CITIZEN'S PETITION

February 1, 2007

Division of Dockets Management
Food and Drug Administration
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 amend the dosage of oral phenylephrine listed in the Final Monograph on oral decongestants[1] and in the Final Rule adding phenylephrine bitartrate.[2]

A. Action Requested

We propose that the maximum dose of oral phenylephrine in the labeling for patients ≥12 years should be increased and that approval for use in children <12 years should be withdrawn. Additional studies should be required to validate that a 25-mg dose would be more efficacious than a 10-mg dose of phenylephrine given every 4 hours, and as safe.

1. Exact Wording of Existing Regulation

a. Phenylephrine hydrochloride (attachment #1)

The existing wording of the Federal Register dated August 23, 1994 on page 43410[1] under section (1), Oral, nasal decongestants – (i) For products containing phenylephrine hydrochloride identified in 341.20 (a) (1) is as follows: *"Adults and children 12 years of age and over: 10 mg every 4 hours not to exceed 60 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. Children 2 to under 6 years of age: 2.5 mg every 4 hours not to exceed 15 mg in 24 hours. Children under 2 years of age: consult a doctor."*

b. Phenylephrine bitartrate (attachment #2)

For dosage listed for phenylephrine bitartrate in the Federal Register, August 1, 2006, page 43362[2], under (iii) For products containing phenylephrine bitartrate identified in 341.20 (a) (4) is as follows: *"Adults and children 12 years of age and over: 15.6 mg every 4 hours not to exceed 62.4 mg in 24 hours. Children 6 to under 12 years of age: 7.8 mg every 4 hours not to exceed 31.2 mg in 24 hours. Children under 6 years of age: Ask a doctor."*

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2. *Proposed Changes*

a. Phenylephrine hydrochloride

Adults and children 12 years of age and over: 25 mg every 4 hours not to exceed 100 mg in 24 hours. Children <12 years of age: ask a doctor.

b. Phenylephrine bitartrate

Adults and children 12 years of age and over: 40 mg every 4 hours not to exceed 160 mg in 24 hours. Children under 12 years of age: Ask a doctor.

B. Statement of Grounds

In our peer reviewed Letter to the Editor published in the July, 2006 issue of *The Journal of Allergy and Clinical Immunology*[3], we concluded that phenylephrine is unlikely to relieve nasal stuffiness at the maximum FDA approved dose of 10 mg (attachment #3). This was based upon nasal airway resistance data from 11 studies containing a 10-mg dose arm evaluated by the FDA Review Panel[4-14] and two subsequently published studies not reviewed by the Panel; an efficacy study favoring phenylephrine[15] and a bioavailability study indicating that only 38% of the dose of phenylephrine reached the systemic circulation.[16]

Subsequent to the publication of our letter, we conducted a systematic review of the literature. Fifteen studies were identified;[4-15,17-19] 12 of them included a 10-mg dose.[4-15] Of these 12 studies, only five (42%) demonstrated a difference from placebo in decreasing nasal airway resistance.[5-8,15] In contrast, 8 of 10 (80%) of studies including the 25-mg dose demonstrated a significant difference from placebo.[4-7,15,17-19] In the Cohen study,[15] for example, which apparently was not reviewed by the Panel, there was a statistically significant dose-response for decreasing nasal airway resistance; the 25-mg dose produced a greater reduction than either the 10-mg or 15-mg doses. All of these were randomized, double-blind, crossover studies that measured both symptom scores and improvement in nasal airway resistance, potentially a "gold standard" for the objective measurement of obstructed nasal airflow.[20]

Eight of the studies including a 10-mg dose met the criteria for a meta-analysis.[21] Phenylephrine 10 mg did not affect nasal airway resistance more than placebo; the mean maximal reduction (95% CI) in relative change of nasal airway resistance from baseline between phenylephrine and placebo was 10.1% (-3.8%, 23.9%). (Note that the 95% CI for the difference between phenylephrine and placebo included zero.) In contrast, there was a significant difference between phenylephrine 25 mg and placebo; the mean reduction in maximal nasal airway resistance was 27.6% (17.5%, 37.7%) (attachment #4). Patient-reported decongestion was not consistently better for any phenylephrine dose compared to placebo, and nasal airway resistance was a more sensitive measurement of

efficacy. However, the heterogeneity across studies included in this meta-analysis suggests possible measurement bias. This limits the conclusion about which is the most efficacious dose.

It is noteworthy that all of the studies performed by Elizabeth Biochemical showed that phenylephrine was significantly better than placebo regardless of dose used,[5,6,17-19] whereas studies conducted by other laboratories generally found no difference between the 10-mg dose and placebo. Also, the magnitude of the difference between phenylephrine 10 mg and placebo (e.g. -41%) in the studies conducted by Elizabeth Biochemical[5,6,17-19] were much larger than the difference found at other laboratories who found a difference between 10 mg and placebo. In Clintest #1, for example, the difference was only -16.5%.[7] This raises the question that there may have been some type of bias in the studies conducted by Elizabeth Biochemical or in the reporting of the results.

A recently published literature review[22] and a Cochrane Review[23] similarly concluded that phenylephrine was not effective orally while there was support for the efficacy of this drug when administered as a topical nasal solution.

None of the 15 studies reviewed for this petition demonstrated a significant difference from placebo for heart rate or blood pressure for all doses studied.[21]

The literature search revealed additional reports pertinent to this petition. Oral decongestants that reach the systemic circulation stimulate α_1 receptors in the nasal mucosa and will also stimulate peripheral α_1 receptors in blood vessels, producing vasoconstriction and an increase in blood pressure in a concentration-dependent manner.[24] Chua and Benrimoj evaluated the literature on the effects of non-prescription sympathomimetic agents on blood pressure.[25] They found that a dose of ≥120 mg of oral phenylephrine was required to increase blood pressure in normotensive subjects, i.e., a dose that was at least 12 times the current maximum FDA-approved dose. In contrast, pseudoephedrine produced a significant increase in blood pressure at ≥120 mg, i.e., only twice the maximum recommended dose. The likely explanation for the difference in therapeutic margins between phenylephrine and pseudoephedrine is the high first pass metabolism of oral phenylephrine.[16] It is unlikely that the differences are related to differences in affinity for the α_1 receptor since very small doses of phenylephrine given intravenously produce a marked pressor effect.[24] Also, Chua and Benrimoj cited a few studies indicating that administration of phenylephrine in the form of eye drops, particularly at higher concentrations, was capable of producing an increase in blood pressure in normotensive subjects.[25] The ophthalmic route circumvents the sulfonation of phenylephrine in the gut and the deamination by monoamine oxidase during the first pass through in the liver.

Elis et al[26] reported that 45 mg of phenylephrine given alone did not increase blood pressure, but when taken with a monoamine oxidase inhibitor (MAOI) produced an alarming increase in BP requiring reversal with phentolamine, an α

blocker. They also noted that phenylephrine 10 mg alone did not produce any effect on blood pressure, but when given concurrently with a MAOI, this dose produced an increase in blood pressure. These data suggest that monoamine oxidase plays an important role in the first-pass metabolism of phenylephrine and blocking the inactivation of phenylephrine by monoamine oxidase allows greater concentrations to reach α_1 receptors.

Since an oral dose of 120 mg or higher of phenylephrine is required to increase blood pressure in normotensive patients, we believe that increasing the labeled dose to 25 mg should not increase the risk of systemic adverse effects. It would be prudent, however, to conduct further safety assessment of the 25-mg dose.

During our systematic review of the literature, an abstract in ClinicalTrials.gov was discovered that is relevant to this petition.[27] Schering-Plough has conducted a double-blind, randomized, placebo-controlled trial comparing phenylephrine 12 mg and pseudoephedrine 60 mg in patients with seasonal allergic rhinitis. The congestion score decreased by 7.1% for phenylephrine compared to 2.2% for placebo treatment (p=0.56). Phenylephrine was not significantly different from placebo at any time point. In contrast, pseudoephedrine decreased the congestion score by 21.7% and was significantly more effective than either phenylephrine or placebo (attachment #5).

Wyeth submitted to FDA on November 16, 2006 the results of three unpublished studies that they contend supports the efficacy of phenylephrine (Docket No. 1976N-0052N). We disagree with their contention. In study AHR-GIA, there was no placebo treatment and the change in nasal airway resistance may have decreased as a function of time and not treatment. Also, they used a p value of <0.1 to indicate "marginally significant", whereas a significant p value is <0.05.

In AHR-4010-3 there were no statistical differences in the results of five of the six study sites. Thus, the statistical difference claimed for the pooled data was driven by only one site. Also, in study #7032 phenylephrine alone was not significantly different from placebo.

Lastly, none of the studies reviewed by the OTC Panel or found in the systematic literature search evaluated the effects of phenylephrine in children <12 years. Therefore, there are no data on either the safety or efficacy of this drug in this vulnerable age group. Consequently, we believe that this drug should only be used in children <12 years under the advice of a licensed prescriber and that FDA should withdraw OTC approval for this age group.

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.

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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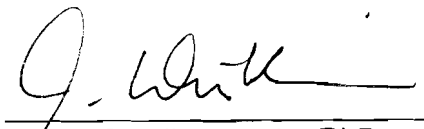

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List of Attachments

1. Dosage of phenylephrine HCl – Fed Reg 1994;59:43410.
2. Dosage of phenylephrine bitartrate – Fed Reg 2006;71:43362.
3. Hendeles and Hatton – letter to the editor, JACI 2006;118:279.
4. Hatton et al – meta-analysis – published online ahead of print.
5. Abstract of results of Schering-Plough Study #P04579.