, however, is any interim study to justify the doses investigated, which we have attempted to fill in with publicly available data.

In the publication for the large 10 to 40 mg IR trial, the authors note that the maximum dose (40 mg) chosen for this trial was based on previous phase 1 safety trials that are said to have found "no significant effect on systolic blood pressure (SPB) or heart rate (HR: MSD Consumer Care, Inc, data on file)" at the 40 mg dose level (Meltzer et al. 2015). This is consistent with data from prior safety studies (presented in Section 2.1.1) showing that clinically relevant PD changes in BP and HR are only noted at doses of 80 to 100 mg and above. However, the safety studies referred to in the publication are not listed at clinicaltrials.gov, although studies were not required to be listed at clinicaltrials.gov until April 2017[52], and the publication does not discuss other reasoning for the doses studied. That said, considering the risks associated with PPA use (as well as why PPA was never included in the FM and was removed off the market in 2006), namely due to hemorrhagic stroke in women of childbearing age, in order to have a viable product for OTC use there must be a margin of safety that limits risk to the consumer. Based on publicly available PD data, the Agency believes that Merck was wise to limit the IR study to 40 mg, i.e., that studying a dose that is about half the dose associated with known systolic blood pressure changes makes clinical sense. For the same reason, we believe that doses higher than 40 mg would not be viable for use in the OTC setting.

Similarly, publicly available data also show that Merck conducted two preliminary studies using the 30 mg ER tablets prior to conducting the large ER trial discussed below. Those studies are listed at clinicaltrials.gov and include the following:

1. Safety Study Comparing Phenylephrine HCl Extended Release Tablets 30 mg and Placebo. (Study identifiers: Merck identifiers: CL2007-07, P07529; NCT00874120[53]). This was a randomized, double-blind, placebo-controlled, multiple-dose crossover ambulatory blood pressure safety study conducted in 2009. The study compared 7 days of treatment with a 30 mg ER oral PE product 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% were males. The primary outcome was average SBP readings for a 5-hour range around the time of maximal concentration. No meaningful differences in mean SBP (SD) were noted between the two treatment arms: 118.3 (9.24) and 118.6 (9.38) for the 30 mg ER and placebo arms, respectively.
2. Bioequivalence of Single Dose Phenylephrine Extended Release Tablets and Phenylephrine HCl Immediate Release Tablets Dosed Every Four Hours (study identifiers: P08340, NCT01354418).

[52] The statutory requirements went into effect on September 27, 2007, and were codified at Section 402(j) of the Public Health Service Act with conforming amendments to the Food, Drug, and Cosmetic Act. However, the regulation became effective on January 18, 2017, and responsible parties have been required to be in compliance starting April 18, 2017.

[53] Results available at clinicaltrials.gov: https://clinicaltrials.gov/ct2/show/NCT00874120.

> While no results are listed at clinicaltrials.gov for this study, the publication of the large Phase 3 extended-release trial (Meltzer et al. 2016) refers to the results as follows:
>
> "A preliminary phase 1 randomized bioequivalence study showed that 30 mg of PEH-modified release (MR) (treatment A) failed to be bioequivalent to three 10 mg IR tablets dosed 4 hours apart in fasting adults (treatment C). The study measured plasma concentrations of parent PEH. The criteria for bioequivalence were not met because the ratios of means and their 90% confidence intervals were not contained within the 80% to 125% acceptance range; the ratio of geometric means for area under the plasma concentration-time curve (nanograms per hour per milliliter) for treatment A versus C was 139.86% (90% confidence interval 124.99e156.48), indicative of a higher exposure of parent PEH attainable with a single dose of 30 mg of PEH-MR compared with 3 doses of 10 mg of PEH-IR (MSD Consumer Care, Inc., Memphis, Tennessee; data on file)."

[redacted]. But, as discussed in the sections below, both trials failed to meet their prespecified endpoints.

3.3.2.2 Dose-Ranging Trial (Merck Protocol #CL2010-06; NCT01330017)

This dose-ranging trial 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 IR PE or placebo in 539 otherwise healthy adults with SAR caused by spring allergens. Based on our review, we consider the trial to have been a late-Phase 2 study, which likely would have been followed by a pivotal Phase 3 trial if it had been successful.

The trial was conducted between March and June 2011 at multiple centers in the United States, funded by Merck & Co., Inc., Kenilworth, New Jersey, and the results were published in a peer-reviewed journal in 2015 (Meltzer et al. 2015) and posted at clinicaltrials.gov[54]. [redacted]. What follows is a summary based on careful review of the results posted at clinicaltrials.gov and the publication.

After a 4-day run-in, subjects (i.e., patients with a documented history of SAR) were randomized to one of five treatment groups of 10, 20, 30, and 40 mg of IR PE tablets or unmatched placebo tablets, administered every 4 hours with not more than six doses in 24 hours for a period of 7 days, and followed-up at the end of treatment and by phone at 3 to 4 weeks. Loratadine 10 mg 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. Reflective nasal congestion symptom scores, assessed on a 4-point, 0 to 3 scale (where 0=absent and 3=severe symptoms), were captured on a paper diary every 12 hours prior to the next dose during the run-in and treatment

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

periods, and instantaneous congestion symptom scores (same scale) were captured once daily prior to the morning dose over the treatment period.

Blinding was as follows. All subjects received PE HCl 10 mg (up to four tablets per dose), placebo (up to five tablets per dose), and loratadine (one tablet daily). Because the PE 10 mg and placebo tablets were red and concave but not exactly matching, the trial is referred to as having been a Phase 2, 'open-label' trial in the publication. However, the listing at clinicaltrials.gov makes clear that all subjects, regardless of treatment allocation, received up to five tablets of [unmatched] placebo, the exact numbers of active and control depending upon randomization to study treatment (i.e., the trial used a so-called 'single-dummy' technique to assist with blinding). Therefore, it could be considered to have been blinded with respect to study subject allocation and study personnel handling of both the treatments and results because both subjects and study personnel were blinded as to treatment allocation (more on this below).

The primary efficacy endpoint was the mean change from baseline in daily reflective nasal congestion scores (rated on a 4-point scale where 0=none and 3=severe), which was defined as the average of morning (AM) and evening (PM) reflective nasal scores over the entire treatment period. Baseline for reflective scores was defined as the average of the daily scores over the four consecutive 24-hour periods prior to randomization, and baseline for instantaneous (secondary endpoint) scores was the Day-1 predose first dose assessment. This [primary] endpoint is acceptable, as it has been used over the last 20+ years successfully as part of the primary endpoint for numerous drug development programs of antihistamines and intranasal drug products and followed the recommendations published in the FDA Guidance for Industry on Development of Drugs for Treatment of Allergic Rhinitis (FDA 2018).

Secondary endpoints included:

- Mean change from baseline in AM and PM reflective symptom scores.
- Mean change from baseline in instantaneous symptom scores.
- Mean change from baseline in daily reflective symptom scores.
- Mean change from baseline in daily instantaneous symptom scores.
- 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.

Powering and statistical analyses were as follows. Using a two-sided test with 5% significance level and a standard deviation of 2.0 units, 100 subjects per arm were calculated to provide a 94% power to detect a difference of at least 1 unit between PE and placebo for the primary endpoint. 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. Control for multiple comparisons between each of the four active doses and placebo for the primary efficacy end point was achieved via a closed family of tests, each at the 0.05 level of significance, proceeding in sequence from the highest to the lowest dose.

A total of 539 subjects were randomized, 109, 108, 107, 112, and 103 to the 10, 20, 30, 40 mg, and placebo groups, respectively, and a total of 507 subjects completed the study, 101, 101, 99, 100, and 100 in the 10, 20, 30, 40 mg, and placebo groups, respectively. Most discontinuations (32) were due to other reasons, and only one was due to a protocol violation. A total of six subjects discontinued due to an AE, 0, 1, 1, 4, and 0 in the 10, 20, 30, 40 mg, and placebo groups, respectively. Only a small number (15) of subjects had a major protocol deviation, of which 5 were due to not meeting inclusion criteria, 4

were due not following procedures, and 3 were due to having received incorrect dosing. The intent-to-treat (ITT) and safety populations (n=539) included all randomized subjects, and efficacy evaluable population (n=517) included all subjects who had at least one full day of nonmissing reflective symptom scores after dosing was initiated.

Demographics and baseline characteristics of the treatment groups were similar (see publication Table 1 for details). Overall, 325/539 (60.3%) subjects were female, 422/539 (78.3%) were white, and 447/539 (82.9%) were non-Hispanic/Latino. The mean (SD) age was 38.7 (12.04) years.

Efficacy results for the ITT population (defined as all randomized participants who received at least one dose of study medication) are summarized in Table 8 and shown graphically by treatment group and day in Figure 16. 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 PE HCl 10, 20, 30, 40 mg, and placebo groups, respectively. None of the active treatment groups had a statistically significant change from baseline in reflective nasal congestion 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 significant secondary endpoint was the change from baseline in PM reflective nasal congestion scores for the 20 mg PE HCl 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 HCl 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 active 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 treatment-emergent AEs was nervous system disorders, reported in 30 of 539 [5.6%]) of all treatment groups, but only in 2 of 103 (1.9%) of placebo-treated subjects. The most common treatment-emergent AE was headache. However, it was not dose related, occurring in 5.5% (6/109), 3.7% (4/108), 2.8% (3/107), and 2.7% (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 dosage level, 2.7% (3/112) and 3.6% (4/112) of patients experienced gastrointestinal side effects of dry mouth and nausea, respectively. One patient in the 40 mg dosage group experienced chest and lower jaw pain that resolved after stopping PE.

It could be said that one drawback to this trial was that the study was considered to have used a partially open-label design because placebo was similar to but not exactly matched with active product. However, the major concern with lack of blinding occurs when a difference between one of the active treatment groups and control (placebo) is found, because the lack of binding could introduce a treatment group bias, i.e., a bias that favors finding a difference between active and control. In this case, the addition of a partial dummying technique to the study assisted but did not completely blind the study, because subjects could count the number of different pills although they would not necessarily know what the numbers meant. For example, if a subject received four of one tablet and one of another, or three of one tablet and two of another, the subject could reasonably assume that they had been allocated to 10 or 40 mg in the first instance, or 20 or 30 mg in the second. However, the case of

receiving five of the same tablets is unique. In addition to knowing that the maximum dose was 40 mg and that each PE tablet was 10 mg, the subject would also have to know that PE and placebo tablets were similar but not identical to discern that they had been allocated to placebo. Otherwise, they would be fully blinded. What is missing here is what subjects in the study were told, as that information is not in either the publication or listed at clinicaltrials.gov, so we simply do not know. That said, 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.

A second drawback is that an active comparator arm, such as PSE, was not included. 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 treatment groups, including dosages up to four-fold the monographed dosage of oral PE HCl, lends credence to the results.

After careful review, we conclude that this study is of high quality (Level 1 evidence) and accurately portrays the treatment effect of orally administered IR PE, including dosages up to four times the monographed dosages.

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

	PE HCl 10 mg	PE HCl 20 mg	PE HCl 30 mg	PE HCl 40 mg	Placebo
Parameter	N=109	N=108	N=107	N=112	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 2015 Meltzer publication and results published at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT01330017).

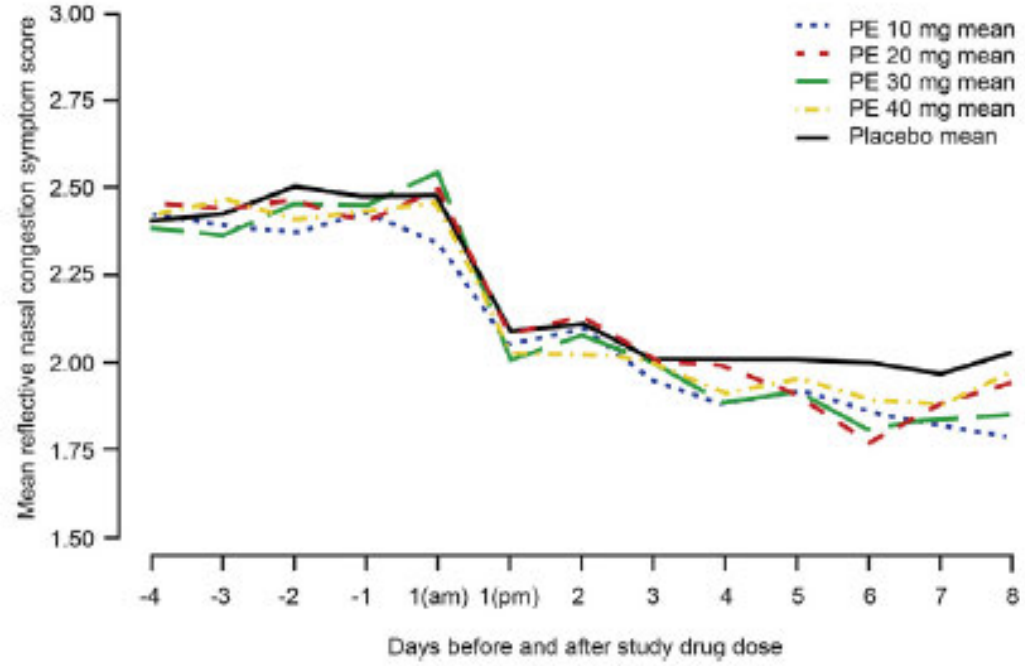
* Reflective nasal congestion scores were captured in participant diaries just before the 8:00 a.m. dose and 12 hours later just before the 8:00 p.m. dose. Participants rated congestion on a 4-point scale of severity from 0 (best) to 3 (worst), with 0=absent symptoms, 1=mild symptoms, 2=moderate symptoms, 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 medication.

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

Figure 16. Merck Protocol #CL2010-06. Reflective Nasal Congestion Scores by Treatment and Study Day (ITT Population)



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

3.3.2.3 Modified-Release 30 mg Trial (Merck Protocol CL2011-06; NCT01413958)

This trial was a Phase 3, 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. While this trial did not use monographed dosages of PE, it nevertheless provides substantive evidence that PE is not effective as an orally administered decongestant, particularly in light of the fact that their bioequivalence study demonstrated higher systemic exposure with 30 mg of PEH-MR compared to 10 mg IR PEH dosed every 4 hours (the monographed dose). After review, we consider that this was likely intended to be a pivotal, Phase 3 study to support a 505(b)(2) application for their extended-release PE product.

The study was conducted between August and October 2011, at 29 study sites, and funded by Merck & Co., Inc., Kenilworth, New Jersey. The results were published in 2016, in a peer-reviewed journal by the same authors as the dose-ranging trial (Meltzer et al. 2016) and posted at clinicaltrials.gov.[55] What follows is a summary based on careful review of results posted at clinicaltrials.gov and the publication.

Study visits included: 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 Guidance, subjects were washed out of any allergy medications that might interfere with study evaluations and recorded reflective and instantaneous nasal congestion symptom scores (on a 0 to 4 scale where 0=none, 3=severe) starting approximately 7 days prior to start of study treatment and extending through the

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

entire treatment period. During study treatment, patients were allowed rescue loratadine 10 mg once daily as needed for intolerable allergic-rhinitis symptoms.

The primary efficacy endpoint was the mean change from baseline in daily reflective nasal congestion scores, defined as the average of morning and evening reflective nasal scores over the 7-day treatment period for the ITT population, which comprised all randomized subjects who received at least one dose of the study medication.

Secondary efficacy measurements included:

- Mean change from baseline in morning and evening reflective symptom scores, daily instantaneous symptom assessment scores, and morning predose instantaneous nasal congestion symptom score (to assess 12-hour duration of action).
- Mean change from baseline for each day for reflective symptom assessment score (to assess onset of action and durability of response), morning and evening reflective and instantaneous symptom assessment scores (calculated and analyzed separately), and 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).

Powering and statistical analyses were as follows. Using a two-sided test with 5% significance level and a standard deviation of 2.0 units, 500 subjects were calculated to provide a 94% power to detect a difference of at least 1 unit between PEH-MR and placebo for the primary endpoint. 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 patients were enrolled and randomized, 288 to PEH-MR and 287 to placebo, and 574 (99.8%) completed the study. Demographics and baseline characteristics of the treatment groups were similar. Participants were mostly female (61%) and white (82%), with a mean age of 40.1 years (see publication Table 1 for details). Mean study compliance was 99.5% and there were no differences between study groups in rescue loratadine use.

The primary efficacy results (mean change from baseline in reflective nasal symptom scores for the ITT population), summarized numerically in Table 9 and graphically in Figure 17, showed no statistically meaningful difference between the active 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 18, clearly demonstrate that active treatment was numerically no better than placebo at any timepoint in the trial. And in fact, while the baseline score for placebo was numerically lower than the active treatment arm, the placebo arm also had numerically more mean improvement over the course of the study (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 treatment-emergent AEs was nervous system disorders (overall 4.0% [23/575]), and the most common treatment-emergent AE was headache, occurring in 3.1% (9/288) and 2.8% (8/287) of the PEH-MR and placebo groups, respectively.

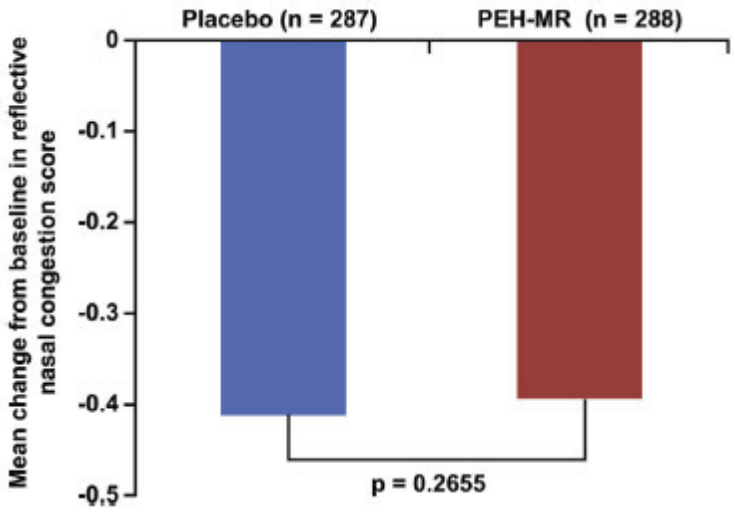
After careful review, we conclude that this study provides high-quality (Level 1) evidence that PE is not an effective nasal decongestant when administered orally in a 30 mg ER formulation that results in systemic exposures that are slightly above the exposures provided by repeated monographed (10 mg) IR dosages.

Table 9. Merck Protocol #CL2011-06. Change From Baseline in Reflective Nasal Congestion Scores Over the Entire Treatment Period (ITT Population)

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 (04880)	-0.412 (0.5383

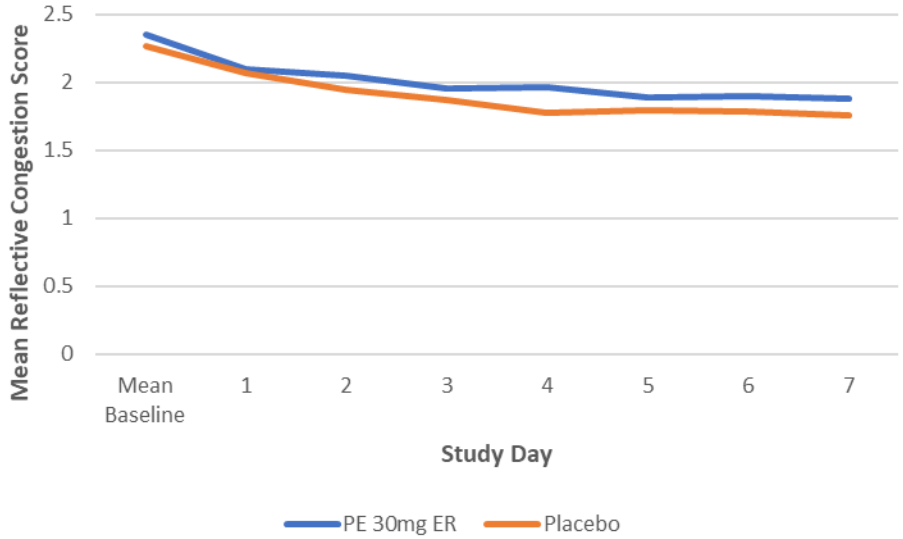
Source: Results published at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT01413958).
Abbreviations: ITT, intent-to-treat; PEH-MR, phenylephrine hydrochloride-modified release

Figure 17. Merck Protocol #CL2011-06. Mean Change From Baseline in Reflective Nasal Congestion Score Over the Entire Treatment Period (ITT Population)



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

Figure 18. Merck Protocol #CL2011-06. Mean Daily Reflective Nasal Congestion Score at Baseline* and Per Day (ITT Population)



Source: Adapted from results published at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT01413958).
* Baseline was defined as the mean from 4 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 participant's diary during the run-in and treatment periods. Participants rated congestion on a 4-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

3.3.2.4 Johnson and Johnson Phase 2 Study (CO-170302131230-URCT; NCT03339726)

This study was conducted by Johnson & Johnson Consumer, Inc. in Canada during the 2017 to 2018 cold season. It was a randomized, double-blind, double-dummy, placebo-controlled, parallel-group study that evaluated the efficacy of an extended-release 30 mg PE oral tablet taken twice daily and an immediate-release 12 mg PEH oral capsule taken four times daily in subjects with nasal congestion due to the common cold. After review, we cannot comment on the exact intent of this study, although it initially appears to have been designed as a Phase 3 study to support approval of an extended-release PE product to be marketed outside the United States.

This study is the only PE efficacy study that we are aware of that has been conducted in subjects with colds since the original panel studies. Unlike the original studies, it used symptom score rather than NAR as the primary endpoint. The study had planned to enroll 450 subjects, a sample size that would have allowed it to support an application for an ER product, although from the fact that it was conducted in Canada and used a 12 mg IR oral PE comparison arm, not necessarily in the United States. For this reason, we believe that the study was designed in a manner as to minimize bias and provide accurate results Unfortunately, the study was only able to enroll 193 subjects prior to the end of the cold season, at which point an interim analysis was conducted and the study was terminated. Further, a positive control arm was not included. Therefore, while a much larger and better controlled than the original panel studies, it is nevertheless not ideal. The only source available for this study is a listing on

clinicaltrials.gov. As a result, certain data are not available, such as baseline values for each treatment group. That said, clinicaltrials.gov includes a redacted protocol and SAP.[56]

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 lease 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.

Treatments included: two doses of extended-release PE (PE-ER) 30-mg tablets 12 hours apart, four doses of immediate release PEH (PE-IR) 12 mg capsules 4 hours apart, and four doses of placebo 4 hours apart. Since the study included a double-dummy design, 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 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 online information.

The primary outcome measure 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 8-point scale where 0=none and 7=severe, with assessments at 2, 4, 6, 8, 10, and 12 hours. The primary efficacy endpoint was analyzed for the ITT population using an ANOVA model with treatment group, study center, and baseline nasal scores as factors.

Secondary efficacy endpoints included:

- Average change from baseline in the Nasal Congestion Severity Score (time frame: 0 to 12 hours) (8-point scale with 0=none and 7=severe).
- Average change from baseline in the Nasal Congestion Severity Score averaged over hours 8 to 12.
- Change from baseline in the Nasal Congestion Severity Score (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 study participants were female (63.2%) and either white (78.2%) or Asian (13.0%), and demographics were similar between the three arms.

Results are shown in Table 10, and graphically over the course of the study in Figure 19 and Figure 20. No benefit was seen for the primary endpoint. A note about the figure is in order. It graphically shows the change in nasal congestion severity scores adapted from data provided at clinicaltrials.gov. However, the results provided at clinicaltrials.gov do not state whether the changes are listed as improvements or getting worse with treatment, i.e., as absolute or relative congestion score changes. The fact that the scores increased over the course of 24 hours of treatment (shown as an upward trend in Figure 20) might imply that these were absolute and not relative changes, as one might reasonably expect all subjects to report an improvement with treatment over the course of the study regardless of

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

treatment allocation, and improvement in scores would be illustrated as downward trend lines toward milder congestion scores (see figures in the two Merck trials above, where the result lines for all treatment arms trended downward toward lower, i.e., milder congestion scores). That said, the fact that this was a cold and not an allergic rhinitis study might conceivably have made a difference if subjects were continuing to get worse during the 24 hours that they were on treatment. Regardless of direction (up or down, worse or better), however, the results for all treatment arms trend in a similar direction, which suggests no beneficial effect of either PE treatment when compared with placebo.

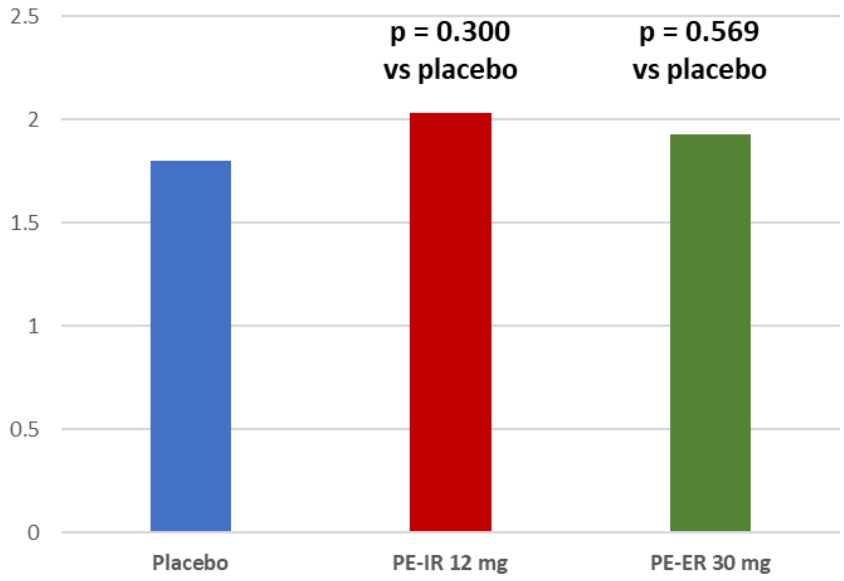
With regard to safety, no adverse events were reported.

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

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

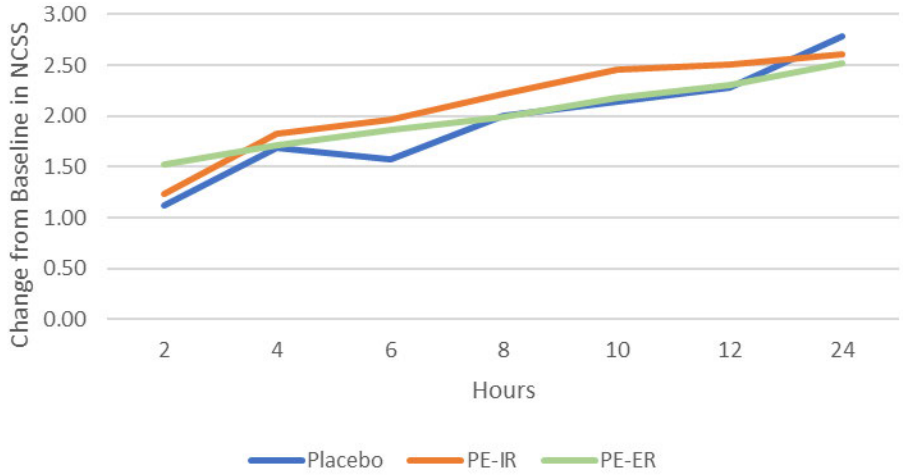
Source: https://clinicaltrials.gov/ct2/show/NCT03339726.
Abbreviations: CI, confidence interval; ER, extended release; IR, intermediate release; J&J, Johnson & Johnson; NA, not applicable; PE, phenylephrine

Figure 19. J&J Study NCT03339726. Primary Endpoint of Mean Change From Baseline in NCSS Over 12 Hours



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

Figure 20. J&J Study NCT03339726. Change From Baseline in NCSS Over 24 Hours*



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

3.3.3 Original Panel Studies

3.3.3.1 Scope of the Review

We reviewed each of the study reports and/or publications for all the original studies that had been submitted to the docket and reviewed by the Panel to support oral PE use. Fourteen such documents were stated to have been reviewed by the Panel to support the effectiveness of oral PE (references 5 to 10, 19 to 26). Unfortunately, several of the references are problematic, either citing an abstract instead of the complete study (reference 25; see discussion in the Appendix, TFM Comment 11), or the wrong study (reference 19 instead of reference 10). As part of our review, we attempted to sort out and address each of these as well.

We also reviewed the findings of the previous FDA statistical review of these and additional studies (as well as the meta-analyses) that were presented at the 2007 NDAC meeting (see the FDA Statistical Presentation section above). The FDA statistical reviewer concluded that the original studies should be judged as inconclusive of efficacy, and at a minimum, we concur. However, the statistical reviewer appears to have focused on the meta-analyses performed by the petitioners and industry, and less so on the original studies themselves. Thus, the reviewer did not comment on a number of significant methodological and statistical issues, as well as potential data integrity issues, with the studies.

3.3.3.2 Preface: Agency's Comments on the Panel's Findings

Prior to presenting our findings, it is important to note that we believe that the Panel did an admirable job, given the quality of the data that was submitted to them. That said, the science has evolved since that time. When considering the studies through a modern drug review lens, all of the studies (both positive and negative) were highly problematic in both design and methodology. All used a highly variable endpoint (NAR) to study a drug in the setting of a highly variable disease state (the common cold) that is no longer used as a primary endpoint to evaluate congestion in pivotal trials.[57] Further, all

[57] The FDA's Guidance for Industry on Developing Drug Products for Treatment of Allergic Rhinitis recommends use of symptom scores for the primary endpoint in clinical trials. See FDA (2018).

the positive studies (and most of the negative studies) were unpublished and therefore never peer-reviewed. Six of the seven positive studies came from a single study center (funded by the manufacturer of Neo-Synephrine), were very small in size, and (except in one instance) the results could not be duplicated at two other study centers (also funded by the same manufacturer) that used a similar study design and methodology.

Additionally, the positive oral PE results do not match what was demonstrated in multiple studies reviewed by the Panel that the dose of orally administered PE that is required to result in clinically relevant systemic (pharmacodynamic) effect is far higher than the monographed dose. Nor do they match what is now known about the bioavailability and PK of orally administered PE. As a result, and in retrospect, we believe that newer data and improvement in study methodologies suggest that the findings of the Panel should be revisited.

And, in fact, we believe that the multiple methodological and statistical issues inherent in the studies reviewed by the Panel make the original studies evaluated for efficacy unacceptable as continued support for the efficacy of monographed doses of oral PE.

3.3.3.3 Preface: Study Context

In order to understand how the original studies fit within the context of today's study design/conduct and review standards, it is important to understand the context / setting in which the Panel reviewed the data submitted to them as well as the advances that have occurred on multiple levels since that time. At the time, PEH had been marketed OTC for many years as an oral nasal decongestant, so there was significant experience with it in this setting.[58] Further, the Panel simultaneously reviewed the data for PE as an intranasal decongestant (i.e., when administered intranasally) and recommended that it receive a GRASE determination at the same time that they reviewed orally administered PE as a nasal decongestant. Knowing that PE is highly effective when administered by the intranasal route may have influenced their decision about PE when administered orally.

This was also a different time, and the understanding of how to design and conduct clinical trials to support the efficacy and safety of a drug has advanced significantly in the interim, including but not limited to sample size calculations, methodology to prevent bias, evaluation of endpoints, and use of different subject populations. In fact, the Panel's review was conducted many years before any of the ICH Good Clinical Practice guidelines / quality standards for the design, conduct, recording, and reporting of trials that involve human subjects were developed.[59]

Finally, the science has changed in the interim, and a full understanding of the clinical pharmacology of PE when administered orally was not appreciated at the time that the Panel issued its recommendations. We now know that in addition to PE having less than 1% systemic bioavailability, the

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[58] According to Wikipedia (https://en.wikipedia.org/wiki/Phenylephrine), phenylephrine was first patented in 1927, and came into medical use in 1938. The leading manufacturer at the time that the FDA first conducted an efficacy review was Sterling-Winthrop, the manufacturer of Neo-Synephrine.

[59] The ICH, or International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, was started in 1990, and has gradually evolved to respond to the increasing global development needs of the pharmaceutical industry. See: https://www.ich.org/. FDA participates in this process; see ICH E6, available at: https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/ich-guidance-documents, which contains guidance on the current ethical and scientific quality standards for designing, conducting, recording, and reporting of trials that involve human subjects.

half-life is also significantly shorter than the original 4-hour dosing interval. These data were not available to the Panel, nor was the technology to fully assess oral bioavailability available until around the turn of this century. Therefore, is it not surprising that the Panel considered the equivocal findings in the original studies as sufficient to support a finding of efficacy (and safety) of PE 10 mg administered orally every 4 hours.

3.3.3.4 Methodological and Statistical Issues

3.3.3.4.1 Design and Methodology

The principal methodology used to assess efficacy in all of the studies evaluated by the original Panel was measurement of airflow and air pressure in the nasal passage, which was used to calculate NAR as an indirect measure the level of congestion. As a result, a word about the methodology is in order. Objective measurement of NAR to assess nasal airway patency is a complex procedure that is subject to multiple methodological issues including (but not limited to) 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. Because of the inherent variability and methodological issues, NAR measures are at best mechanistic in nature. In an effort to standardize the technique, several methodologies were published. Many of the studies submitted to and reviewed by the Panel used a modification of a methodology referred to as the Butler-Ivy technique published in 1943 (Butler 1943), and four of the seven positive studies specifically mention use of a modified version of this technique.[32]

That stated, with the exception of the studies reviewed by the Panel and discussed in the ANPR, we are not aware of any NAR studies that have been accepted by the Agency in support of the development of any drug since that time, even as part of Phase 1 drug development. Instead, clinical symptom scores have been / are considered by the Agency to be the gold standard for development of all allergic rhinitis drugs developed in the last >30 years.[60] While symptom scores were used in the studies considered by the Panel, the results were not the primary efficacy endpoint in any of the studies and were generally not even considered if the NAR results were negative.

One example of the inherent variability in the use of NAR as an endpoint was available to and cited by the Panel, but only for safety (McLaurin et al. (1961), reference 11).[61] It was a placebo- and active-controlled (ephedrine 25 mg, PSE 60 mg, PE 10 mg, and PPA 25 mg) double-blind, crossover study (88 subjects). Goals included the PD response to each drug, subjective therapeutic effect, adverse reactions (what they called side effects), NAR improvement at 60 minutes, and how close the subjective findings matched the objective ones. However, the study failed to demonstrate any positive NAR findings for PE, PPA, or PSE, although it did demonstrate some effect from ephedrine (see description in Table 15). For this reason, it was not considered in the effectiveness discussion, while at the same time it illustrates

[60] Nasal inspiratory flow rate has not been accepted by the Agency as a primary endpoint variable for approval of any prescription cough-cold drugs since at least prior to the 1990s. All of the topical intranasal drugs and second generation H_1 blockers (antihistamines) approved in the 1990s and since have used nasal symptom scores as the primary endpoint. See the corresponding FDA Guidance for Industry; FDA (2018).

[61] Cough-Cold ANPR, 41 FR 38312 (September 9, 1976) at 38400, reference 11: McLaurin et al. (1961).

the methodological issues with use of NAR as an endpoint, including that two ingredients that are generally considered to be effective as oral decongestants failed to show a positive effect.

Because the endpoint of NAR has not been used in drug development in the modern era, some retrospective thoughts are also in order to place the information into the appropriate clinical as well as statistical context. As stated above, the Agency is aware that there is significant variability in this endpoint, and that the variability and quality of results are highly dependent on multiple technical issues related to the testing process. However, the exact magnitude of that variability is unknown. As a result, from a statistical viewpoint one cannot perform an appropriate [retrospective] sample size calculation for studies that used this endpoint. Similarly, we have no current experience with this endpoint to ascertain the magnitude of difference between active and placebo might be clinically meaningful, and we have not been able ascertain this information from the literature. However, it is likely that the magnitude of the variability is so great that a very large sample size would have been needed to show a meaningful statistical or clinical difference between study drug (PEH) and control (placebo). Even the largest study, BEI 1025, only evaluated 25 subjects per arm (in a parallel design) with NAR as the primary endpoint. The bottom lines is that we believe the sample sizes for all of the original studies were far, far smaller than what is likely to have been needed to obtain either statistically or clinically meaningful results.

3.3.3.4.2 Disease Context

One should also consider the disease platform that was used to study the efficacy of oral PE, as decongestants are accepted as treatment of congestion in patients with both colds and allergic rhinitis. All but one of the studies evaluated subjects in the setting of the common cold. In order to qualify, subjects had to have two days of congestion symptoms, which was followed in most instances with two days of testing of the alternative treatment in a crossover design. Use of the common cold for studying congestion is a platform known to be highly variable, thereby creating significant variability in the results. In fact, one study (not reviewed by the Panel) noted differences in NAR results over days 1 to 5 in subjects who were experiencing upper respiratory infection symptoms (Bickerman 1971). Whereas, patients with allergic rhinitis often have congestion for considerable periods of time, thereby resulting in a far more stable platform even for single-dose or short-term studies such as these.

3.3.3.4.3 Conduct

Going beyond the methodology used to evaluate nasal congestion, the design and conduct of these studies is also a major issue. As mentioned earlier, all were conducted at a time when ethical and quality standards for the design and conduct of clinical trials involving human subjects were essentially nonexistent. In fact, one could even consider that it was the DESI process itself that highlighted deficiencies in the standards for such studies, leading to the eventual international recognition that such standards were needed (and the formation of the ICH in 1990). So, it is not surprising to find that, when considered by modern standards, there are significant deficiencies when reviewing the design and conduct of these studies, as outlined further below.

3.3.3.4.4 Statistical Issues

From a statistical point of view, we also found multiple issues. All except one of the studies (see the Original Cough-Cold Advisory Panel Recommendations section for details) were small, crossover, single-center studies. All evaluated very small sets of subjects (see Table 3, which shows the remarkably small N's in the 10 Sterling-Winthrop studies that comprised 6 of the 7 positive studies, and Table 2 for the

other studies). Other than blinding, methodology to reduce bias was not discussed in any of the study reports. Statistical endpoints and methodology were not explicitly presented, nor was a sample size calculation discussed in any of the study reports. Given the known variability of the endpoint being used and disease state being studied, any reasonable sample size calculation would likely yield the need for sample sizes that are many, many times larger than employed in any of the studies. Finally, statistical analyses appear to have been performed at each time point without adjustment for multiplicity.

3.3.3.4.5 Sterling-Winthrop Studies

The 11 studies submitted by Sterling-Winthrop[62], the manufacturer of Neo-Synephrine brand of phenylephrine hydrochloride, represent six of the seven studies considered by the original Panel to have demonstrated the effectiveness of oral PE. Therefore, they likely influenced the original Panel's efficacy conclusions and recommendations. As noted elsewhere, one study (NAPR reference 5) was a descriptive, preparatory study for the rest of the studies and should be ignored.

The other ten (ANPR references 6 to 11 and 20 to 24) were very small, single-dose, double-blind, placebo-controlled, single-center, two-way crossover studies in subjects with the common cold. These 10 studies were conducted at three different research laboratories, Elizabeth Biochemical Labs, Cintest Division of Hill Top Laboratories in Cincinnati, and Huntingdon Research Center, and all of the study reports were prepared by the Sterling-Winthrop Research Institute in Rensselaer, NY. All were unpublished study reports, and as such they were never peer-reviewed. Additionally, to our knowledge, none of the protocols were submitted to the docket, and therefore could not be reviewed as part of our retrospective review.

All 10 used similar protocols and methodology, the major differences being the doses (between 5 and 25 mg) and comparator ingredients evaluated. The oral PE doses and numbers of subjects studied at each dose level are shown in Table 3, which shows the number of completed subjects at each oral PE dose level in each of the studies. It will be seen that the total number of subjects enrolled at any given dose was remarkably small and likely far too small to yield meaningful results. Further, several did not enroll the planned number of subjects (Elizabeth studies 4 and 5). Given that all were performed at a time prior to when modern concepts about study design were developed, they were highly problematic in that they used the same endpoints and study populations, and had the same statistical issues, that are discussed in this section. There was also significant heterogeneity of results both within and among the three study centers, as discussed further in the Potential Data Integrity and Other Issues in the Sterling-Winthrop Studies section below. And finally, when looked at by dose studied, numerically about half of the total number of subjects studied at any given dose level failed to show efficacy (bottom of Table 3). Given the heterogeneity of the endpoint and methodology used, as well as the population that was evaluated, the number of subjects studied is far, far below the number that one would expect would be needed to demonstrate efficacy. Therefore, we consider that these studies do not live up to today's standards and do not represent an accurate description of the effectiveness of oral PE as a decongestant.

[62] Docket references 5, 6 to 10, and 20 to 24. Study reports prepared by N.A. Hulme at the Sterling-Winthrop Research Institute, Rensselaer, NY.

3.3.3.4.6 Whitehall Labs (BEI 1025) Study

The BEI 1025 study, performed by Whitehall Labs was reviewed by the original Panel, and a description of the study design may be found in the Original Cough-Cold Advisory Panel Recommendations, Whitehall Labs (BEI 1025) Study section. The study report was submitted to the docket, and the study report refers to a protocol for the study, but to our knowledge that protocol was not submitted to the docket and could not be reviewed as part of our retrospective review.

This was the only study with a parallel group design, and it was the only non-Sterling-Winthrop study that was considered to be positive. It was stated to have been a double-blind, placebo controlled, parallel group study in 200 subjects with the "common cold". All subjects received 4 doses of 10 mg of PEH or placebo over 12 hours. Whereas all 200 subjects were evaluated for symptoms, only 50 subjects (25 per arm) received rhinometry, which was the primary endpoint. These measurements were performed at 0, 15, 30, 60 and 120 minutes after the first dose. No differences were seen in systolic or diastolic BP, implying that a PD effect was not seen in this study (Figure 3). However, they did report changes in both NAR (Table 4 and Figure 2) as well as 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.

Just as for the other studies, there were issues with this study, including: that the methodology to reduce bias and the scoring methodology were not specified, and no adjustments were made for multiplicity. Since we were unable to review the protocol, it is not clear how symptoms were rated. Baseline symptoms appear to have been rated on a scale of 5 from mild to very severe, with improvement rated on a 0-2 scale with 0 being no change and 2 being much improved, and this evaluation appears to have been performed by both the subjects and investigators. However, we do not know the frequency of the scoring, whether it was instantaneous or reflective, and how much weight was placed on subjective investigator judgement, which we know is often biased and is no longer accepted by the Agency as part of drug registration trials. 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, we do not know how much the investigator reporting of symptoms influenced those results. Further, one must ask why a nasal decongestant, which would ONLY be expected to help obstructive symptoms, would also help runny nose or sneezing symptoms, which throws suspicion on the results for the obstructive symptoms. Therefore, the results of this study must be judged accordingly.

Additionally, the primary endpoint of NAR over 2 hours following the first dose was reported as percent change from baseline (Figure 2). In the figure, percent change is on the right and absolute change is on the left, and percent reduction at each timepoint is shown in Table 4. In general, percent change tens to magnify any differences, whereas absolute measurements do not. In fact, the magnitude of difference in absolute changes seen in NAR results (left side of Figure 2) were quite small, and 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). It is also important to note that the study did not specify what difference in absolute change might be clinically meaningful. Therefore, overall, the clinical value of this study is questionable.

3.3.3.4.7 Summary

After careful review, we note that there were many methodological and statistical issues with these studies. We believe that these issues significantly limit any judgement of a statistical "win", and more importantly a clinical "win", for any of these studies. In fact, if these studies were submitted to the Agency today all would at most be considered Phase 1 studies at best. As a result, we believe that these studies do not stand up to the new data that are now available with regard to the efficacy of orally administered PE as a nasal decongestant.

3.3.3.5 Negative Original Studies

A review of the original studies would not be complete without discussing the negative studies as well as the ones that were considered supportive of the GRASE determination. There were at least six negative studies of which the Panel was aware. Four of these (Huntingdon 1 and 2, and Cintest 2 and 3) were part of the 10 studies from the same sponsor, Sterling-Winthrop, and (because of the design and methodological issues discussed in the sections above) need not be discussed further. So, what about the others?

One other negative study should be briefly noted, but otherwise ignored because it is not helpful. This study was cited by the Panel, but only for safety (McLaurin et al. (1961), reference 11),[61] failed to demonstrate any positive NAR findings for PE, PPA, or PSE, although it did demonstrate some effect from ephedrine(see discussion in the Methodological and Statistical Issues section above). Therefore, the data from this study provides no useful information.

The only significant negative study among the original studies discussed in the ANPR is the failed Columbia University study discussed below.

3.3.3.5.1 Columbia University Study (Rogers / Bickerman publications)

The results of the Columbia University study may be found the Original Cough-Cold Advisory Panel Recommendations, Columbia University Study (Rogers / Bickerman publications) section. It was the only negative or failed study discussed in the ANPR. It is stated to have demonstrated no effect on NAR from placebo, 10, 20, or 40 mg of oral PEH over a 4-hour observation period, whereas PSE 60 mg and PPA 40 mg each produced significant NAR reductions persisting for at least 3 hours.

However, there are some issues with the ANPR citation, and therefore where the data cited in the ANPR originated. The ANPR cited the study as reference 25 (Rogers 1973), whereas the reference itself has no specific data to support the reported findings, and that fact was noted in a comment submitted in response to the ANPR and discussed in the TFM as Comment 11. We believe that the data originate from a previous 1971 publication by one of the same authors (Bickerman 1971), the only differences being that the older reference lacks the data from the 20 and 40 mg PEH doses and the number of subjects cited in the ANPR is different. Please see Appendix, TFM Comment 11 for ANPR Reference 25 for a full discussion.

As we reviewed the information provided in the 1971 Bickerman publication (results in Table 11 and in Figure 6), it became clear that these researchers had tried to both address and overcome some of the variables that make NAR evaluations so difficult and unreliable. First, they studied all the parameters of how to assess NAR, including how to build a NAR evaluation device that would provide reproduceable results. Second, they elected to not focus on subjects with the common cold, but rather, to focus on both healthy individuals and subjects with chronic, mostly non-atopic, nasal congestion (causes

otherwise not specified) that respond to decongestants. They started by investigating 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 as subjects experienced an upper respiratory infection (or common cold). They then studied these subjects over a period of several years, and armed with this background information, they could evaluate the effects of various decongestants in those subjects with chronic nasal congestion. This provided a much more stable platform and group of subjects in which they could conduct their trials over an extended period of time, as well as minimize the variables that could affect the results and enable them to interpret the findings with more assurance. Having their specific findings regarding lack of efficacy for the higher 20 and 40 mg doses would have been helpful, but even without those data the rest of the information is supportive of lack of effectiveness of the monographed 10 mg oral PE dose, particularly in light of the two positive controls that were also studied. One should bear in mind, however, that while these investigators attempted to address many of the significant methodological issues inherent in NAR measurements, and while their findings are perhaps more believable than the other studies described in the ANPR, NAR results are still at best to be considered as Phase 1 information.

Table 11. Bickerman 1971. Effect on Nasal Airway Resistance of Four Oral Drugs in Patients With Chronic Nasal Congestion (0.2 L/s Expiration)*

Drug	Control	½ 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 non-atopic 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 non-seasonal rhinitis, including topical placebo, oxymetazoline, and phenylephrine nasal sprays, and oral pseudoephedrine, phenylpropanolamine, phenylephrine, and placebo. Results are shown in the table and graphically in Figure 6.
Abbreviations: N, not stated; PE, phenylephrine; PPA, phenylpropanolamine; PSE, pseudoephedrine

3.3.3.6 Potential Data Integrity and Other Issues in the Sterling-Winthrop Studies

After a thorough review of all the available evidence, it is also possible that there may have been bias and/or data integrity issues at least one study center, Elizabeth Biochemical Labs, where five of the seven positive oral PE studies were conducted. That stated, it is important to note that we consider the methodological and statistical issues to be valid and overwhelming, whereas the data presented in this section is of a more speculative nature and should be considered as concerning but unproven.

Except for one additional study (Cintest 1), which also appears to have some issues (see discussion below), the results from the Elizabeth study site could not be duplicated at the two other Sterling-Winthrop study sites that used a similar study design and methodology. Nor could they be duplicated by other investigators, including in a study conducted at Columbia University, a study that was considered as "negative" by the Panel and presented by the petitioners in 2007 (see Figure 6 and the Negative Original Studies section), or in two EEU studies that were conducted by Schering-Plough using a more stable study population (subjects with allergic rhinitis), study environment, and established clinical endpoints (primary) along with a NAR endpoint (secondary) (see the EEU Studies (2007 NDAC) section).

In fact, the study reports from two studies conducted at the other two Sterling-Winthrop sites contemporaneously implied that the credibility of the results from the Elizabeth site might have been in question.

1. The study report for Cintest study #2 noted that, having failed to duplicate any of the Elizabeth results, researchers from that site visited the Elizabeth site to observe testing in an effort to understand why they were unable to duplicate the Elizabeth findings. They came away without a satisfactory answer as to what they had done differently that had produced such markedly different results.[63] Therefore, the lack of reproducibility of results from the Elizabeth site calls into question whether there were in fact bias and/or integrity issues at that study site.
2. The study report for Huntingdon study #1 contains a table (Table 12) comparing the standard deviations (SD) in the studies that had been conducted at the Elizabeth, Cintest, and Huntingdon study sites. This table was created because the investigators wanted to understand why they were unable to duplicate the results from the Elizabeth study site. While it is unclear how this table was derived and the results are not complete for each dose studied, the table nevertheless speaks for itself because it was done by the Huntingdon study site to address the question of why they could not duplicate the results from another site. One will immediately note that the magnitude of the standard deviations for the results at Elizabeth were considerably smaller than the studies conducted at the other two study sites, regardless of the drug or dose studied. It should be noted that the study report does not suggest that this information might point to an integrity issue at the Elizabeth study site. However, given the small sample size and the variability of the methodology and subject population, as well as the results of studies that have been reported since that time, the small SD of results at the Elizabeth site can only be interpreted in one of two ways. Either the results reflect excellent study management that could not be duplicated at the other two sites, which does not make scientific sense based on the PK and PD data and the known variability in the methodology, or they reflect data that are simply too good to be real. As a result, the issue of bias and possible data integrity issues at the Elizabeth site must be seriously entertained.

Table 12. Comparison of Standard Deviation Values for Decongestant Studies Conducted at Elizabeth Biochemical Labs, Cintest Labs, and Huntingdon Research Center

	Time Point (Minutes) and SD								
Product/Dose/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, ANPR Reference 20, Table II.
Abbreviation: PPA, phenylpropanolamine

[63] Cintest study 2, ANPR reference 23.

Given the information above and the considerable heterogeneity of results amongst the studies, we compared the findings from each of those studies within the context of our larger review. We again noted that the findings were highly inconsistent between two of the five studies conducted at Elizabeth Biochemical Labs (Elizabeth 1 to 5) and four of the five studies conducted at two other labs (Huntingdon 1 to 2 and Cintest 1 to 3), the exception being Cintest 1. We also noted that the three key positive studies, Elizabeth 2, Elizabeth 5, and Cintest 1 (see Table 3), all appear to have been outliers in that, not only do their results not match the results obtained in the other studies, there are internal inconsistencies such that they do not match what would be expected in such studies.

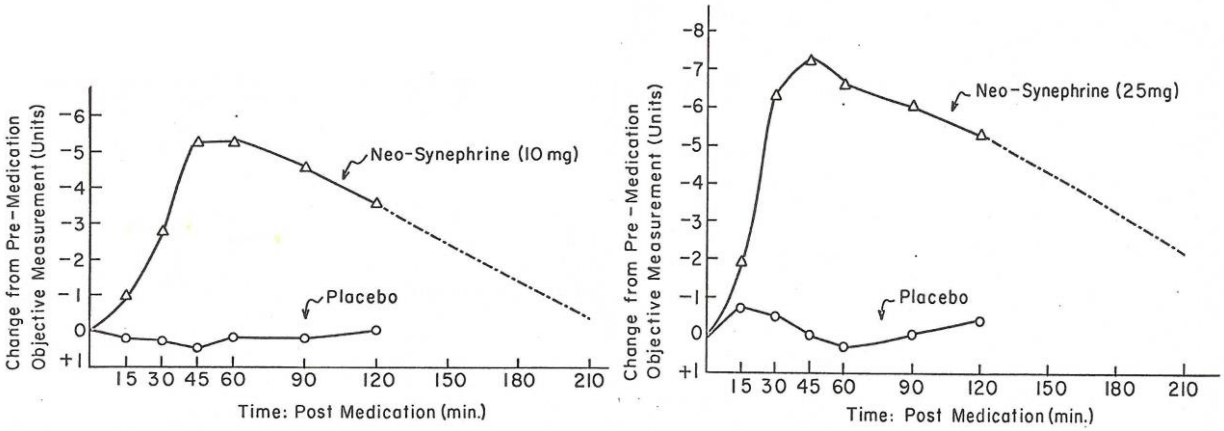
For example, the NAR results from these three studies do not match what is now known about the overall systemic bioavailability and pharmacodynamic effects of orally administered PE. Based on the bioavailability data, we estimate that an orally administered PE dose of about 100 mg would be needed result in sufficient systemic exposure that a nasal decongestant effect might be expected, which also happens to be the dose that results in clinically relevant systemic PD effects (i.e., elevations in systolic blood pressure). However, these studies included measurements of PD effects, and positive NAR results were often reported in the face of no clinically relevant changes in BP or HR, raising suspicion that these results were spurious or incorrect.

Additionally, the NAR response curves do not match what is now known about the AUC (systemic exposure) curve after an orally administered dose of PE, including the timing of the peak and the duration of systemic exposure to the active parent PE. Based on the AUC information, one would expect that the decongestant effect, if present, would occur at an early timepoint and be very short-lived. This was not the case in the three key positive studies. Further, the results for the Elizabeth 2 and 5 studies match perfectly with what would be expected based on what was known at that time about systemic exposure of PE, in fact near textbook perfectly so. Additionally, no change from baseline was observed for placebo, a decidedly unexpected finding. The results of Cintest 1 also raise concern because the onset and duration of effect were later and more sustained (see Figure 8) than in any other study and cannot be easily explained on a scientific basis. All of these findings raise concern regarding any meaningful interpretation of the results.

To illustrate our concerns, graphical representations of the results from Elizabeth 2 are presented in Figure 21, Elizabeth 5 in Figure 22, Cintest 1 in Figure 23, and Cintest 3 in Figure 24. The near-perfect results for Elizabeth 2 and 5 will be seen visually. Note that the NAR curves show dose ordering, that placebo remains stable over time, and the curves match what was known at the time about the systemic availability of PE (i.e., exposure over a 4-hour time frame). Whereas, in two studies conducted at the Cintest study site (Cintest 1 and 3), placebo and active roughly paralleled each other over time with no dose ordering. Also, note the duration of the response curves in Cintest 1 (Figure 23), discussed above, that was later and more prolonged than in any other study. By contrast, the results for Cintest 3 (Figure 24) illustrate what was found in the seven other studies, with gradual drift in NAR results for both oral PE and placebo and no significant difference between treatment groups.

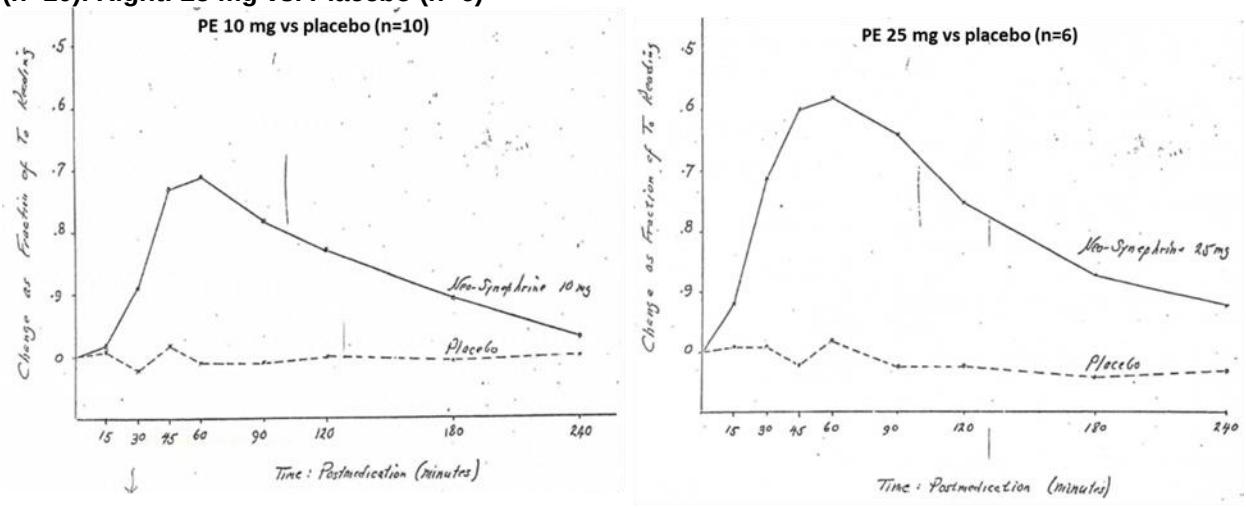
Before looking at the figures, it is important to note differences in the *y*-axis for several of the studies. Elizabeth 2 reported absolute change from baseline, whereas studies at the Cintest site reported the change in percentage of the baseline reading, which is an odd way of presenting the data. As a result, the sets of figures from the two sites cannot be directly compared. However, the slopes, AUCs and differences between study (PEH) and control (placebo) arms are visually apparent.

Figure 21. Absolute Change From Baseline in Elizabeth 2 NAR Results. Left: 10 mg vs. Placebo (n=16). Right: 25 mg vs. Placebo (n=6)



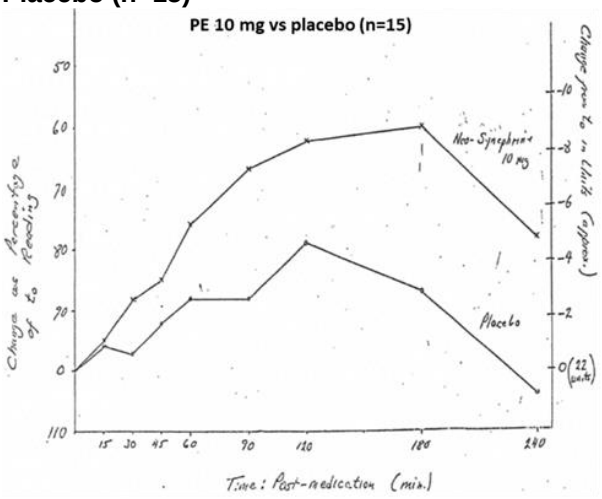
Source: Elizabeth 2 study.
Results beyond 120 minutes are extrapolated.
Abbreviation: NAR, nasal airway resistance

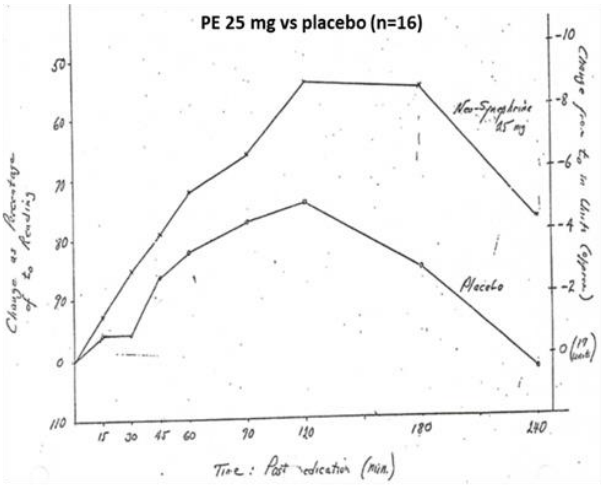
Figure 22. Absolute Change From Baseline in Elizabeth 5 NAR Results. Left: 10 mg vs. Placebo (n=10). Right: 25 mg vs. Placebo (n=6)

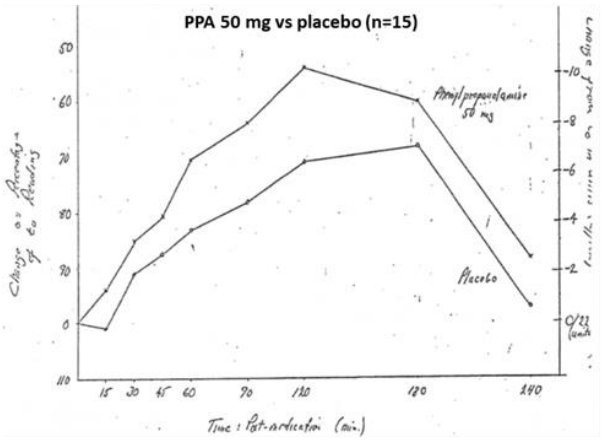


Source: Elizabeth 5 study.
Abbreviations: NAR, nasal airway resistance; PE, phenylephrine

Figure 23. Change in Percentage of the Baseline Reading for Cintest 1 NAR Results. Top Left: PE 10 mg vs. Placebo (n=15). Top Right: PE 25 mg vs. Placebo (n=66). Bottom: PPA 50 mg vs. Placebo (n=15)

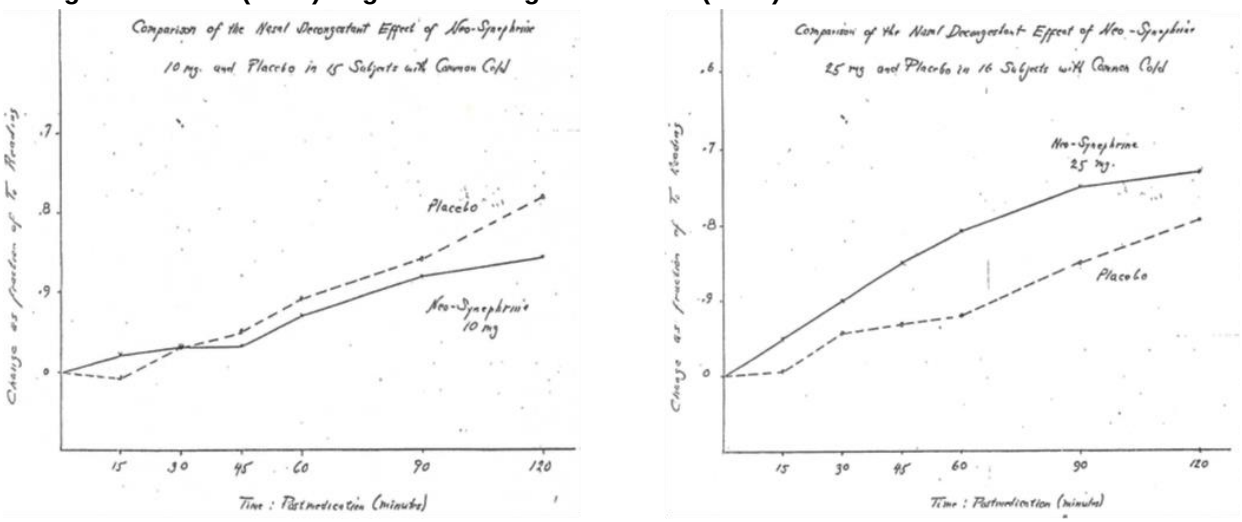






Source: Cintest 1 study.
Abbreviations: NAR, nasal airway resistance; PE, phenylephrine; PPA, phenylpropanolamine

Figure 24. Change in Percentage of the Baseline Reading for Cintest 3 NAR Results. Left: PE 10 mg vs. Placebo (n=15). Right: PE 25 mg vs. Placebo (n=16)



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

A final piece of evidence comes from information embedded in an Appendix to an article published by the petitioners in 2010. Of note, our review (presented above) was conducted before we became aware this information. In addition to noting that several of the Elizabeth studies seemed to drive the positive results (and the results in their meta-analysis) the petitioners also noted the lack of variability in the two Elizabeth results when compared with other studies. As a result, they decided to perform a statistical analysis of the variability of results in Elizabeth studies 2 and 5, following a forensic recommendation of Buyse et al. (1999), by evaluating digit preference in the third [last] significant digit (tenths column) of the reported data results.[64] Their results are shown in Table 13. While they cleared Elizabeth study 5 *from a statistical perspective*, they noted that Elizabeth Study #2 had a disproportionately high occurrence of the digit "5", shown in red font in Table 13, that was consistent across time points (not shown), which they believe provides "sufficient statistical evidence to cast doubt upon the results."

Table 13. Appearance of Digits in the Tenths Column of Elizabeth Studies 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

X^2=55.6 ($P<10^{-8}$) for Study 1 (Elizabeth 2).
X^2=15.2 (P=0.060) for Study 2 (Elizabeth 5).

Source: Shuster et al. (2010).

As a result, in addition to the many methodological and statistical issues that make accepting these studies highly problematic, the possibility is also raised of there having been a data-integrity issue in Elizabeth study 2. [redacted]

[64] Note: The actual raw data are not in the study report. What is present is mean data for each subject, timepoint, and nostril, which is stated to represent the mean of 5 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 13 represents the mean of 10 NAR measurements.

[redacted]

4 Potential Impacts of Changing the GRASE Status of Oral PE and Plans to Address Those Impacts

4.1 Introduction to the Anticipated Downstream Effects

The Agency anticipates that any action that were to change the GRASE status of oral PE might potentially result in significant downstream effects, including effects on both industry and consumers, because the only other oral decongestant, PSE, is now regulated as 'behind-the-counter.' As a result, PE is the only oral nasal decongestant available in front of the counter, and most OTC cough-cold products that had formerly contained PSE (prior to passage of the CMEA in 2006) now contain PE instead. This section focuses on those potential downstream effects. What follows is a brief introduction to what we believe might be the impacts, which we hope will serve as an introduction to a full discussion of both the anticipated and unanticipated/unintended consequences if oral PE were to be removed from the marketplace. We believe that those consequences must be carefully considered prior to taking any action.

First, we present the historical use data, which provides the context to understand just how significant removal of oral PE from the marketplace might be. This is followed by a brief discussion on impacts on industry. And lastly, we provide a brief introduction to what we believe might be the impacts on consumers as well as potential plans to address those impacts. Even though we present information on the potential impacts on industry, we request that the Advisory Committee focus all discussion on how to anticipate and deal with both the anticipated consequences as well as the potential unintended consequences for consumers, and not focus on the potential impacts for industry.

4.2 Historical Context: Use Data

To gain insight into the potential impact on use, we examined both the historical and current sales patterns of OTC cough/cold/allergy oral products containing PE as well as PSE in the context of when PSE went 'behind-the-counter' in 2006. The Division of Epidemiology II provided sales data for OTC cough/cold/allergy oral products containing PE or PSE from manufacturers[65] to U.S. retail and non-retail[66] settings of care (2000 to 2022), and from U.S. retail stores[67] to consumers (2018 to 2022). The

[65] The manufacturer sales data were obtained from the NSP database, which measures the volume of prescription and OTC drug products moving from distributors and manufacturers into various outlets within the retail and non-retail markets. It captures ~90% of the total pharmaceutical market. Any capture of non-pharmaceutical product sales is a collection of convenience and not by database design. As such, NSP's coverage on OTC products is generally less than 50%.

[66] The retail settings include chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service pharmacies. The non-retail settings include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

[67] The OTC retail sales data were obtained from the OTCims and PL-ILR databases, which provide point-of-sale (POS) data from consumer purchases for over the counter (OTC) products and private label OTC products from a panel of retailers. Both databases are sourced from the same diverse and representative panel of approximately

Division of Epidemiology II also provided estimates of the sales in dollars (manufacturers' selling prices or wholesalers' purchase prices before mark-up are applied) from the retail sales data (2018 to 2022) (Table 14). However, sales estimates in dollars from the manufacturers' sales data were not provided because those data significantly underestimate the amount when compared to the retail-sales data.

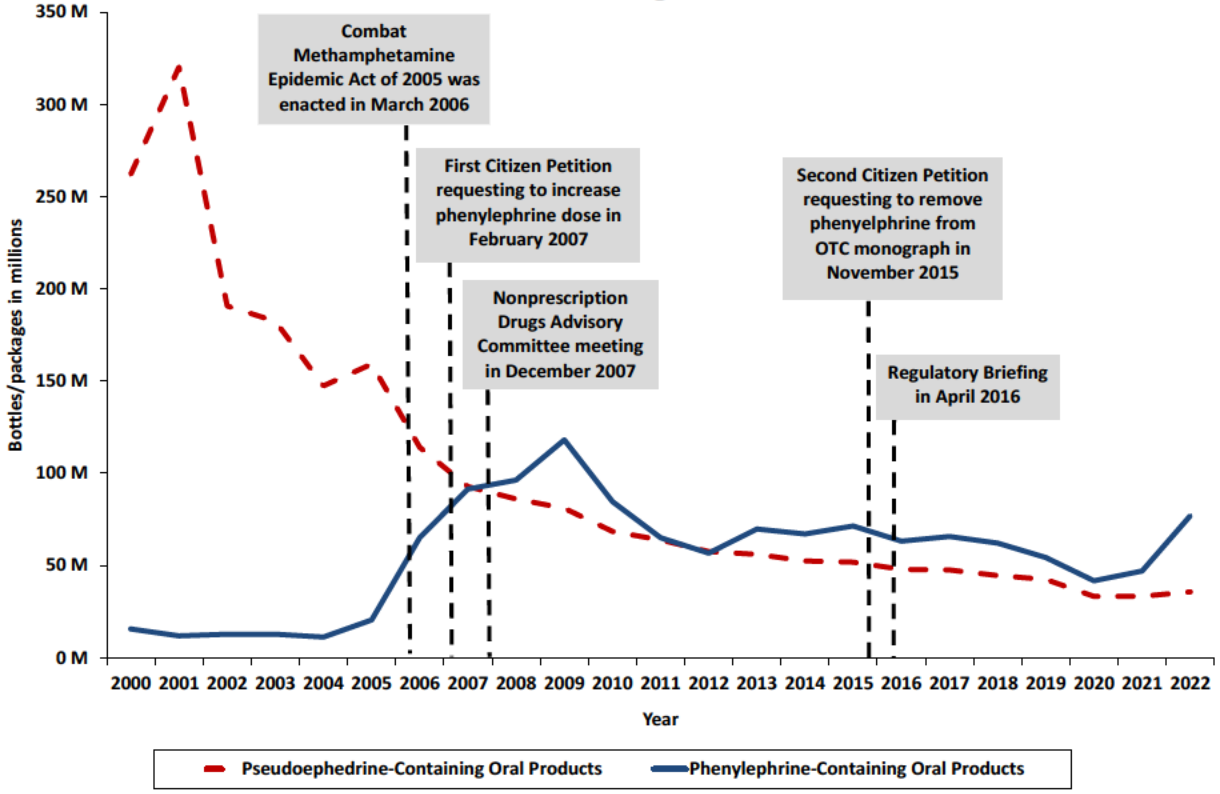
When examining historical manufacturer sales data for these products from 2000 to 2022 (Figure 25), we noted a significant decline in PSE-containing product sales even prior to the enactment of the CMEA in 2006, with a commensurate rise in PE-containing products starting in 2004 and peaking in 2009, after which sales of both PE- and PSE-containing oral products have continued to gradually decline until 2020, when sales of PE-containing oral products increased again.

The most current estimates of retail sales data are from 2022, when an estimated 242 million bottles/packages of OTC cough/cold/allergy oral products containing PE were sold from retail stores, representing approximately 1.763 billion dollars in sales, compared with an estimated 51 million bottles/packages of OTC cough/cold/allergy oral products containing PSE, representing approximately 542 million dollars in sales (Figure 26 and Table 14). It should be noted, however, that the true extent of use of OTC cough/cold/allergy oral products containing PE or PSE is likely underestimated because the retail sales data do not capture sales activity from Costco, convenience stores, specialty stores, internet sales, phone sales, or kiosks.

Several things are evident in these data. Sales of products containing PE, which amounted to only a small percentage of the market prior to 2006, have risen and displaced products containing PSE as an OTC decongestant, although sales of PSE, while smaller, remain. That said, overall sales of both ingredients have gradually declined from 2009 to 2020, and it is unclear why this is the case. One possibility for the reduction in PE sales is that consumers, having purchased PE- instead of PSE-containing products, have gradually recognized that PE does not provide the intended relief of congestion, and therefore have gradually stopped purchasing those products. However, this would not explain the accompanying reduction in PSE sales, although that may also be explained by a gradual loss of public awareness of the availability of 'behind-the-counter' PSE. The dip in sales starting in 2020 may be temporary, due to the decrease in upper respiratory infections that accompanied coronavirus disease 2019 precautions.

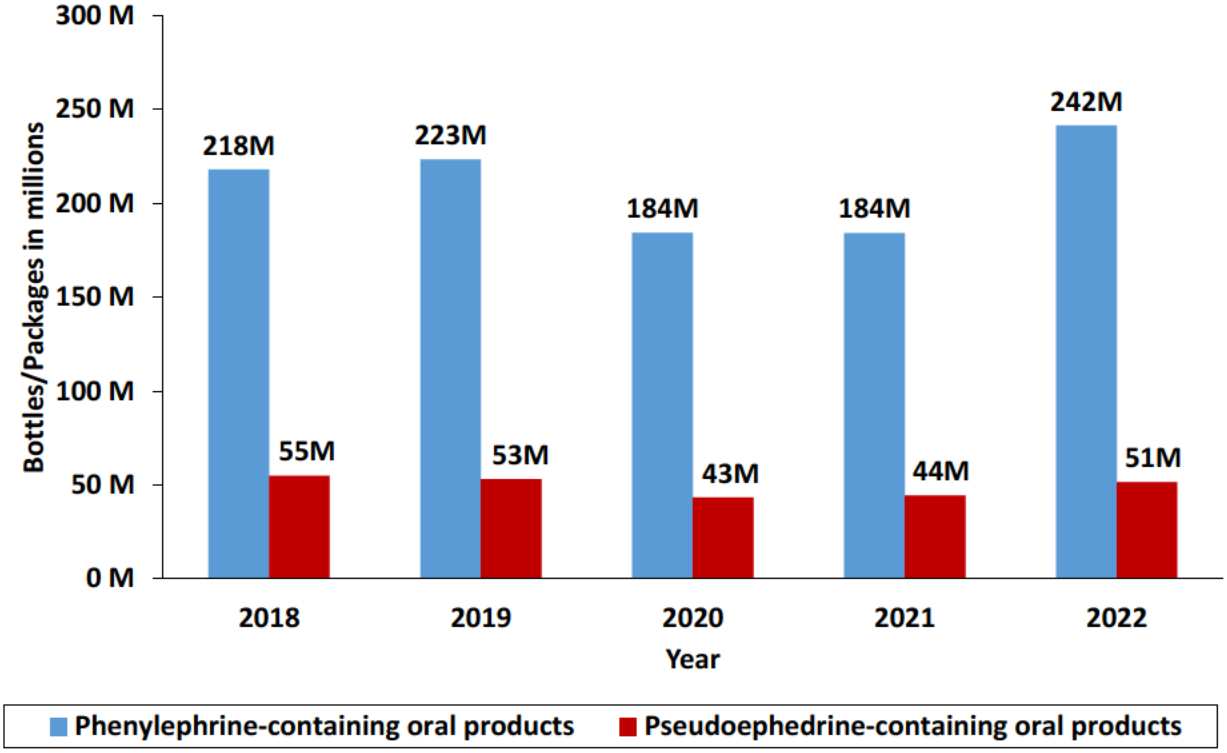
63,000 retail outlets across the U.S. We used these two databases to provide nationally estimated number of units sold to consumers from U.S. retail store outlets (e.g., supermarkets, drug stores, mass merchandisers). For insight into OTC products marketed under store names (e.g., CVS, Walmart), the PL-ILR database was utilized to capture OTC private label products.

Figure 25. National Annual Estimates of Bottles/Packages of Over-the-Counter (OTC) Cough/Cold/Allergy Oral Products Containing Phenylephrine or Pseudoephedrine Sold From Manufacturers[1] to U.S. Retail and Non-Retail[2] Settings of Care, 2000 to 2022



Source: National Sales Perspectives™, 2000-2022. Data extracted May 2022 and February 2023.
[1] Manufacturer sales data of OTC cough/cold/allergy oral products containing phenylephrine were 32% or less of the retail sales data of these products from 2018 to 2022 and should not be directly compared to the retail sales data because they were substantially underestimated.
[2] Non-retail settings include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Figure 26. National Annual Estimates of Bottles/Packages Sold for Over-the-Counter (OTC) Cough/Cold/Allergy Oral Products Containing Phenylephrine or Pseudoephedrine From U.S. Retail Stores[1] to Consumers, 2018 to 2022



Source: OTC International Market Tracking and Private Label Ingredient Level Report, 2018-2022. Data extracted February 2023.
[1] Retail sales data do not capture sales activity from Costco, convenience stores, specialty stores, internet sales, phone sales or kiosks.

Table 14. National Annual Estimates of Bottles/Packages and Dollars[1] of Over-the-Counter (OTC) Cough/Cold/Allergy Oral Products Containing Phenylephrine or Pseudoephedrine Sold From U.S. Retail Stores[2] to Consumers, 2018 to 2022

	Year									
	2018		2019		2020		2021		2022	
	Bottles/Packages	%	Bottles/Packages	%	Bottles/Packages	%	Bottles/Packages	%	Bottles/Packages	%
Total Over-the-Counter Oral Decongestants	272,945,288	100.0%	276,557,888	100.0%	227,415,027	100.0%	228,456,546	100.0%	293,008,234	100.0%
Phenylephrine-Containing Oral Products	218,098,664	79.9%	223,465,762	80.8%	184,201,982	81.0%	184,149,349	80.6%	241,559,923	82.4%
Pseudoephedrine-Containing Oral Products	54,846,624	20.1%	53,092,126	19.2%	43,213,045	19.0%	44,307,197	19.4%	51,448,311	17.6%
	Dollars	%	Dollars	%	Dollars	%	Dollars	%	Dollars	%
Total Over-the-Counter Oral Decongestants	1,760,178,088	100.0%	1,822,427,879	100.0%	1,547,567,494	100.0%	1,672,149,712	100.0%	2,304,987,237	100.0%
Phenylephrine-Containing Oral Products	1,258,958,330	71.5%	1,327,116,650	72.8%	1,116,711,698	72.2%	1,213,497,701	72.6%	1,763,442,986	76.5%
Pseudoephedrine-Containing Oral Products	501,219,758	28.5%	495,311,229	27.2%	430,855,796	27.8%	458,652,012	27.4%	541,544,251	23.5%

Source: OTC International Market Tracking and Private Label Ingredient Level Report, 2018-2022. Data extracted February 2023.
[1] Sales in dollars represent the price of a manufacturer's pack before the wholesaler mark-up is applied.
[2] Retail sales data do not capture sales activity from Costco, convenience stores, specialty stores, internet sales, phone sales or kiosks.

4.3 Potential Impacts on Industry

Please note that we will not be discussing any potential impacts on industry at this AC meeting.

That stated, as exemplified by the use data above, a significant impact on industry is inevitable and must be anticipated. Manufacturers, warehousers, and pharmacies all have a large supply chain investment in stocks of PE, either as a precursor chemical, ingredient itself, or in a finished product. There will also be significant retooling costs to industry.

In addition to the multiple OTC products, there are also prescription (NDA and ANDA) combination products that include PE. Since the approvals of these products relied on the Agency's GRASE findings for the PE ingredient in the combination, if the status of PE in the OTC monograph is changed to non-GRASE, the basis of approval of these products will be altered and the Agency will need to consider withdraw of approval of these products.

Further, any commercial INDs for oral PE-containing products would be impacted by removal of PE from the CCABA monograph.

4.4 Potential Impacts on Consumers

We are aware that a number of excellent treatments are available for the treatment of nasal congestion, and in particular, congestion associated with allergic rhinitis. That stated, as may be seen from the use data above, a significant amount of money is spent by consumers every year on the purchase of products that contain at least one ingredient (oral PE) that may not be effective. In addition to avoiding unnecessary costs of taking a drug with no benefit and lowering of overall healthcare costs, other potential benefits might be derived by changing the GRASE status of oral PE. These include but are not limited to avoiding any delay in care due to taking a drug that has no benefit, avoiding the risks of potential allergic reactions or other side effects related to use of PE in combination products, avoiding the inherent risks (especially for combination therapies) of taking more in order to seek some benefit, avoiding the risks of medication use in children, and avoiding missed opportunities for use of more effective treatments (including seeing a doctor if needed).

However, other significant effects on consumers may be anticipated if oral PE is no longer available for purchase that are potentially negative in nature. Most consumers may simply need instruction on the alternatives, including how to obtain 'behind-the-counter' pseudoephedrine or to use alternative treatments, including intranasal decongestants (including intranasal PE), intranasal steroids, intranasal antihistamines, or intranasal saline products. However, availability of oral pseudoephedrine, while subject to interstate commerce and thus the CMEA, is also subject to additional restrictions that may be imposed by states. Therefore, it may not be available to all consumers, depending upon locality. Further, some consumers may believe that [oral] PE is helpful to them, resulting in frustration and anger if it is no longer available to purchase. Still other consumers may switch to competing treatments that have their own risks, benefits, and limitations of use.

Thus, in addition to asking you the AC members to focus on the scientific evidence regarding the effectiveness of oral PE as a decongestant, we ask that you also address any potential unintended consequences that may arise should the Agency take an action to change the GRASE status of oral PE. We will provide some context for this discussion by asking experts to discuss the available approved Rx and OTC therapies at the NDAC meeting, and we will ask you to focus on other risk management and risk communication strategies, including educational plans for how to avoid unintended risks with use of other OTC products, safety issues related to the use of drugs that contain other active ingredients, and

safety issues related to the off-label use of other products or ingredients, including use of homeopathic and 'nutraceutical' products that are largely unregulated. We will also ask you to focus on the education of consumers regarding alternatives to phenylephrine (including both oral and intranasal products), how to obtain pseudoephedrine from behind-the-counter, and education of consumers who have a preference for phenylephrine regarding why it is being removed from the market.

We anticipate that we would work with communication specialists within the Agency, professional organizations, industry, and consumer organizations as part of a comprehensive strategy to address these issues, and we welcome your input into that strategy.

We thank you in advance for your thoughtful participation.

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Guidances for Industry

FDA, 2018, Guidance for Industry; Allergic Rhinitis: Developing Drug Products for Treatment, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/allergic-rhinitis-developing-drug-products-treatment-guidance-industry.

5.1 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 (Coronavirus Aid, Relief, and Economic Security Act, signed into law on March 27, 2020: 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.

6 Appendix With Supplementary Tables

6.1 TFM Comment 11 for ANPR Reference 25

TFM Comment 11 noted that the ANPR had cited a study that did not contain the information referenced in the text. This study had been reported as a double-blind, placebo-controlled, crossover study in 20 patients with chronic rhinitis, which not only could not demonstrate any significant decrease in NAR after doses of 10, 20, or 40 mg of phenylephrine, but also showed significant decreases in NAR persisting for at least 3 hours after two positive controls (40 mg of PPA or 60 mg of PSE).

The problem, however, is that the citation in the text (Rogers, Reilly, and Bickerman 1973, reference 25) is for a conference abstract of a study stated to have been performed in 104 subjects with chronic rhinitis, with no further data provided with regard to doses studied or the results. This discrepancy was noted in the 1985 TFM Comment 11,[68] which noted that several citations to reference 25 in the ANPR body text are incorrect in that no data are contained in reference. In response, the Agency stated that the actual citation could not be found, although the Agency's response did note that several other ANPR citations to reference 25 were in fact citing an earlier publication by the same authors published 2 years previously (Bickerman 1971), the results of which are presented in Table 11 at the end of the Negative Original Studies section.

With the exception of the number of subjects studied, we note that the title of the publication and the description of the study parameters (including study population, trial design, study arms, and studied ingredients and doses) in the ANPR text exactly match a much fuller description provided in the earlier 1971 publication. Further, the cited abstract also matches with their earlier publication. Therefore, we believe it likely that this was the origin of the data cited in the ANPR, and that abstract cited simply is an update for the previous publication and study, with additional arms that had not been previously included in the earlier publication. For this same reason, we also believe that the number of subjects who the ANPR cited are incorrect, especially since no other study that we reviewed included either that number of subjects or those study arms. Further, after extensive publication searches, we were unable to find any other studies of oral PE from this time period not included in this document. Since the

[68] 50 FR 2220 (January 15, 1985) at 2226, Comment 11.

original Panel comprised experts in the field, it is also possible that the Panel had access to information not in the cited abstract (i.e., in reference 25) that had been presented at that conference but were not in the abstract text.

Therefore, while the ANPR only cited the 1973 reference, we believe that it should have cited both the 1971 and 1973 references as the source of the material in the text. Note that the results published by Bickerman in 1971 were republished (with permission) by the petitioners in graphical format (Figure 6) in 1993 (Hendeles 1993) and again in 2006 (Hendeles and Hatton 2006), and discussed by the petitioners at the NDAC meeting in 2007. Please see the 2007 NDAC Presentation for details.

6.2 Supplementary Tables

Table 15. Oral PE Efficacy Studies Reviewed by the 1976 Cough-Cold Panel

Study/Site Info/ Docket Number	Drugs/ Doses	N	Study Design and Results
Sterling-Winthrop (Lands to Luduena) 5-23-59) Ref 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: Sterntein and Schur. 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.
Elizabeth 1 (Hulme to Suter 6-28-67) Ref 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) Ref 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. 2-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 were also 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.

Study/Site Info/ Docket Number	Drugs/ Doses	N	Study Design and Results
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. 2-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. 2-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.
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. 2-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.

Study/Site Info/ Docket Number	Drugs/ Doses	N	Study Design and Results
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 Labs 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 were 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. 2-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	First study conducted at Cintest Division of Hill Top Laboratories, Cincinnati, OH, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY. 2-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.
Cintest 2 (Hulme to Blackmore 1-23-70) Reference 23	PE 10 PE 15 PE 20 Placebo	16 16 16 48	Second study conducted at Cintest Division of Hill Top Laboratories, Cincinnati, OH, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY. 2-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.

Study/Site Info/ Docket Number	Drugs/ Doses	N	Study Design and Results
Cintest 3 (Hulme to Blackmore 5-18-70) Reference 24	PE 10 PE 15 PE 25 Placebo	16 16 16 48	Third study conducted at Cintest Division of Hill Top Laboratories, Cincinnati, OH, and study report by N.A. Hulme at Sterling-Winthrop Research Institute, Rensselaer, NY. 2-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 et al., 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, non-atopic 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, we believe that what was cited as reference 25 in the ANPR was actually information based on an earlier publication by Bickerman et al. in 1971 that contained the following:
Bickerman et al. 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 non-atopic. 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 non-seasonal 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 ½ hour and continuing through 4 hours. PPA results were significant at ½ hour up to 3 hours, and PE was only significant (p=0.3 level) at 3 hours (see Figure 6).
BEI 1025 (Cohen 6-1975) Reference 26	PE 10 mg q4h ×3 doses Placebo	100 100	This study was 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 4 doses of PE 10 mg or placebo every 4 hours and evaluated over 12.5 hours post-first dose. 50 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 post-dosing. Results were significant for both objective and subjective symptom scores when compared with placebo.

Study/Site Info/ Docket Number	Drugs/ Doses	N	Study Design and Results
McLauren et al., 1960 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 5-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 5-6 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 5 treatments. Unfortunately, the data tables do not convey the numbers in each treatment group, making interpretation of the results problematic. However, 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 significant. 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: BP, blood pressure; DBP, diastolic blood pressure; Eph, ephedrine; NAR, nasal airway resistance; PE, phenylephrine; PEH, phenylephrine hydrochloride; PPA, phenylpropanolamine; PSE, pseudoephedrine; q4h, every 4 hours; SBP, systolic blood pressure

Table 16. Monograph Ingredients Contained in the Over-the-Counter (OTC) Cough and Cold Drug Products

Antihistamine	Decongestant	Expectorant	Antitussive	Bronchodilator
Oral Products				
Brompheniramine maleate[2]	Phenylephrine hydrochloride[1,3]	Guaifenesin[1]	Chlophedianol hydrochloride[2]	Ephedrine[2,3]
Chlorcyclizine hydrochloride[2]	Phenylephrine bitartrate[3]		Codeine[2,4,5]	Ephedrine hydrochloride[2,3]
Chlorpheniramine maleate[2]	Pseudoephedrine		Codeine phosphate[2,4,5]	Ephedrine sulfate[2,3]
Dexbrompheniramine maleate[2]	hydrochloride[1,3]		Codeine sulfate[2,4,4]	Racephedrine
Dexchlorpheniramine maleate[2]	Pseudoephedrine sulfate[1,3]		Dextromethorphan[1]	hydrochloride[2,3]
Diphenhydramine citrate[2,5]			Dextromethorphan hydrobromide[1]	
Diphenhydramine			Diphenhydramine citrate[2,5]	
hydrochloride[2,4,5]			Diphenhydramine hydrochloride[2,4,5]	
Doxylamine succinate[2]				
Phenindamine tartrate[2]				
Pheniramine maleate[2]				
Pyrilamine maleate[2]				
Thonzylamine hydrochloride[2]				
Triprolidine hydrochloride[2]				
Topical and/or Inhaled Products				
	Levmetamfetamine		Camphor	Epinephrine
	Ephedrine[3]		Menthol	Epinephrine bitartrate
	Ephedrine hydrochloride[3]			Racepinephrine
	Ephedrine sulfate[3]			hydrochloride
	Naphazoline hydrochloride			
	Oxymetazoline hydrochloride			
	Phenylephrine hydrochloride			
	Propylhexedrine			
	Xylometazoline hydrochloride			

Source: Monographs listed below.

[1] Four ingredients have OTC labeling down to 2 years of age: Dextromethorphan and dextromethorphan hydrochloride, guaifenesin, phenylephrine hydrochloride, and both pseudoephedrine salts.

[2] Professional labeling is available at the end of the monograph with dosing down to 2 years of age, with two exceptions: A) triprolidine has professional labeling down to 4 months of age, and B) guaifenesin has OTC labeling down to 2 years of age and professional labeling stating that single-ingredient guaifenesin may be used for treatment of "stable chronic bronchitis."

[3] Pseudoephedrine and ephedrine ingredients are behind-the-counter.

[4] Diphenhydramine hydrochloride is also in the Antiemetic Drug Products for OTC Human Use Monograph (M009 previously 21 CFR § 336), with dosages for adults and children 12 years of age and over (25 to 50 mg every 4 to 6 hours, not to exceed 300 mg in 24 hours, or as directed by a doctor) and children 6 to 11 years (12.5 to 25 mg every 4 to 6 h, not to exceed 150 mg in 24 hours).

[5] Diphenhydramine hydrochloride and diphenhydramine citrate are also in the Nighttime Sleep-Aid Drug Products for Over-the-Counter Human Use monograph (M010 previously 21 CFR § 338). For diphenhydramine hydrochloride, the dosage is for adults and children 12 years of age and over (50 mg at bedtime as needed, or as directed by a doctor). For diphenhydramine citrate, the dosage is for adults and children 12 years of age and over (76 mg at bedtime prn, or as directed by a doctor).

Table 17. CCABA Monograph Oral Ingredients: OTC and Professional Dosages and Age Groups*

	OTC Dosage			
Ingredient	**Adults and Children 12 years and Older**	**6-11 years**	**2-5 years**	**Professional Ages and Dosage**
Antihistamines – M012.72(d) (previously 21 CFR 341.72 (d))				
Brompheniramine maleate	4 mg q4-6h, NTE 24 mg/24h, or as directed	2 mg q4-6h, NTE 12 mg/24h, or as directed	Consult a doctor	2-5y: 1 mg q4-6 h, NTE 6 mg/24h
Chlorcyclizine hydrochloride (*dosed q6-8h)	25 mg q6-8h, NTE 75 mg/24h, or as directed	Consult a doctor	Consult a doctor	6-11y: 12.5 mg q6-8h, NTE 37.5 mg/24h 2-5y: 6.25 mg q6-8h, NTE 18.75 mg/24h
Chlorpheniramine maleate	4 mg q4-6h, NTE 24 mg/24h, or as directed	2 mg q4-6h, NTE 12 mg/24h, or as directed	Consult a doctor	2-5y: 1 mg q4-6h, NTE 6 mg/24h
Dexbrompheniramine maleate	2 mg q4-6h, NTE 12 mg/24h, or as directed	1 mg q4-6h, NTE 6 mg/24h, or as directed	Consult a doctor	2-5y: 0.5 mg q4-6h, NTE 3 mg/24h
Dexchlorpheniramine maleate	2 mg q4-6h, NTE 12 mg/24h, or as directed	1 mg q4-6h, NTE 6 mg/24h, or as directed	Consult a doctor	2-5y: 0.5 mg q4-6h, NTE 3 mg/24h
Diphenhydramine citrate	38 to 76 mg q4-6h, NTE 456 mg/24h, or as directed	19 to 38 mg q4-6h, NTE 228 mg/24h, or as directed	Consult a doctor	2-5y: 9.5 mg q4-6h, NTE 57 mg/24h
Diphenhydramine hydrochloride	25 to 50 mg q4-6h, NTE 300 mg/24h, or as directed	12.5 to 25 mg q4-6h, NTE 150 mg/24h, or as directed	Consult a doctor	2-5y: 6.25 mg q4-6h, NTE 37.5 mg/24h
Doxylamine succinate[1]	7.5 to 12.5 mg q4-6h, NTE 75 mg/24h, or as directed	3.75 to 6.25 mg q4-6h, NTE 37.5 mg/24h, or as directed	Consult a doctor	2-5y: 1.9 to 3.25 mg q4-6h, NTE 18.75 mg/24h
Phenindamine tartrate	25 mg q4-6h, NTE 150 mg/24h, or as directed	12.5 mg q4-6h, NTE 75 mg/24h, or as directed	Consult a doctor	2-5y: 6.25 mg q4-6h, NTE 37.5 mg/24h
Pheniramine maleate	12.5 to 25 mg q4-6h, NTE 150 mg/24h, or as directed	6.25 to 12.5 mg q4-6h, NTE 75 mg/24h, or as directed	Consult a doctor	2-5y: 3.125 to 6.25 mg q4-6h, NTE 37.5 mg/24h
Pyrilamine maleate	25 to 50 mg q6-8h, NTE 200 mg/24h, or as directed	12.5 to 25 mg q6-8h, NTE 100 mg/24h, or as directed	Consult a doctor	2-5y: 6.25 to 12.5 mg q6-8h, NTE 50 mg/24h
Thonzylamine hydrochloride	50 to 100 mg q4-6h, NTE 600 mg/24h, or as directed	25 to 50 mg q4-6h, NTE 300 mg/24h, or as directed	Consult a doctor	2-5y: 12 to 25 mg q4-6h, NTE 150 mg/24h
Triprolidine hydrochloride (*has infant dosing)	2.5 mg q4-6h, NTE 10 mg/24h, or as directed	1.25 mg q4-6h, NTE 5 mg/24h, or as directed	Consult a doctor	4-5y: 0.938 mg q4-6h, NTE 3.744 mg/24h 2-3y: 0.625 mg q4-6h, NTE 2.5 mg/24h Infants 4m to-<2y: 0.313 mg q4-6h, NTE 1.252 mg/24h

Ingredient	OTC Dosage Adults and Children 12 years and Older	6-11 years	2-5 years	Professional Ages and Dosage
Oral Antitussives – M012.74(d)(1) (Previously 21 CFR 341.74 (d)(1))				
Chlophedianol hydrochloride	25 mg q6-8h, NTE 100 mg/24h, or as directed	12.5 mg q6-8h, NTE 50 mg/24h, or as directed	Consult a doctor	2-5y: 12.5 mg q6-8 h, NTE 50 mg/24h
Codeine, codeine phosphate, and codeine sulfate	10 to 20 mg q4-6h, NTE 120 mg/24h, or as directed	5 to 10 mg q4-6h, NTE 60 mg/24h, or as directed Use a special measuring device.	Consult a doctor	2-5y: 1 mg/kg of body weight as 4 equally divided doses, or 2y (~12 kg): 3 mg q4-6h, NTE 12 mg/24h 3y (~14 kg): 3.5 mg q4-6h, NTE 14 mg/24h 4y (~16 kg): 4 mg q4-6h, NTE 16 mg/24h 5y (~18 kg): 4.5 mg q4-6h, NTE 18 mg/24h Use a calibrated measure. Adjust for low weight. Children <2 y are more susceptible to respiratory depression, coma, death.
Dextromethorphan and dextromethorphan hydrobromide	10 to 20 mg q4h, or 30 mg q6-8h, NTE 120 mg/24h, or as directed	5 to 10 mg q4h, or 15 mg q6-8h, NTE 60 mg/24h, or as directed	2.5 to 5 mg q4h, or 7.5 mg q6-8h, NTE 30 mg/24h, or as directed	--
Diphenhydramine citrate 341.14(a)(5)	38 mg q4h, NTE 228 mg/24h	19 mg q4h, NTE 114 mg/24h	Consult a doctor	2-5y: 9.5 mg q4-6h, NTE 57 mg/24h
Diphenhydramine hydrochloride 341.14(a)(6)	25 mg q4h, NTE 150 mg/24h, or as directed	12.5 mg q4h, NTE 75 mg/24h, or as directed	Consult a doctor	2-5y: 6.25 mg q4-6h, NTE 37.5 mg/24h
Oral Bronchodilators – M012.76(d)(1) (Previously 21 CFR 341.76(d)(1))				
Ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride	12.5 to 25 mg q4h prn, NTE 150 mg/24h	Ask a doctor	Ask a doctor	6-11y: 6.25 to 12.5 mg q4h, NTE 75 mg/24h 2-5y: 0.3 to 0.5 mg/kg of body weight q4h, NTE 2 mg/kg/24h
Expectorants – M012.78(d) (Previously 21 CFR 341.78 (d))				
Guaifenesin	200 to 400 mg q4h, NTE 2400 mg/24h	100 to 200 mg q4h, NTE 1200 mg/24h	50 to 100 mg q4h, NTE 600 mg/24h	OK as a single ingredient for “stable chronic bronchitis” (same dosage)

	OTC Dosage			
Ingredient	**Adults and Children 12 years and Older**	**6-11 years**	**2-5 years**	**Professional Ages and Dosage**
Oral Nasal Decongestants – M012.80(d)(1) (Previously 21 CFR 341.80 (d)(1))				
Phenylephrine hydrochloride	10 mg q4h, NTE 60 mg/24h	5 mg q4h, NTE 30 mg/24h	2.5 mg q4h, NTE 15 mg/24h	--
Phenylephrine bitartrate	15.6 mg q4h, NTE 62.4 mg/24h	7.8 mg q4h, NTE 31.2 mg/24h	Ask a doctor	--
Pseudoephedrine hydrochloride and pseudoephedrine sulfate	60 mg q4-6h, NTE 240 mg/24h	30 mg q4-6h, NTE 120 mg/24h	15 mg q4-6h, NTE 60 mg/24h	--

Source: CCABA Monograph.

* This table presents only the dosing directions for each ingredient. Warnings and other labeling are NOT shown.

[1] Although the Panel recommended OTC dosages of 7.5 to 12.5 mg, the original Proposed Rule proposed that the OTC dose of doxylamine succinate be limited to 7.5 mg (41 FR 38312, 1976-9-9 at 38313).

Abbreviations: 6-11y, 6 to 11 years (i.e., “6 to under 12 years”); 2-5y, 2 to 5 years (i.e., “2 to under 6 years”); CCABA, Cough, Cold, Allergy, Bronchodilator, and Antiasthma; NTE, not to exceed; OTC, over-the-counter; q4h, once every 4 hours; q4-6h, once every 4-6 hours; q6-8h, once every 4-8 hours

Table 18. CCABA Monograph Topical and/or Inhaled Ingredients: OTC Dosages and Age Groups[1]

	OTC Dosage (No Professional Labeling)		
Ingredient	**Adults and Children 12 Years and Older**	**6-11 Years**	**2-5 Years**
Topical Antitussives – M012.74(d)(2) (Previously 21 CFR 341.74 (d)(2))			
Camphor Ointment (4.7 to 5.3%)	Adults and children 2 years and older: Rub on throat and chest in a thick layer up to 3 times/day		
Menthol Ointment (2.6 to 2.8%)	Adults and children 2 years and older: Rub on throat and chest in a thick layer up to 3 times/day		
Menthol Lozenge (5 to 10 mg)	"Adults and children 2 to under 12 years of age: Allow lozenge to dissolve slowly in the mouth. May be repeated every hour prn, or as directed		
Camphor for Inhalation (6.2%)	"[bullet] adults and children 2 years and older: (select one of the following, as appropriate: For products formulated to be added directly to cold water inside a hot steam vaporizer. [bullet] use 1 tablespoonful of solution for each quart of water or 1 1/2 teaspoonfuls of solution for each pint of water [bullet] add solution directly to cold water only in a hot steam vaporizer [bullet] follow manufacturer's directions for using vaporizer or For products formulated to be placed in the medication chamber of a hot steam vaporizer. [bullet] place water in the vaporizer and follow manufacturer's directions for using vaporizer [bullet] place solution in the medication chamber only) [bullet] breathe in the medicated vapors [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor."		
Menthol for Inhalations (3.2%)	"[bullet] adults and children 2 years and older: (select one of the following, as appropriate: For products formulated to be added directly to cold water inside a hot steam vaporizer. [bullet] use 1 tablespoonful of solution for each quart of water or 1½ teaspoonfuls of solution for each pint of water [bullet] add solution directly to cold water only in a hot steam vaporizer [bullet] follow manufacturer's directions for using vaporizer or For products formulated to be placed in the medication chamber of a hot steam vaporizer. [bullet] place water in the vaporizer and follow manufacturer's directions for using vaporizer [bullet] place solution in the medication chamber only) [bullet] breathe in the medicated vapors [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.		
Inhaled Bronchodilators – M012.76(d)(2) (Previously 21 CFR 341.76(d)(2))			
Epinephrine, epinephrine bitartrate, and racepinephrine hydrochloride (1% aq soln)	Adults and children 4 years of age and older: 1-3 inhalations not more than every 3 hours, NTE 12 inhalations/24 hours		Under 4 years of age: Ask a doctor

	OTC Dosage (No Professional Labeling)		
Ingredient	**Adults and Children 12 Years and Older**	**6-11 Years**	**2-5 Years**
Intranasal Decongestants – M012.80(d)(2) (Previously 21 CFR 341.80(d)(2))			
Levmetamfetamine: Inhalation (800 mL air, 0.4 to 0.150 mg of levmetamfetamine)	"Adults: 2 inhalations in each nostril not more often than every 2 hours."	(with adult supervision) 1 inhalation in each nostril NMT q2h	Ask a doctor
Ephedrine, ephedrine hydrochloride, and ephedrine sulfate: Nasal Drops or Spray (0.5% aqueous solution)	2 or 3 drops or sprays in each nostril no more often than q4h	(With adult supervision) 1 or 2 drops or sprays in each nostril no more often than q4h	Consult a doctor
Ephedrine, ephedrine hydrochloride, and ephedrine sulfate: Nasal Jelly (0.5% water-based jelly)	"Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 4 hours."		NOT STATED
Naphazoline hydrochloride: Nasal Drops or Spray (0.5% aqueous solution)	1 or 2 drops or sprays in each nostril NMT q6h	Do not give to children under 12 years of age unless directed by a doctor.	
Naphazoline hydrochloride: Nasal Drops or Spray (0.25% aqueous solution)	--	(With adult supervision) 1 or 2 drops or sprays in each nostril NMTq6h	Consult a doctor
Naphazoline hydrochloride Nasal Jelly (0.5% water-based jelly)	Place a small amount in each nostril and inhale well back into the nasal passages, NMT q6h	Do not give to children under 12 years of age unless directed by a doctor.	
Naphazoline hydrochloride Nasal Jelly (0.25% water-based jelly)	--	(With adult supervision) Place a small amount in each nostril and inhale well back into the nasal passages, not more often than q6h	Consult a doctor
Oxymetazoline hydrochloride Nasal Spray or Drops (0.05% aqueous solution)	"Adults and children 6 to under 12 years of age (with adult supervision): 2 or 3 drops or sprays in each nostril not more often than every 10 to 12 hours. Do not exceed 2 doses in any 24-hour period."		Consult a doctor
Oxymetazoline hydrochloride (0.025% aqueous solution delivered by calibrated dropper or metered-dose spray that delivers NMT 0.027 mg per 3 drops or 3 sprays)	--		2 or 3 drops or sprays in each nostril not more often than q10-12h, NTE 2 doses in any 24-hour period

	OTC Dosage (No Professional Labeling)		
Ingredient	**Adults and Children 12 Years and Older**	**6-11 Years**	**2-5 Years**
Oxymetazoline hydrochloride Nasal Jelly (0.05-percent water-based jelly)	"Adults and children 6 to under 12 years of age (with adult supervision): place a small amount in each nostril and inhale well back into the nasal passages. Use not more often than every 10 to 12 hours. Do not exceed 2 doses in any 24-hour period."		Consult a doctor
Phenylephrine hydrochloride Nasal Drops or Spray (1 % aqueous solution)	2 or 3 drops or sprays in each nostril NMT q4h	Do not give to children under 12 years of age unless directed by a doctor.	
Phenylephrine hydrochloride Nasal Drops or Spray (0.5 % aqueous solution)	2 or 3 drops or sprays in each nostril NMT q4h	Do not give to children under 12 years of age unless directed by a doctor.	
Phenylephrine hydrochloride (0.25% aqueous solution)	(With adult supervision) 2 or 3 drops or sprays in each nostril NMT q4h		Consult a doctor
Phenylephrine hydrochloride (0.125% aqueous solution)	--	--	(With adult supervision) 2 or 3 drops or sprays in each nostril NMT q4h
Phenylephrine hydrochloride Nasal Jelly (1% water-based jelly)	Place a small amount in each nostril and inhale well back into the nasal passages, NMT q4h	Do not give to children under 12 years of age unless directed by a doctor	
Phenylephrine hydrochloride Nasal Jelly 0.5% water-based jelly)	Place a small amount in each nostril and inhale well back into the nasal passages, NMT q4h	Do not give to children under 12 years of age unless directed by a doctor	
Phenylephrine hydrochloride Nasal Jelly (0.25% water-based jelly)	--	(With adult supervision) place a small amount in each nostril and inhale well back into the nasal passages, NMT q4h	Consult a doctor
Propylhexedrine Inhalation (800 mL air, 0.4 to 0.5 mg of propylhexedrine)	"Adults and children 6 to under 12 years of age (with adult supervision): 2 inhalations in each nostril not more often than every 2 hours."		Consult a doctor
Xylometazoline hydrochloride Nasal Drops or Spray (0.1% aqueous solution)	2 or 3 drops or sprays in each nostril NMT every 8 to 10 hours	Do not give to children under 12 years of age unless directed by a doctor.	

	OTC Dosage (No Professional Labeling)		
Ingredient	**Adults and Children 12 Years and Older**	**6-11 Years**	**2-5 Years**
Xylometazoline hydrochloride (0.05% aqueous solution in a container having either a calibrated dropper or a metered-dose spray that delivers no more than 0.054 mg of xylometazoline per 3 drops or 3 sprays)	--	(With adult supervision) 2 or 3 drops or sprays in each nostril NMT every 8 to 10 hours, NTE 3 doses in any 24-hour period	(With adult supervision) 2 or 3 drops or sprays in each nostril NMT every 8 to 10 hours, NTE 3 doses in any 24-hour period
Xylometazoline hydrochloride Nasal Jelly (0.1% water-based jelly)	Place a small amount in each nostril and inhale well back into the nasal passages, NMT every 8 to 10 hours	Do not give to children under 12 years of age unless directed by a doctor.	
Xylometazoline hydrochloride Nasal Jelly (0.05% water-based jelly)	--	(With adult supervision) place a small amount in each nostril and inhale well back into the nasal passages, NMT every 8 to 10 hours	Consult a doctor

Source: CCABA Monograph.
[1] This table presents only the dosing directions for each ingredient. Warnings and other labeling are NOT shown.
Abbreviations: CCABA, Cough, Cold, Allergy, Bronchodilator, and Antiasthma; OTC, over-the-counter; NTE, not to exceed; NMT, prn, as needed; not more than or not more often than; 6-11y, 6 through 11 years (i.e., 6 to under 12 years); 2-5y, 2 through 5 years (i.e., 2 to under 6 years)

Table 19. Permitted Cough/Cold Combinations in M012.85 (Previously 21 CFR 341.40)

M012.40 Letter	Antihistamine	Analgesic Acetaminophen Aspirin/Antacid	Oral Demulcent	Oral Nasal Decongestant	Oral Antitussive	Expectorant	Oral Anesthetic	Local Antitussive	Other
a	x	x							
b	x			x					
c	x	x		x					
d	x				x				
e	x			x	x				
f	x	x			x				
g	x	x		x	x				
h					x	x			
i				x	x				
j				x	x	x			
k					x		x	x	
l		x			x				
m		x		x	x				
n		x		x	x	x			
o		x				x			
p				x		x			
q		x		x		x			
r		x		x	x				
s				x			x		
t				x	x		x	x	
u									Camphor, menthol, eucalyptus ointment
v									Levmetamfetamine, camphor, menthol, methyl salicylate, lavender oil nasal inhaler
w			x		x			x	
x			x	x					
y			x	x	x				
z			x		x		x	x	
aa			x	x			x		
bb			x		x		x		

Source: M012.40 (previously 21 CFR 341.40).