

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research



OFFICE DIRECTOR'S BACKGROUND MEMORANDUM

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Date: Friday, December 23, 2005
To: Pulmonary and Allergy Drugs Advisory Committee and the Non-prescription Drugs Advisory Committee
Re: **Meeting on the continued medical essentiality of CFC-based epinephrine MDIs for non-prescription treatment of asthma**

Since 1978, the U.S. Food and Drug Administration has designated the medical products that are exempt from the general ban on the use of chlorofluorocarbons (CFCs) in aerosol products by listing them as “essential uses” of CFCs in the Code of Federal Regulations (CFR) under 21 CFR 2.125. (Note that since January 1, 1996, new CFCs can only be produced or imported into the U.S. for use in essential medical products.) When first promulgated, this regulation had broad classifications of medications considered essential and a mechanism for adding new uses, but no mechanism for determining when uses should no longer be essential.

In July 2002, the FDA modified this regulation in a number of ways, both to make it more consistent with the U.S.’s obligations under the Montreal Protocol on Substances that Deplete the Ozone Layer and in order to define criteria to be used to determine when CFC use for individual drug moieties could no longer be essential. When such criteria are considered to be met, the use could be removed by FDA from the listing of essential uses in § 2.125 through notice and comment rulemaking. For instance, such rulemaking has recently been completed for albuterol, stating that albuterol will no longer be considered an essential use of CFCs as of December 31, 2008. The revisions to § 2.125 also included a reorganization that listed products no longer as broad classes, but rather as separate moieties, to allow the delistings to be specific to a particular drug moiety. This reflects, at least in part, the fact that in the early notice and comment rulemaking for the revisions to § 2.125, FDA received strong public opposition to determining essentiality by drug class, but rather FDA was strongly encouraged to do such determinations on a “moiety-by-moiety” approach. In the final rule published in July of 2002, the FDA indeed did not include a therapeutic class approach to determining non-essentiality. I will give a detailed presentation on the history of CFC regulations and the Montreal Protocol at the meeting on January 24, but much of what you need to know for background can be found in the relevant Federal Register notice for the final rule revising § 2.125, which is attached.

One potential difficulty of “moiety-by-moiety” as the sole approach for determining continuing essentiality is that this approach does not effectively deal with individual moieties that are either not being reformulated into non-CFC based products or in which the reformulation work is not progressing expeditiously. This results from the fact that the trigger for beginning rulemaking to delist a moiety is a preliminary determination by FDA that adequate alternatives exist with that moiety. So, if there are no marketed alternatives with the same moiety, this trigger would never be met and therefore the usual pathway to delisting a product would never be invoked. On the other hand, changes in the practice of medicine and in the availability of non-CFC based alternatives in closely related moieties could render a drug currently listed under § 2.125 as no longer essential, even if not reformulated into a non-CFC alternative with the same moiety. Therefore, the final rule revising § 21 CFR 2.125 allowed for FDA to convene the PADAC periodically anytime after January 2005 to consider if metered dose inhalers remaining on the market containing CFCs remain essential, even if these products were not being reformulated.

The criteria listed for this decision are described in § 2.125(g)(1) (which refers back to § 2.125(f)(1)). The criteria for removing an essential use, when there is no alternative with the same active moiety, are:

- Substantial technical barriers do not exist to formulating the product without ozone depleting substances (ODSs);
- The product does not provides an otherwise unavailable important public health benefit; and
- Use of the product releases cumulatively significant amounts of ODSs into the atmosphere or the release is not warranted in view of the unavailable important public health benefit.

It is particularly in applying the second criterion to the product in question where your expert advice is sought for this meeting. The question that FDA would like you to be prepared to discuss for the upcoming meeting is:

- given the current practice of medicine and overall treatment goals and therapeutic strategies for asthma, does the use of CFCs in epinephrine MDIs available without a prescription, remain an essential use at the current time?

Bear in mind that if you advise epinephrine MDIs are no longer essential, for FDA to affect that advice, we would still go through notice and comment rulemaking, meaning the public and other concerned parties would have the ability to weigh in on the proposed delisting prior to it happening. Also bear in mind that if your recommendation is that epinephrine remains essential, we will likely have to revisit the question in future years.

No direct alternative product for the epinephrine CFC-MDIs (e.g., an HFA-propelled epinephrine MDI) is currently available. For the purposes of the discussion, please assume that no direct alternative products with epinephrine in an MDI will be available in the near future. Therefore, the discussion in many ways turns on the role of OTC epinephrine MDIs in the treatment of asthma and whether its role is medically essential

under the criterion listed above, that is that epinephrine MDIs provide an otherwise unavailable important public health benefit.

At the meeting on January 24, 2006, you will hear an FDA presentation on the background of the Montreal Protocol and the phase-out of CFCs overall, and the current regulatory status of epinephrine. We expect you will hear from the pharmaceutical sponsors of the epinephrine MDI products and from the public in the open public hearing. We would ask you to weigh all this information and utilize your own expertise and informed opinions in reaching a recommendation to the FDA. We also thank you in advance for your time and thoughtful consideration.