# CITIZEN'S PETITION

November 4, 2015

US Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

The undersigned submit this petition under 21 CFR Part 10.30 to request the Commissioner of Food and Drugs to remove oral phenylephrine from the Final Monograph for OTC nasal decongestant products.

## A. Action Requested

To issue a final rule removing oral phenylephrine from the Final Monograph for OTC nasal decongestant drug products and to remove phenylephrine bitartrate from the 2006 amendment.

### *1. Exact Wording of Existing Regulation*

a. Phenylephrine hydrochloride

The existing wording of the Federal Register dated August 23, 1994 on page 43386[1] under section III is as follows "Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC nasal decongestant drug products are generally recognized as safe and effective and not misbranded. Specifically, the following ingredients are included in the final monograph as OTC oral nasal decongestants: Phenylephrine hydrochloride, pseudoephedrine hydrochloride, and pseudoephedrine sulfate."

b. Phenylephrine bitartrate

The existing wording of the Federal Register dated August 1, 2006 on page 83358[2] is as follows: "The Food and Drug Administration (FDA) is issuing a final rule to amend the final monograph (FM) for over-the-counter (OTC) nasal decongestant drug products (drug products used to relieve nasal congestion due to a cold, hay fever, or other upper respiratory allergies) to add phenylephrine bitartrate (PEB), both individually and in combination drug products in an effervescent dosage form, as generally recognized as safe and effective (GRASE)."

## 2. *Proposed Changes*

a. Phenylephrine hydrochloride

Based on the available evidence, the agency is issuing a final rule establishing conditions under which OTC nasal decongestant drug products are generally recognized as safe and effective and not misbranded. Specifically, the following ingredients are included in the final monograph as OTC oral nasal decongestants: pseudoephedrine hydrochloride, and pseudoephedrine sulfate. Phenylephrine has been removed from the final monograph.

b. Phenylephrine bitartrate

The Food and Drug Administration (FDA) is issuing a final rule to amend the final monograph (FM) for over-the-counter (OTC) nasal decongestant drug products (drug products used to relieve nasal congestion due to a cold, hay fever, or other upper respiratory allergies) to remove phenylephrine bitartrate (PEB), both individually and in combination drug products in an effervescent dosage form.

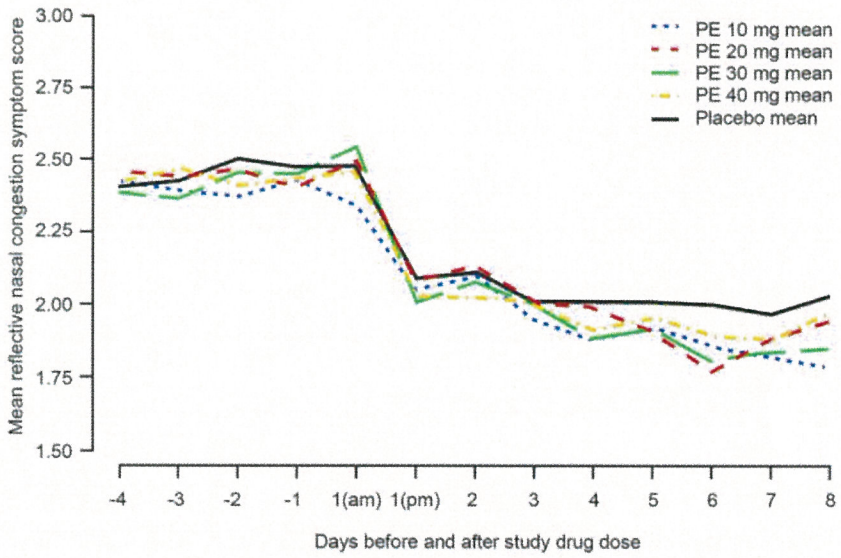
## B. Statement of Grounds

On February 6, 2007, we submitted a Citizen's Petition to FDA requesting that the dosage of oral phenylephrine (PE) be re-evaluated and that approval for use in children < 12 years be withdrawn (Docket # 2007P-0047/CP1).[3] The basis of the request was our systematic review and meta-analysis of the studies considered by the agency when including oral PE in the Final Monograph for OTC nasal decongestant drug products.[4] Also, there is no data on the safety of PE in children <12 yr.

The agency convened its Nonprescription Drugs Advisory Committee on December 14, 2007[5] and they concluded that available evidence "is suggestive of efficacy" mainly based on nasal airway resistance data. Also, nine of the 12 committee members voted that "new studies on response to higher doses were required" and a member of the Division of Nonprescription Drug Products expressed a preference for subjective symptom scores over objective measurement of nasal airway resistance to support the use of PE for temporary relief of nasal congestion.

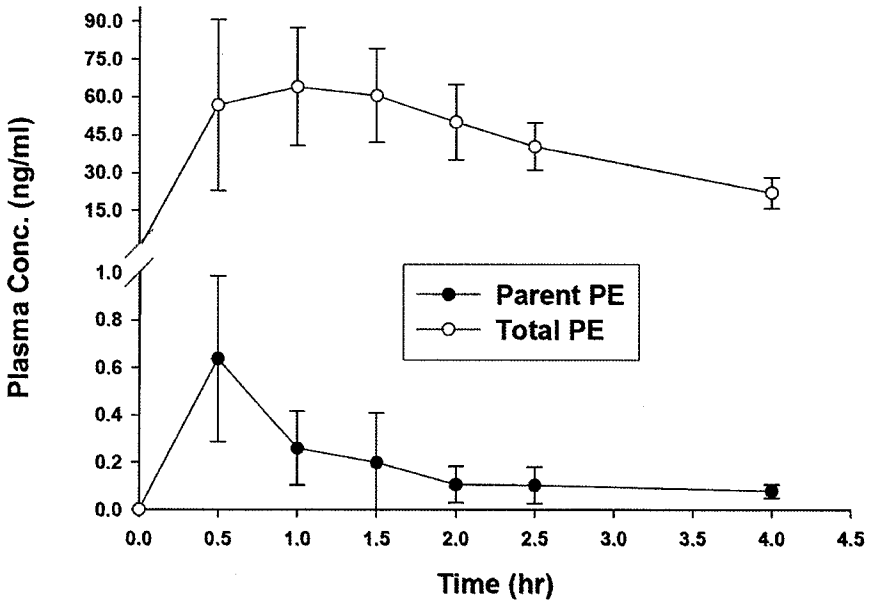
Schering-Plough Pharmaceuticals responded to the recommendations of the Committee and the Division by conducting a multicenter, phase 2, parallel trial among 539 adults with seasonal allergic rhinitis.[6] Subjects were treated with either PE 10 mg tablets at fixed doses of 10, 20, 30 or 40 mg or placebo for 7 days. Subjects were given 5 tablets for each dose consisting of various combinations of Sudafed-PE and a red concave placebo that was not exactly matching. Thus, the study was not quite double-blind but neither investigators nor subjects knew what dose they were assigned. The primary efficacy endpoint was

the mean change from baseline to the end of the study period in daily reflective nasal congestion score. There were no significant differences between placebo and active treatment groups:




PE was well tolerated at doses up to 30 mg; the frequency of gastrointestinal complaints was numerically greater in the 40 mg dose group.

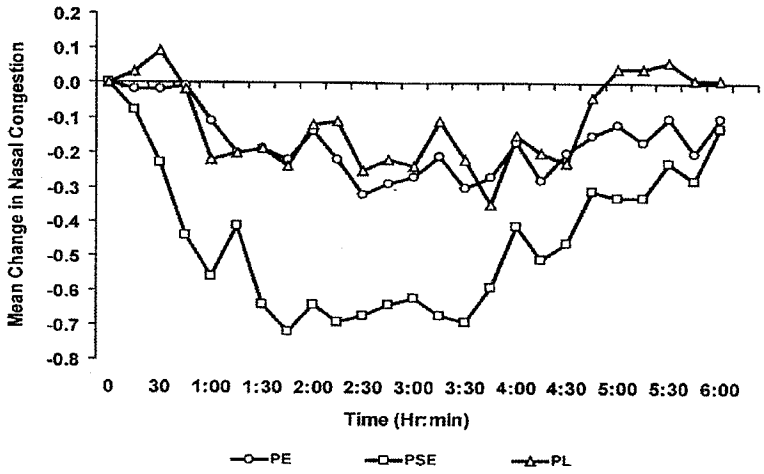
Another manufacturer, McNeil Consumer Healthcare, conducted a pharmacokinetic, safety and cardiovascular tolerability study of PE.[7] It was a randomized, double-blind, placebo controlled single dose, four-treatment crossover study in 28 healthy subjects. There was no difference in safety endpoints between placebo and 10, 20 and 30 mg of PE even though systemic exposure increased disproportionately with dose. This is noteworthy since both the relief of congestion and systemic endpoints such as change in blood pressure and pulse are mediated by alpha adrenergic stimulation. The absence of a significant effect on the latter at the higher doses suggest that the concentrations reached are not sufficient to stimulate alpha adrenergic receptors. Consistent with this concept is a bioavailability study of oral PE conducted by Schering-Plough and presented at the 2007 Advisory Committee Meeting.[8] In that study, the area under the plasma concentration time curve for the unconjugated, pharmacologically active PE was only 1% of the total plasma concentration, indicating very poor oral bioavailability i.e., inactivation in the gut and during the first pass through the liver by monoamine oxidase and sulfotransferases:



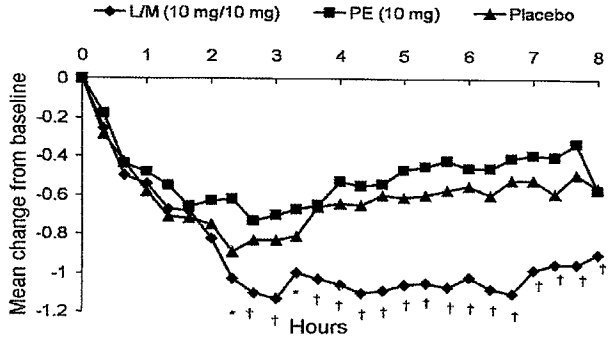

Unconjugated PE plasma concentrations from several more recent studies have been within the same range.[9-11] Interestingly, co-administration of PE with acetaminophen doubles the bioavailability of PE[10-11] presumably by inhibiting sulfotransferases in the gut.

In contrast to oral administration, alpha adrenergic stimulation is observed when PE is administered intravenously[12] or topically in the nose[13] or eyes.[14]

Two additional studies published in 2009 provide further evidence of the absence of a decongestant effect from the FDA-approved nonprescription dose of 10 mg. Horak et al[15] conducted a 3-way crossover, placebo-controlled study of the nasal decongestant effect of single doses of PE 12 mg, pseudoephedrine 60 mg or placebo among 39 grass-sensitive adults exposed to grass pollen in the Vienna Challenge Chamber. PE was not significantly different from placebo in the mean change in subjective nasal congestion scores whereas pseudoephedrine, a positive control in the study, decreased congestion significantly greater than placebo and PE:




Lastly, Day et al[16] reported the results of a single-dose, double-blind, double-dummy, randomized, parallel group, single-center study of loratadine-montelukast, PE 10 mg and placebo among 379 subjects with seasonal allergic rhinitis exposed to ragweed pollen in an Environmental Exposure Unit. While the antihistamine-leukotriene receptor antagonist combination (L/M) significantly decreased nasal congestion scores over a six hour period when compared to placebo, there was no difference between PE and placebo:




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

Thus, the results of the 4 studies reported after the 2007 Advisory Committee Meeting[6,7,15,16] clearly demonstrate that PE is no more effective than placebo in decreasing nasal congestion and increasing the dose fourfold did not provide additional benefit.

## C. Environmental Impact Statement

We do not have the resources to conduct an environmental impact analysis. However, FDA has previously determined that amending the final monograph to include phenylephrine bitartrate does not have a significant environmental

impact.[2] Thus, it is unlikely that this petition, if approved, will have an environmental impact.

### *D. Economic Impact Statement*

We do not have the resources to determine the economic impact on small entities. However, removing PE from the OTC market place will not adversely affect patients with nasal stuffiness. Pseudoephedrine is available behind the counter in pharmacies. Alternatively, those with a viral upper respiratory tract infection can purchase OTC topical nasal decongestants such as phenylephrine, oxymetazoline (Afrin®) or naphazoline while those with nasal stuffiness from allergic rhinitis can purchase OTC nasal corticosteroids such as fluticasone (Flonase®) or triamcinolone (Nasacort®). These products are of proven efficacy and safety, and are available in convenience stores, grocery stores, as well as in front of the counter in pharmacies.

### E. Certification

The undersign certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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