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Charles J. Raubicheck
Frommer Lawrence & Haug LLP
745 Fifth Avenue
New York, NY 10151

Re: Docket No. 2005P-0291/CP1

Dear Mr. Raubicheck:

This letter responds to your citizen petition dated July 22, 2005, requesting that the Food and Drug Administration (FDA) require applicants filing an abbreviated new drug application (ANDA) or a section 505(b)(2) new drug application (NDA) for inhalation drug products that contain a combination of albuterol sulfate and ipratropium hydrobromide, administered by nebulization for the treatment of chronic obstructive pulmonary disease (COPD), to submit certain information regarding the safety of the proposed drug product. You request that applicants be required to submit information on: (1) the identity, quantity, and limits of impurities in the drug product; (2) biological safety qualification testing of the drug substance degradation or reaction impurities that exceed a threshold level; and (3) results of studies that identify, quantitate, and limit the amount of recurring leachables into the drug product from the container closure system. Although we deny your petition request, the information that you request be required in ANDAs or 505(b)(2) applications for inhalation products that contain a combination of albuterol sulfate and ipratropium hydrobromide is already recommended by the FDA guidances described below.

You cite two FDA guidance documents in your petition: (1) *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation* (July 2002) (CMC guidance); and (2) *Q3B(R) Impurities in New Drug Products* (November 2003) (Impurities guidance).¹ The CMC guidance provides recommendations on the chemistry, manufacturing, and controls documentation that should be submitted in NDAs and ANDAs for nasal spray and inhalation solution, suspension, and spray drug products intended for local and/or systemic effect. The Impurities guidance provides recommendations on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances. Further, FDA has issued draft guidances on impurity topics specifically for ANDA applicants that provide useful information. These draft guidances include: (1) *ANDAs: Impurities in Drug Products* (August 2005), and (2) *ANDAs: Impurities in Drug Substances* (January 2005). FDA guidance documents represent the current thinking of the agency regarding the subject of the guidance (21 CFR 10.115). Guidance documents

¹ *Q3B(R)* was revised and issued as *Q3B(R2) Impurities in New Drug Products* in July 2006.

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do not, however, establish legally enforceable rights or responsibilities, and they do not legally bind the public or FDA (§ 10.115(d)(1)).

We have chosen to proceed by issuing guidance rather than by regulation because we recognize that our knowledge and understanding of these types of drug products and the procedures for minimizing impurities are constantly evolving. Guidance can be updated more quickly than regulations to account for new developments, technologies, or studies. In addition, a company or manufacturer is not required to follow the approach outlined by the guidance document, and may choose to use an approach other than the one set forth in a guidance document. For example, a company may take advantage of improvements in technology even before we have issued a revised guidance to update our recommendations. However, the alternative approach must comply with the relevant statutes and regulations (§ 10.115(d)(2)). Consequently, we recommend that ANDA and 505(b)(2) applicants for inhalation drug products containing a combination of albuterol sulfate and ipratropium hydrobromide, administered by nebulization for the treatment of COPD, submit information in accordance with the above-indicated FDA guidances. In all cases, applicants must comply with applicable statutes and regulations to ensure the safety and efficacy of the proposed product under the conditions of use prescribed, recommended, or suggested in the labeling.

Accordingly, your petition is denied. Thank you for your interest in promoting public awareness of the safe use of medications.

Sincerely,



Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research