



IPAC

INTERNATIONAL PHARMACEUTICAL AEROSOL CONSORTIUM

07/03/04 10:12:45

**IPAC Comments on
Notice of Proposed Rulemaking for
Use of Ozone-Depleting Substances: Removal of
Essential Use Designations**

(69 *FED. REG.* 33602, June 16, 2004)

03P-0029

C 22

Table of Contents

INTRODUCTION	1
COMMENTS ON THE PROPOSED RULE.....	2
A. APPLICATION OF THE CRITERIA TO REMOVE THE ESSENTIAL USE DESIGNATION FOR SINGLE-MOIETY ALBUTEROL CFC MDIS.....	2
▪ Non-ODS Products have the Same Active Moiety with the Same Route of Administration, for the Same Indication, and with Approximately the Same Level of Convenience of Use	
▪ Supplies and Production Capacity for the Non-ODS Products Will Exist at Levels Sufficient to Meet Patient Need	
▪ Adequate US Postmarketing Use Data Are Available for the Non-ODS Products	
▪ Patients are Adequately Served by the Non-ODS Products	
B. EFFECTIVE DATE FOR FINAL RULE.....	6
CONCLUSION	7

I

INTRODUCTION

The International Pharmaceutical Aerosol Consortium (IPAC) is an association of leading manufacturers of MDIs for the treatment of asthma and chronic obstructive pulmonary disease (COPD). These comments are submitted on behalf of AstraZeneca, Aventis, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline and IVAX. IPAC was created in response to the mandates of the Montreal Protocol. Since its inception more than fifteen years ago, IPAC has sought a smooth and efficient transition from CFC MDIs that balances public health and environmental protection. IPAC is firmly committed to the transition from CFC MDIs as evidenced by the extraordinary investment and efforts that its members have undertaken for over more than a decade.

IPAC has long engaged in policy development relating to the MDI transition at the international level and within national governments. IPAC participated in the rulemaking process culminating in the issuance of the FDA's Final Rule entitled *Use of Ozone-Depleting Substances; Essential Use Designations* (67 FED. REG. 48370, July 24, 2002: the "2002 Rule"), including submission of detailed comments on the criteria to be used to assess the essentiality of CFC MDIs. IPAC fully supports the 2002 Rule and called for its effective date to be accelerated in order to promote the real beginning of the transition to the replacement CFC-free products.

These comments are submitted in response to the Notice of Proposed Rulemaking entitled *Use of Ozone-Depleting Substances, Removal of Essential-Use Designations* (69 FED. REG. 33602, June 16, 2004 -- the "Proposed Rule"). As detailed in these comments, it is clear that the criteria set forth in § 2.125(g)(4) have been or can be met by the end of 2005 and, therefore, IPAC requests that FDA issue, no later than December 31, 2004, the Final Rule declaring single-moiety albuterol CFC MDIs¹ non-essential with an effective date of December 31, 2005.

While these comments reflect the views of all IPAC members, some members will also separately submit comments supplementing this submission.

¹ Throughout these comments any reference to albuterol CFC MDIs refers to single-moiety products, unless otherwise noted.

II

COMMENTS ON THE PROPOSED RULE

A. APPLICATION OF THE CRITERIA TO REMOVE THE ESSENTIAL USE DESIGNATION FOR SINGLE-MOIETY ALBUTEROL CFC MDIS

The 2002 Rule establishes the MDI transition policy for the United States and is based upon a moiety-by-moiety approach, *i.e.*, the essentiality of MDIs is to be assessed by active ingredient. The 2002 Rule sets forth four main criteria for the removal of the essential use designation for CFC MDIs. As discussed below, IPAC firmly believes that each of the criteria has been or can be met by December 31, 2005.

Non-ODS Products Have the Same Active Moiety with the Same Route of Administration, for the Same Indication, and with Approximately the Same Level of Convenience of Use

IPAC agrees with the FDA and US Stakeholders Group on MDI Transition ("the Stakeholders") that this criteria has been met.

Supplies and Production Capacity for the Non-ODS Products Will Exist at Levels Sufficient to Meet Patient Need

MDI manufacturers have provided FDA with substantial, detailed information regarding the issue of supply and production capacity, both in public comments filed to the FDA docket on the Proposed Rule and statements made during the June 10, 2004, meeting of FDA's Pulmonary-Allergy Drugs Advisory Committee. The proposed rule correctly points out that MDI companies will require some time to develop sufficient production capacity to meet patient needs. The proposed rule assumes that this "production scale-up would presumably start when we publish the Final Rule eliminating the essential use of ODSs in albuterol MDIs" and suggests that the effective date could be no less than one year after publication of the Final Rule to allow time for the production scale-up to be completed. However, some companies have stated their intention to scale-up production prior to the Final Rule. GlaxoSmithKline, for example, has stated that it has already begun to develop additional production capacity and by December 31, 2005², it will have production capacity in place for 30 million HFA MDI units per year. IVAX, whose albuterol HFA MDI is currently under active review by

² See 9 July letter from Mr. Jonathan Box, GlaxoSmithKline, filed to FDA docket.

FDA, has clearly stated that it can have production capacity in place to produce 50-60 million units by the end of 2005, if necessary.

In any event, FDA should not unduly delay the transition process by failing to issue the Final Rule promptly, *i.e.*, no later than December 31, 2004. Given the risks discussed below, and the need for some production scale-up time, FDA can best serve the process by issuing the rule promptly. FDA has previously stated that it will publish the Final Rule by March 2005. Issuing the Final Rule 90 days earlier is achievable and, indeed, prudent under the circumstances.

Adequate US Postmarketing Use Data Are Available for the Non-ODS Products

IPAC concurs with FDA and the Stakeholders that this criteria has been met. Two non-ODS alternatives to albuterol CFC MDIs have been on the market for some time (Proventil HFA for seven years and Ventolin HFA for more than two years). As FDA points out, significant data exists with regard to the use of these products. There is no indication of unexpected adverse events or any problems with safety, effectiveness, tolerability, and patient compliance.

Patients are Adequately Served by the Non-ODS Products

The Proposed Rule states that the two currently available non-ODS alternatives: (i) were determined to be safe and effective during the new drug application process, (ii) are similarly tolerated compared to albuterol CFC MDIs, and (iii) have comparable compliance rates with albuterol CFC MDIs. The Proposed Rule concludes, therefore, that "all of the information available (to FDA) currently indicates that Proventil HFA and Ventolin HFA will adequately serve all patient populations currently using albuterol CFC MDIs."³ However, because the existing albuterol CFC MDI market is generic, FDA has expressed some concern that the cost impacts relative to the CFC products and HFA MDIs will mean that "some patients whose drug expenditures are not covered by third parties may choose not to buy these MDIs."⁴ The analysis undertaken in the Proposed Rule acknowledges that there is insufficient evidence available to precisely quantify or measure the patient impact of any price differential.

IPAC fully respects FDA's desire to proceed with care where patient health is concerned and, indeed, is committed to working with FDA and the Stakeholders to ensure that the transition of these products occurs in a smooth and safe manner. IPAC believes that existing patient assistance programs for prescription medication and other

³ 69 FED. REG. at 33607.

⁴ *Id.*

commitments by MDI companies, combined with focused and effective initiatives to educate physicians and patients, can adequately address any potential barriers to patients posed by the price differential and allow the transition to proceed in a safe and timely manner such that patients are adequately served. IPAC would be very pleased to collaborate with FDA, patient and physician stakeholders, and other interested parties to develop a comprehensive, effective outreach and education program to promote awareness and understanding of key aspects of the MDI transition among patients and physicians. Elements of such a program could include:

- creation of clear, patient-friendly educational brochures and other materials⁵ reviewing the transition, the proper use and care of new HFA MDIs, and information regarding existing patient assistance programs and companies' commitments regarding professional samples; and
- development, in collaboration with FDA and patient/physician stakeholders, of suitable and efficient methods to target dissemination of educational materials, where appropriate, to particularly vulnerable patient populations.

IPAC has previously undertaken similar educational efforts and is well-positioned to play a role in these important initiatives.

Until the transition actually begins, it will be impossible to predict with certainty precisely how it will proceed for each patient. However, simply delaying the transition presents risks while not ameliorating any of the uncertainty. For example, as the Proposed Rule notes, CFC supply for albuterol MDIs could be negatively impacted by (i) the 2005 closure of the Dutch facility that currently represents the sole production site of pharmaceutical-grade CFCs for the US market, and (ii) mounting international pressure to conclude the essential use process for these products.⁶

FDA has identified several important benefits to an early phase-out date for albuterol CFC MDIs:

- Controlled transition from CFC MDIs to HFA MDIs, avoiding any possible shortfall in the availability of pharmaceutical-grade CFCs;
- Environmental and human health benefits associated with the reduction of ODS emissions;

⁵ All materials and initiatives will be carefully prepared to ensure compliance with applicable regulatory and statutory requirements.

⁶ See 69 FED REG. at 33614.

- International cooperation and compliance with the Montreal Protocol – an important environmental treaty; and
- Encouraging innovation of environmentally-friendly technologies and acknowledging industry's substantial efforts to research and develop replacements for ODS products.

IPAC strongly agrees that these are important benefits. The international community has recognized that the completion of the albuterol MDI transition is crucial since these products represent at least half of the CFC MDI market in the United States and around the world. Canada, Australia, and more than a dozen European countries (*e.g.*, Germany, France, UK) have already successfully transitioned patients to CFC-free albuterol products. The transition has progressed very smoothly in these countries and without harm to patients. In light of the progress by many other developed countries and the wide availability of albuterol CFC-free products around the world, it is unclear for how much longer the international community will be willing to approve CFC volumes for single-moiety albuterol products in the US. Therefore, FDA has aptly pointed out that it is critical to select a phase-out date for these products that maintains international cooperation.

Regarding encouragement of innovation and acknowledgement of industry's good faith efforts to develop CFC-free products, IPAC wishes to emphasize that well over a decade ago, its member companies and other MDI companies received a clear directive from the United States and the international community to reformulate MDIs as soon as possible. As a result, MDI companies and the United States government undertook an extraordinary and unprecedented partnership to balance the critical environmental interest of ozone protection with the equally vital objective of ensuring patient care. Industry's core responsibility was to diligently research and develop safe, effective CFC-free alternatives. This was a lengthy, challenging process requiring full drug research and development programs, including extensive clinical trials, and involving substantial investment from reformulating companies. For its part, the United States government undertook a parallel responsibility to secure "essential use" CFCs during the development process and to ensure prompt removal of non-essential CFC MDIs as soon as new and reformulated products become available. A failure of the United States to honor its commitment at this late stage would greatly disadvantage companies that acted in good faith and made extraordinary investments to develop ozone-friendly MDIs.

Finally, IPAC concurs with the Stakeholders that rather than presenting a possible risk to patients, the phase-out of CFC albuterol MDIs will bring benefits to patients of improved treatment regimes.

B. EFFECTIVE DATE FOR FINAL RULE

The public comment period for the Proposed Rule closes on August 16, 2004. Given the critical nature of this issue, FDA should act as soon as possible and, as noted above, should issue a Final Rule no later than the end of this year. In light of the substantial time and effort taken by FDA in preparation of the Proposed Rule, as well as the extensive public input already received from major interested parties, an approximately 120-day period is more than sufficient to allow the preparation of a thoughtful, comprehensive Final Rule.

III

CONCLUSION

IPAC respectfully requests that FDA issue the Final Rule, no later than December 31, 2004, removing single-moiety albuterol CFC MDIs from the list of essential uses in 21 CFR 2.125(e) effective December 31, 2005.

DC01/460491.3