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July 22, 2005

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Division of Dockets Management (HFA-305)  
Food and Drug Administration  
Room 1061  
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CITIZEN PETITION

The undersigned submits this Citizen Petition, in quadruplicate, pursuant to 21 U.S.C. § 355(j) and FDA regulation 21 C.F.R. § 10.30.

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**A. Action Requested**

That the Food and Drug Administration (FDA) refuse to approve Abbreviated New Drug Applications (ANDAs) or Section 505(b)(2) New Drug Application (NDAs) for inhalation drug products containing a combination of the active ingredients albuterol sulfate and ipratropium hydrobromide ("albuterol-ipratropium inhalation drug products"), administered by nebulization for the treatment of chronic pulmonary obstructive disorder ("COPD"), unless each such ANDA or Section 505(b)(2) NDA contains, for reasons of safety:

- the results of studies that **identify, quantitate and limit impurities** in the drug product;
- **biological safety qualification testing of drug substance degradation or reaction impurities** exceeding threshold levels; and
- the results of studies that **identify, quantitate and limit recurring leachables** into the drug product from the container closure system.

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**B. Statement Of Grounds**

Inhalation drug products, especially those administered by nebulization, require special safety assessments for impurities, because a significantly large

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volume of substances (active drug ingredient, propellant, solvent and/or excipients) is introduced into the lungs with every dose. For albuterol-ipratropium inhalation drug products, this principle is especially important, since the volume of such substances introduced into the lungs is approximately 45 times greater with these products (dose/volume (63 mcl VS 3 ml) than the volume with typical metered-dose inhaler drug products. In order to assure the safety of COPD patient populations, particularly since such patients often have other health complications, it is important for FDA to require manufacturers to assure that albuterol-ipratropium inhalation drug product formulations are controlled for impurities and leachables, through the procedures and tests outlined in this petition.

**1. Listing and Limits for Impurities in Specifications  
of Albuterol-Ipratropium Inhalation Drug Products**

Certain impurities can be introduced in a solution dosage form of an inhalation drug product intended for administration via nebulization, such as an albuterol-ipratropium inhalation drug product. This can occur as a result of: (a) different sources of a drug substance (active ingredient); (b) different synthetic routes producing a drug substance; (c) different method of manufacture of a drug substance; (d) different long-term storage conditions of a drug substance or the drug product; and (e) different excipients and/or components used in the drug product.

Known impurities in the drug substances present in albuterol-ipratropium inhalation drug products include albuterol aldehyde in albuterol sulfate, and ipratropium alcohol in ipratropium hydrobromide. Furthermore, the specifications for albuterol sulfate are quite broad, in order to accommodate non-inhalation use of this substance, so that there may be other unknown impurities in the drug substance albuterol sulfate from a particular source.

FDA has established criteria for impurities in inhalation solution drug products, which include albuterol-ipratropium inhalation drug products. See FDA's *Draft Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing and Controls Documentation* ("Inhalation Solution Guidance", copy attached as Exhibit A), July, 2002, p. 12. These criteria mandate that:

- (a) the levels of impurities in an inhalation solution drug product, including but not limited to degradation products of each drug substance, be determined by validated analytical procedures;

- (b) acceptance criteria be set for individual and total impurities; and
- (c) all impurities appearing at levels of 0.1% or greater be individually listed in the drug product specification, and appropriate limits for each such impurity should be set forth in the specification. *Id.*

This petition urges FDA to assure that the above specification requirements and reporting of results for impurities at levels of 0.1% or greater are complied with in all ANDAs and Section 505(b)(2) NDAs for albuterol-ipratropium inhalation drug products, for the protection and safety of COPD patients who take these drug products on a chronic basis.

Analytical results for impurities should be reported in an ANDA or Section 505(b)(2) NDA for all relevant batches of the drug product (clinical safety and efficacy batches, stability batches, biobatch). See FDA's *Guidance Q3B(R): Impurities in New Drug Products*, November 2003, ICH, Rev. 1 ("Impurities Guidance," copy attached as Exhibit B hereto), p. 4.

## **2. Biological Safety Qualification for Albuterol and Ipratropium Degradation / Reaction Impurities**

Beyond the studies described above, additional biological safety data for certain albuterol sulfate and ipratropium hydrobromide impurities should be submitted in all ANDAs and Section 505(b)(2) NDAs for albuterol-ipratropium inhalation drug products.

The Impurities Guidance requires the qualification (establishing the biological safety) of impurities that are degradation products of a drug substance, or reaction products of a drug substance with an excipient and/or immediate container-closure system ("degradation / reaction impurities"). (Impurities Guidance, Exhibit B, pp. 1, 4). Biological safety qualification of such impurities is mandated when the levels of the impurities in an inhalation solution drug product exceed certain thresholds. *Id.*, pp. 3-7, Attachment 1. The threshold for biological safety qualification of a degradation / reaction impurity is based on the maximum daily dose of the drug product, and is expressed as a percentage of the drug substance or total daily intake (TDI) of the impurity. *Id.*, Attachment 1.

A single dose of Dey Laboratories' DuoNeb<sup>®</sup>, the reference listed drug for albuterol-ipratropium drug inhalation products, contains 3.0 mg of albuterol sulfate

and 0.5 mg of ipratropium hydrobromide, and the total recommended daily dose is one such dose administered 4 times daily, with up to 2 additional doses if needed. Therefore, the maximum daily dose is 18 mg of albuterol sulfate and 3 mg of ipratropium hydrobromide.

The Impurities Guidance calls for biological safety qualification of a degradation / reaction impurity when the maximum daily dose of the drug product is between 10 mg and 100 mg and the impurity exceeds a threshold of 0.5% of the drug substance or 200  $\mu\text{g}$  of the TDI of the impurity. (Impurities Guidance, Exhibit B, Attachment 1). Such qualification is also required when the maximum daily dose is less than 10 mg and such an impurity exceeds a threshold of 1.0% of the drug substance or 50  $\mu\text{g}$  of the TDI of the impurity. *Id.*

Accordingly, since the maximum daily dose of albuterol sulfate in an albuterol-ipratropium inhalation drug product is 18 mg, biological safety qualification is required for an albuterol sulfate degradation / reaction impurity present at a level greater than the threshold of 0.5% of albuterol sulfate or 200  $\mu\text{g}$  of the TDI of the impurity, whichever is lower.

In addition, since the maximum daily dose of ipratropium hydrobromide in an albuterol-ipratropium inhalation drug product is 3 mg, biological safety qualification is required for an ipratropium hydrobromide bromide degradation / reaction impurity present at a level greater than the threshold of 1.0% of ipratropium hydrobromide or 50  $\mu\text{g}$  of the TDI of the impurity, whichever is lower.

When the above thresholds are exceeded, biological qualification of the degradation / reaction impurity requires: (a) submission of published safety or clinical studies establishing the biological safety of the impurity at the level observed; or (b) the conduct and submission of toxicity studies (one species, up to 90 days, with histopathology) demonstrating biological safety. (Impurities Guidance, p. 6, Attachment 3). As an alternative to option (b), a clinical safety study of reasonable duration should be required.

These additional premarket tests are necessary in an ANDA or Section 505(b)(2) NDA for an albuterol-ipratropium inhalation drug product, to demonstrate that identified drug substance degradation and reaction impurities in the product, that are quantitated at a threshold level of potential concern, do not present safety hazards to ultimate patients.

### 3. Testing for Leachables

For safety considerations, the container closure system of inhalation solution drug products should be composed of materials that minimize leachables. (Inhalation Solution Guidance, p, 23). For inhalation solutions packaged in semipermeable containers (e.g., low density polyethylene), where there is protective packaging or if the immediate containers are exposed to components of the packaging that include paper labels, FDA requires that the presence and levels of leachables originating from the packaging or labels be determined. *Id.*, p.19. Procedures used for these determinations should be validated, and have suitable detection and quantitation limits for leachables. *Id.* Acceptance criteria for the leached compounds should be toxicologically qualified and documented. *Id.*

For semipermeable containers, the absence of small chain hydrocarbons should also be shown, and specifications for the absence of small chain hydrocarbons, antioxidants and Irganox compounds (present if low density polyethylene containers are used) should be established, utilizing state of the art, sensitive analytical methods.

Further, the identity and concentration of recurring leachables in an inhalation solution drug product should be determined through the end of the product's shelf life. (Inhalation Solution Guidance, p, 23). The results of leachables testing should be compared with the extractables profile of the container closure components derived from various control extraction study conditions. The levels of extractables should be greater than the levels of leachables. *Id.* If this is not the case after three months of accelerated stability testing conditions, real-time long-term data are necessary to establish an expiration date. *Id.*

FDA should require such leachable testing before approving any ANDA or Section 505(b)(2) NDAs for an albuterol-ipratropium inhalation drug product.

#### C. Environmental Impact

Petitioner claims a categorical exclusion from the requirement of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

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**D. Economic Impact**

Pursuant to 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of this Petition.

**E. Certification**

The undersigned certifies that, to their best knowledge and belief, this Suitability Petition includes all information and views upon which the Petition relies, and includes representative data and information known to Petitioner which are unfavorable to the Petition.

Respectfully submitted,

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By   
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Enclosures

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