DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 13 2006

The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Waxman:

Thank you for your letter dated August 23, 2006, regarding provisions in the 2006 reauthorization of the Patriot Act setting a September 30, 2006, deadline for moving all pseudoephedrine products behind-the-counter and concerns about the effectiveness of phenylephrine, an alternative over-the-counter (OTC) decongestant.

The Combat Methamphetamine Act of 2005 (CMEA) was incorporated into the Patriot Act and signed into law on March 9, 2006. Although the CMEA requires "behind-the-counter" sale of all OTC decongestants that are methamphetamine precursors, including pseudoephedrine, consumers can continue to obtain pseudoephedrine-containing products without a prescription. The CMEA did not require or recommend that manufacturers modify their formulations to replace pseudoephedrine with an alternative active ingredient and no changes have been made regarding the Food and Drug Administration's (FDA) past determinations about the safety and efficacy of pseudoephedrine.

Both pseudoephedrine and phenylephrine were evaluated under the OTC drug review dating back to the 1970's. An outside expert advisory panel evaluated both active ingredients, and deemed both as effective and safe decongestants at specified doses. Some manufacturers have elected to bring new decongestant formulations containing phenylephrine to the OTC market as permitted under the OTC monograph for decongestant drugs or under the new drug application (NDA) process. Changes to products regulated under the OTC monograph process, that are permissible under the monograph, do not require approval prior to marketing, and are limited to specific, immediate release formulations of single ingredient or combination ingredient products that have been found to be generally recognized as safe and effective (GRASE). Formulation changes that are made to approved NDA products require prior approval.

The determination of GRASE status for both pseudoephedrine and phenylephrine was based on notice and comment rulemaking. FDA published the report of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Drug Products in the *Federal Register* of September 9, 1976. The panel conducted a review of the information

available about products that were marketed OTC as decongestants at that time. In follow-up, FDA published a Tentative Final Monograph for nasal decongestants in the *Federal Register* of January 15, 1985, and a Final Monograph (FM) on August 23, 1994. The information and data received by FDA in response to each notice was discussed in the subsequent notice. GRASE doses and dosing regimens for pseudoephedrine and phenylephrine were established through this process. Since the publication of the FM, FDA has not received any comments or citizen petitions requesting FDA change the GRASE status of these ingredients.

With regard to Dr. Hendeles' and Haddon's letter in the *Journal of Allergy and Clinical Immunology*, we offer several points:

1. The letter notes that the relative bioavailability of phenylephrine is 38 percent versus 90 percent for pseudoephedrine. There are many other factors that contribute to the potency of an active ingredient. A comparison of the relative bioavailability alone of two different ingredients is not an adequate mechanism for comparing the efficacy of the ingredients. Clinical dosing for a drug generally would account for its bioavailability.
2. The panel report provides a summary of the data reviewed by the panel that supported their recommendation of a phenylephrine 10 milligram dose every four hours. Dr. Hendeles suggests that there were only four studies supporting efficacy whereas the panel report suggests there is more data. All of the data that Dr. Hendeles cites in his letter appear to have been reviewed by the panel.
3. Dr. Hendeles' letter, as noted in your letter, seems to take issue with the fact that the data supporting phenylephrine came from unpublished manufacturer sponsored studies. Studies that are unpublished cannot be viewed less favorably than published studies. All studies reviewed as part of the OTC monograph process are placed in a docket for public inspection. When FDA is provided with the data from unpublished studies, FDA's review can be more rigorous than the review of editors for studies published in a peer reviewed article. New drugs evaluated for approval today under the NDA process commonly depend on manufacturer-sponsored unpublished studies.
4. The availability of studies that seem to support efficacy, and of others that do not, is not a unique occurrence. Aside from various study design and conduct issues, it is often difficult to consistently establish a clinically significant treatment effect for active ingredients in some disease processes during each trial conducted. This is true of nasal symptoms and has been described in the labeling for some products (e.g., ceterizine). The conclusion about the effect of an active ingredient in light of both positive and negative trials is made based on the totality of findings and quality of the data. The number of each type of study outcome is not generally a major factor in this determination.
5. Dr. Hendeles comes to a different conclusion than the expert panel. This difference of opinion alone is not a sufficient basis for FDA to take this to an advisory committee at this time.
6. The design, analysis, and interpretation of studies have evolved in the last 30 years. In this regard, phenylephrine is not unique from the other drug ingredients evaluated in the 1970's and 1980's for OTC or prescription use. FDA is aware that GRASE status for OTC monograph ingredients relies, in many instances, on data that were not

derived from what are currently considered state of the art clinical trials. The advisory panel did find that, on balance, there were sufficient favorable data to include pseudoephedrine and phenylephrine in the OTC monograph. GRASE status for a particular therapeutic category, such as decongestants, is not dependent on a finding of comparability among various ingredients. It is anticipated that various chemical entities within a category will demonstrate differences from one another (e.g., the GRASE dose and dosing interval of pseudoephedrine and phenylephrine are different) and that individual patients will respond somewhat differently to each drug. If a consumer does not feel that phenylephrine provides the type of relief that they obtained with pseudoephedrine, they have the option of not purchasing it and purchasing pseudoephedrine instead.

FDA believes that ample opportunity was provided for interested parties to comment during the rulemaking process and to provide data that refute the findings discussed in the rulemakings. We are not aware of data that refute the conclusions of the advisory panel and subsequent OTC monograph review and, therefore, do not have substantive material to present for discussion at an advisory committee meeting. FDA continues to work with drug sponsors to explore ways to reformulate products to mitigate the abuse potential of such products without significantly impacting the patient benefit these safe and effective products have provided.

FDA has communicated with Dr. Hendeles and explained that he can submit a citizen petition requesting that FDA take an action related to phenylephrine. Any petition he submits will have to include data to support a request for FDA action. Submission of a citizen petition would give all interested individuals the opportunity to weigh in on this issue. At present, we do not plan to take this issue to an advisory committee, but would reconsider if sufficient additional information becomes available.

Thank you again for contacting us concerning this matter. Please let us know if you have further questions.

Sincerely,

Michael Mital

for David W. Boyer
Assistant Commissioner
for Legislation