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

OFFICE DIRECTOR'S BACKGROUND MEMORANDUM

Memorandum author:	Robert J. Meyer, MD, Director, ODE II
Date:	Tuesday, July 05, 2005
To:	Pulmonary and Allergy Drugs Advisory Committee (PADAC)
Re:	**July 14th meeting on the CFC transition**

On July 14, 2005, the PADAC will meet to provide FDA advice as to whether certain Ozone-Depleting Substances (ODS) listed as essential uses, remain essential. More specifically, FDA is seeking your advice on whether certain meter dose inhalers (MDIs) that remain on the market containing chlorofluorocarbons (CFCs), for which there are no non-CFC current reformulations or direct alternative products (see List A below), remain essential.

BACKGROUND

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 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 1st, 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.

On July 24, 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 to define the criteria FDA uses to determine when CFC use for individual drug moieties are no longer essential (67 FR 48384). When such criteria are considered met, FDA may remove the essential use from the listing in 21 CFR 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 31st, 2008 (70 FR 17168, April 4, 2005). The revisions to section 2.125 also included listing products not in broad therapeutic classes, but as separate moieties. This allows FDA to make non-essential use determinations specific to a particular drug moiety. FDA made these revisions, at least in part, in response to strong public opposition to making essential use determinations by drug

class, and instead, strong encouragement to make such determinations using a "moiety-by-moiety" approach.

I will give a detailed presentation on the history of CFC regulations and the Montreal Protocol at the meeting on July 14th, but much of what you need to know for background can be found in the relevant Federal Register notice for the final rule revising 21 CFR 2.125, which is attached.

DISCUSSION

One potential difficulty with the "moiety-by-moiety" approach for determining continuing essentiality of a use is that this approach does not effectively deal with individual moieties that are either not being reformulated into non-CFC based products or for which the reformulation work is not progressing adequately. 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 for that moiety. If there are no marketed alternatives, rulemaking would not be triggered and the typical pathway for delisting a product could not 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 section 2.125 no longer essential, even if not reformulated. Therefore, the final rule revising 21 CFR 2.125 allowed for FDA to convene the PADAC periodically anytime after January 2005 to consider if MDIs remaining on the market containing CFCs remain essential, even if these products were not being reformulated.

FDA will base a decision on whether the listed products remaining on the market containing CFCs remain essential based on whether or not they continue to meet the regulatory criteria on which they were designated an essential use(21 CFR 2.125(g)(2)). This includes the use of relevant advisory committee input. The criteria listed for this consideration are as follows (see 21 CFR 2.125(f), where they define the conditions of essentiality for a new use of CFCs):

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

Your expert advice is particularly valuable in applying the second criterion to the relevant products cited in List A below and therefore, the July 14th meeting will focus on assessment of this second criterion. FDA will consider, as appropriate, other information and seek other expertise pertaining to the first and third criterion.

The question that FDA would like you to be prepared to discuss on July 14th is: Given the existing pharmaceutical market and the current practice of medicine, do the products

in List A below remain essential uses of CFCs? Bear in mind that if you advise us that a product is no longer essential, for FDA to affect that advice, we still must hold an open public meeting and go through notice and comment rulemaking, meaning the public and other concerned parties would have the ability to weigh in on the proposed delisting.

To aid in your deliberations over whether individual moieties remain essential, it is important for you to know what moieties still are marketed in CFC-containing products and listed under 21 CFR 2.125(e) as essential, as well as what products are currently approved and/or marketed that do not contain CFCs. Therefore List A below includes those moieties for which there are no current reformulations or direct alternative products and therefore are relevant to today's discussion under 21 CFR 2.125(g)(2). Other products currently listed under section 2.125(e) may be currently unavailable for other reasons, and therefore could be delisted under alternative criteria (see sections 2.125(g)(1) or 2.125(g)(3)). Also I have provided a list of potentially relevant marketed non-CFC products to help you consider whether the moieties cited in List A remain essential (List B).

LIST A. Moieties currently listed under 21 CFR 2.125(e) for which no current reformulated or direct alternative product exists:

1. Beta-agonists*
- metaproterenol (Alupent)
- pirbuterol (Maxair)

2. Inhaled Corticosteroids
- flunisolide (Aerobid),
- triamcinolone (Azmacort)

3. Cromones
- Cromolyn (Intal)
- Nedocromil (Tilade)

4. Albuterol/Ipratropium (Combivent)

Comment: Consider including the proprietary names, which members may be familiar with. Also, do you think you should also include the names of the potentially relevant marketed non-CFC products? It might be good for them to see, for instance, the inhaled steroids that would be on the market if these went away.

*Note that epinephrine would also be correctly included in this list. However, since this is an OTC drug product, this moiety will need to be separately considered so that the Advisors can properly include members of the Non-prescription Drugs Advisory Committee. FDA plans to hold a subsequent, timely meeting to specifically discuss epinephrine and the issue of OTC rescue bronchodilator availability.

To aid in your deliberations over whether the individual moieties cited in List A remain essential under the second criteria cited in section 2.125(f), as discussed above, I have also provided a list of potentially relevant marketed non-CFC products (List B). This list is provided to aid your consideration as to whether an adequate, alternative therapy is available. This list of non-CFC products does not include products for nebulization and

does not include non-inhalation treatments of asthma and Chronic Obstructive Pulmonary Disease (COPD). However, under the criteria in section 2.125(f), the full range of available therapies can be considered in your deliberations and recommendations.

List B. Non-CFC asthma/COPD inhalation treatments available/approved in the U.S.:

1. Beta-agonists:
   - albuterol (Proventil HFA S, Albuterol HFA, IVAX's albuterol sulfate HFA – all MDIs)
   - levalbuterol (Xopenex HFA - MDI)
   - salmeterol (Serevent Diskus – MDPI (multidose dry powder inhaler))
   - formoterol (Foradil Aerolizer – DPI (dry powder inhaler))

2. Inhaled Corticosteroids
   - Budesonide (Pulmicort Turbuhaler – MDPI; moiety is also available as a nebulized suspension)
   - fluticasone (Flovent Diskus - MDPI and Flovent HFA - MDI)
   - mometasone (Asmanex – MDPI)
   - beclomethasone (QVAR - MDI)

3. Cromones: none

4. <u>Anticholinergics</u>
   - ipratropium (Atrovent HFA - MDI)
   - tiotropium (Spiriva - DPI)

5. <u>Corticosteroid/LABA combination</u>
   - salmeterol/fluticasone (Advair Diskus - MDPI)