

IPAC

INTERNATIONAL PHARMACEUTICAL AEROSOL CONSORTIUM

1301 K Street NW • Suite 900 • East Tower • Washington DC • 20005-3317
Telephone +1 202 230 5133 • Telefax +1 202 230 5333
Internet: <http://www.ipacmdi.com>

11 April 2005

Dr. Helen Tope
Mr. Jose Pons Pons
Dr. Ashley Woodcock
Co-Chairs, UNEP Medical Aerosols Technical Options Committee

Re: ***Supplemental IPAC Comments to MATOC***

Dear Dr. Tope, Mr. Pons Pons, and Dr. Woodcock:

On 4 April 2005, the US Food and Drug Administration (FDA) issued its “Final Rule”¹ on the removal of the essential use designation for salbutamol MDIs.² This rulemaking constitutes the United States’ plan of action on salbutamol pursuant to Decision XV/5.

In light of this significant development, IPAC wishes to supplement its 28 March submission to MATOC to review key points set forth in the United States’ plan of action and summarise implications for the 2006 and 2007 nominations for essential use CFCs.

¹ 70 FED. REG. 17168; April 4, 2005 (*Use of Ozone-Depleting Substances; Removal of Essential Use Designation*).

² As in our 28 March submission, references to “salbutamol MDIs” refer only to single-moiety products. Salbutamol is referred to as albuterol in the United States.

Key Points of US Action Plan on Salbutamol

1. **HFA Albuterol Production Capacity**

In issuing the Final Rule, the United States has established an end date to the salbutamol transition of 31 December 2008. IPAC believes that there is no justification for such a delayed phase-out date. FDA's primary stated rationale for the end 2008 date is that it represents a "conservative estimate of when sufficient supplies and production capacity will exist and a later effective date will better ensure that shortages do not happen and a smoother transition will be made."³ However, the manufacturers of the HFA salbutamol products currently on the market have made clear public commitments to have sufficient production capacity in place by the end of 2005 – 3 years before the United States' phase-out date.⁴ FDA expresses a general concern that "unanticipated delays and shortages could push the date on which adequate product capacity and supplies are in place significantly beyond December 31, 2005."⁵ However, these concerns are theoretical, and FDA provides no rationale at all in support of its conclusion that three years – rather than, for example, three months – of "buffer" time are necessary. Indeed, FDA states that they "are unable to evaluate the likelihood or length of any possible delays."⁶

FDA refers to the manufacturers' commitments as "merely" projected dates and notes that the companies did not provide a basis for these projections (e.g., timelines, construction and installation schedules). It is important to note, however, that in its July 2002 regulation establishing the criteria for non-essentiality in the US and at the June 2004 public hearing, FDA never indicated that it would need this kind of detail. Moreover, it is our understanding that after the manufacturers submitted their letters to FDA stating their respective commitments on production capacity, FDA made no effort to communicate to any of these companies that further information was needed.⁷

³ Final Rule at 17178.

⁴ The combined production capacity of these two companies by the end of 2005 will be 60 million HFA MDIs. The current salbutamol market ranges from 46-50 million MDI units annually and this demand has been stable for more than a decade. In addition, IVAX has also committed to having production capacity for 50-60 million HFA MDIs by December 2005. While FDA did not consider IVAX's HFA salbutamol MDI as an alternative under the rulemaking, this is an important factor for the future. Copies of correspondence from GSK, Schering and IVAX to FDA confirming these commitments has previously been circulated to the MATOC Co-Chairs.

⁵ Final Rule at 17178.

⁶ *Id.*

⁷ IPAC member GlaxoSmithKline confirms that FDA never sought this kind of detailed information and, therefore, we assume that FDA did not request this information from other MDI companies.

2. Impact on Patients

FDA concludes that patients will be adequately served by the HFA MDIs currently available on the US market and, importantly, that “the price of albuterol HFA MDIs will not prevent patients from being adequately served.”⁸ In our initial submission, in response to MATOC’s request, IPAC provided substantial detailed information on the salbutamol market in the United States, particularly the issue of increased prices for HFA-based MDIs versus CFC salbutamol MDIs. While IPAC questions FDA’s revised economic analysis and assumptions on the US salbutamol market, and projected price impacts for patients, we fully concur with the conclusion that patients will be adequately served by available HFA MDIs. We also agree with FDA that the manufacturers’ commitments regarding, among other things, expanded patient assistance programs and free samples, will provide a “safety net for lower-income patients.”⁹ These programs will be available as of 31 December 2005 and FDA does not question this fact. Indeed, the discussion of the effective date is focused on the issue of production capacity (addressed above) and FDA does not provide a persuasive rationale relating to patient care for delaying the transition until 2008.

3. Future Essential Use Authorisations

FDA explicitly did not consider whether the Protocol Parties would continue to authorise essential use volumes for the United States for salbutamol MDIs, stating (incorrectly in IPAC’s view) that to do so would go beyond the scope of its rulemaking criteria.¹⁰ However, the Final Rule does correctly recognize that:

If the United States were to continue sale and distribution of ODS products after adequate alternatives products were available, this could lead other Parties to do the same, eventually threatening the integrity of the Montreal Protocol. ... The continued existence of a strong Montreal Protocol is in the best interest of the public health of the United States, and our failure to take timely action on albuterol MDIs could potentially weaken the Montreal Protocol.¹¹

IPAC firmly concurs with this statement, but believes that a 31 December 2008 effective date is wholly inconsistent with its spirit. This incongruity is particularly glaring given

⁸ Final Rule at 17175.

⁹ *Id.*

¹⁰ Final Rule at 17179. Ironically, FDA stated that “sale of remaining stocks of albuterol CFC MDIs was one of the factors we considered in establishing an effective date...” – without providing any justification as to how this fits into its regulatory criteria. (*Id.*).

¹¹ Final Rule at 17180.

that FDA has concluded that US patients will be adequately served by two of the three CFC-free alternatives that are now available, as well as the clear evidence on the record that sufficient production capacity to meet patient need for HFA MDIs will be in place by the end of 2005.

Conclusion

A phase-out date of 31 December 2008 for salbutamol MDIs is unfounded and not supported by the rationale contained in the United States' salbutamol action plan. More importantly for MATOC's purposes, such a date is inconsistent with Decision IV/25 and other Protocol decisions on the essential use process. By that date, two safe and effective CFC-free albuterol products would have been on the US market for close to seven years and three such products for four years. Therefore, for the reasons set forth above and as detailed in our initial Submission, IPAC recommends that TEAP recommend against approval of essential use volumes nominated for 2006 and 2007 for single-moiety salbutamol MDIs intended for sale and distribution in non-Article 5(1) Parties.

We appreciate your consideration of these comments.

Sincerely,

A handwritten signature in black ink, appearing to read "Joseph M. Ferraro". The signature is written in a cursive style with a horizontal line at the end.

Chair