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March 8, 2004

*By Hand*

Food and Drug Administration  
Dockets Management Branch (HFA-305)  
Food and Drug Administration  
Department of Health and Human Services  
5600 Fishers Lane Room 1061  
Rockville, Maryland 20852

RE: Second Supplemental Submission Re: Citizen Petition  
Submitted by the US Stakeholders Group on MDI Transition  
(FDA Docket No. 03P-0029)

Dear Sir or Madam:

The International Pharmaceutical Aerosol Consortium (IPAC)<sup>1</sup> hereby submits additional supplemental comments to the Citizen Petition submitted by the U.S. Stakeholders Group on MDI Transition (Stakeholders' Petition) on January 29, 2003. Specifically, IPAC urges FDA to expeditiously issue proposed and final rules to remove albuterol metered-dose inhalers (MDIs) from the agency's list of essential uses of ozone-depleting substances (ODS) at 21 CFR § 2.125(e), with an effective date no later than December 31, 2005.

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<sup>1</sup> IPAC is an association of leading manufacturers of metered-dose inhalers (MDIs) used for the treatment of asthma, chronic obstructive pulmonary disease (COPD), and other respiratory illnesses. IPAC members are: AstraZeneca, Aventis Pharmaceuticals, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, and IVAX.

Armstrong Pharmaceuticals • AstraZeneca • Aventis Pharmaceuticals  
Boehringer Ingelheim • Chiesi Farmaceutici • GlaxoSmithKline • IVAX

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The Stakeholders' Petition requests FDA to initiate rulemaking to remove albuterol MDIs from the agency's list of essential uses of ODS. IPAC welcomes FDA's commitment to act on the Stakeholders' Petition, stated in the agency's December 22, 2003 Notice of Regulatory Plan, by issuing a proposed rule by March 2004.<sup>2</sup> However, IPAC believes that FDA should issue the final rule sooner than the March 2005 date projected in FDA's notice; it is not unreasonable to expect that FDA could evaluate comments and issue a final rule within 2004.

Furthermore, IPAC agrees with the tentative determination by FDA that the regulatory criteria for removal of an essential use have been met with regard to albuterol MDIs, as well as the tentative determination by FDA and the Environmental Protection Agency (EPA) that currently marketed CFC-free MDIs are satisfactory alternatives to CFC albuterol MDIs.<sup>3</sup> IPAC believes that based on information on the record, FDA should propose to remove CFC albuterol from its essential use list with that removal to take effect by December 31, 2005.

Last year, IPAC supported a proposed Montreal Protocol decision that would have ended essential use authorizations for CFCs for single-moiety albuterol MDIs after 2005. As detailed in the attached IPAC statement to the 15<sup>th</sup> Meeting of the Parties to the Montreal Protocol, the decision was consistent with patient health and good for the environment. Ultimately this decision was not adopted by the Parties, due in significant part to US opposition. IPAC was disappointed in the outcome and we continue to believe that ceasing new CFC production and importation for single-moiety albuterol MDIs by end 2005 is reasonable and prudent, in light of the closure by December 31, 2005 of the CFC production facility in Weert, Netherlands - the principle supplier of pharmaceutical-grade CFCs to the United States - and the wide availability of CFC-free albuterol MDIs in developed countries. Consistent with that position, IPAC believes that FDA should propose a December 31, 2005 effective date for albuterol non-essentiality in the United States.

Indeed, as the representative association of several leading MDI manufacturers, IPAC believes that the removal of albuterol MDIs from the list of essential uses is overdue. As an industry, we have known since at least 1992 - 12 years - that the use of CFCs in MDIs was slated for phase out and that we needed to reformulate our products to CFC-free versions. The threat to the ozone layer represented by CFCs, and the resulting developments under the Montreal Protocol,

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<sup>2</sup> See Use of Ozone-Depleting Substances: Removal of Essential Use Designation; Albuterol, 68 Fed. Reg. 72479 (Dec. 22, 2003) (hereinafter "Notice of Regulatory Plan").

<sup>3</sup> Id.

have made it clear that CFC MDIs were destined for replacement or removal from the market.

Responsible MDI manufacturers, both branded and generic, responded by investing in excess of a billion dollars in research, development, and manufacture of CFC-free alternatives. Moreover, in the United States, each CFC-free MDI has had to undergo extensive clinical testing and satisfy other rigorous regulatory requirements for approval as an entirely new drug product. This commitment has yielded positive results: several CFC-free alternatives have been approved and on the market for a number of years in markets around the world. In the United States, two CFC-free albuterol MDIs have been on the market for two years now. Having urged the MDI industry for over a decade to reformulate their products, it would be manifestly inconsistent for the U.S. Government to punish the companies that have invested so much and to reward other companies - which have made no effort to phase out CFC use - by proposing an inappropriate delay in albuterol non-essentiality.

Importantly, patients and their physicians have taken the lead in promoting the transition to CFC-free MDIs in the United States, through the U.S. Stakeholders Group. The Stakeholders Group strongly supports albuterol non-essentiality in the U.S., based on their belief that patients will experience an overall benefit from the re-evaluation of their treatment regimens and that failure to make the transition to CFC-free treatments in a timely manner will create significant health risks to patients due to future CFC MDI supply uncertainty. The Stakeholders' Petition points out that physicians serving on FDA's Pulmonary and Allergy Drugs Advisory Committee (PADAC) "have expressed concern that some patients may be relying too heavily on albuterol 'rescue' inhalers and might benefit from regular maintenance products."<sup>4</sup> In 1999, the PADAC heard testimony that the CFC MDI transition offers a "unique opportunity to refocus attention on the proper diagnosis and management of asthma and to revitalize the relationship between physicians and other health care providers and patients."<sup>5</sup> IPAC strongly agrees that the transition provides an important opportunity to educate patients and improve disease management.

IPAC further notes that the U.S. Stakeholders Group has submitted comments to the FDA docket in support of a 2005 end date for the use of CFC albuterol MDIs in the United States.

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<sup>4</sup> See Citizen Petition at 4.

<sup>5</sup> See Citizen Petition at 4.

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In summary, IPAC urges FDA to issue a proposed rule by March 31, 2004, and a final rule no later than December 31, 2004, to remove albuterol MDIs from the agency's list of essential uses by no later than December 31, 2005. IPAC thanks FDA for its time and attention to this very important matter.

Sincerely,

A handwritten signature in cursive script, appearing to read "Joseph M. Ferrara".

Joseph Ferrara  
IPAC Chair