

General Background
Pulmonary - Allergy Drugs Advisory Committee Meeting
June 10th, 2004

This meeting is being convened to discuss whether the use of chlorofluorocarbons (CFCs) as propellants in albuterol metered-dose inhalers (MDIs) is no longer an essential use under the criteria in 21 CFR § 2.125(g).

BACKGROUND

The ozone layer that is present in the earth's stratosphere helps protect the environment from ultraviolet (UV-B) radiation. Research conducted in the 1970s indicated that when certain synthetic halogenated hydrocarbons (including CFCs) are released into the environment, they can migrate to the stratosphere, where they contribute to the depletion of the ozone layer. While CFCs are very useful compounds due in part to their relative inertness and stability, these properties also contribute to their long residence in the stratosphere. To the extent depletion occurs due to CFCs and other halogenated hydrocarbons in the stratosphere, penetration of the atmosphere by UV-B radiation increases. Increased exposure to UV-B radiation produces health and environmental damage, including increased incidence of skin cancer and cataracts, suppression of the immune system, damage to crops and aquatic organisms, and increased formation of ground-level ozone. The thinning of the ozone layer has been of considerable consequence to public health due to these effects.

The initial hypothesis linking CFCs to the depletion of the stratospheric ozone layer appeared in a paper by Mario J. Molina and F.S. Rowland in 1974. This research later won them the Nobel Prize. Since 1974, the scientific community has made remarkable advances in understanding atmospheric processes affecting stratospheric ozone and in analyzing data measuring ozone depletion, both over the polar regions and globally. In response to the initial research indicating that CFCs could cause stratospheric ozone depletion and thereby lead to damage to human health and the environment, the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA) and other government agencies acted on March 1978, to ban the use of CFCs as aerosol propellants in all but "essential applications." The 1978 ban reduced the use of CFCs in aerosols in this country by approximately 95 percent, eliminating nearly half of the total U.S. consumption of these chemicals (including banning the use in all consumer aerosols). In order to define what medical uses would be considered "essential," the FDA promulgated a regulation (21 CFR 2.125) in that same year listing the general categories of its regulated products that would be

considered essential uses of CFCs. These uses were predominantly, but not exclusively, MDIs for the treatment of asthma and COPD.

On September 16, 1987, the United States and 22 other countries signed the Montreal Protocol on Substances that Deplete the Ozone Layer (Montreal Protocol) committing to reduce production and importation of certain CFCs to 50 percent of 1986 levels by 1998. Currently, over 180 countries are parties to the Montreal Protocol. As the evidence regarding the impact of ozone-depleting substances, including CFCs, on the ozone layer became clearer, the phaseout of CFCs was accelerated under the Protocol, which was amended in 1992 at the Meeting of the Parties in Copenhagen. These amendments committed the economically developed countries to eliminate the production and importation of CFCs by January 1, 1996. However, this amendment allowed production and importation of CFCs for essential uses (in MDIs for the treatment of asthma and COPD). These essential uses were to be requested annually and voted on at meetings of the parties to the Montreal Protocol. Since 1994, the United States and other parties to the Montreal Protocol have annually requested, and been granted, essential-use exemptions for the production or importation of CFCs for their use in MDIs for the treatment of asthma and COPD. This process continues today, though it is the intent of the Montreal Protocol that even these essential uses be phased out as soon as technically and economically feasible alternatives are available.

In 1990, Congress amended the Clean Air Act to, among other things, better protect stratospheric ozone and to complement and be consistent with the U.S. obligations under the Montreal Protocol. EPA promulgated regulations implementing the Montreal Protocol and the stratospheric ozone protection provisions of the 1990 amendments shortly thereafter. The prohibition on production and transfer of CFCs contains an exception for essential uses and, more specifically, for essential MDIs. The definition of essential MDI under the implementing regulations requires that the MDI be intended for the treatment of asthma or COPD, be essential under the Montreal Protocol, and if the MDI is for sale in the United States, be approved by FDA and listed as essential in FDA's 21 CFR 2.125.

In the latter part of the 1990s, FDA undertook revisions to 21 CFR 2.125 to better reflect our obligations under the Montreal Protocol, the 1990 amendments, and EPA's regulations, and to encourage the development of ozone-friendly alternatives to medical products containing CFCs. Specifically, the rule was amended to allow for removal of listed essential uses as acceptable alternatives became available, and this revision contained the necessary criteria for such a finding of non-essentiality. The rule as finalized provided that to remove an essential-use designation, FDA must find that:

- At least one non-CFC product with the same active drug is marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the CFC

product containing that active moiety (while these alternatives are not required to be MDIs, the presumption is that HFA-MDIs would most easily fit this criteria compared to, for example, dry powder inhalers);

- Supplies and production capacity for the non-CFC product(s) exist or will exist at levels sufficient to meet patient need;
- Adequate U.S. postmarketing use data are available for the non-CFC product(s); and
- Patients who medically required the CFC product are adequately served by the non-ODS product(s) containing that active moiety and other available products.

To remove the essential-use designation of an active moiety marketed in a CFC product represented by one NDA, there must be at least one acceptable alternative, while for an active moiety marketed in ODS products and represented by two or more NDAs, such as albuterol, there must be at least two acceptable alternatives. (Note: a copy of the final rule for 21 CFR 2.125 as revised is in this briefing document).

ALBUTEROL ESSENTIALITY

Albuterol CFC MDIs have become the short-acting, “reliever” beta agonist of choice in asthma and also are frequently used in COPD patients as well for the same purpose of achieving relatively rapid bronchodilation. Over 50 million albuterol canisters are sold or distributed in the United States per year. The volume of albuterol used in the United States is such that it has consistently accounted for more than half of the total U.S. CFC essential use nomination made to the Montreal Protocol in recent years.

While for much of the early years of albuterol’s availability in the U.S. market it was available only in branded products (Ventolin from GSK and Proventil from Schering-Plough), albuterol has been available in generic products since 1996. The generics, including a product from a Schering-Plough subsidiary (Warrick Pharmaceuticals) now predominate the U.S. market, with the branded CFC products and HFA products representing a minority of sales.

FDA approved NDA 20-503 for Proventil HFA, albuterol sulfate MDI, on August 15, 1996 and this product was introduced into the U.S. market later that year. FDA approved NDA 20-983 for Ventolin HFA, also an albuterol sulfate MDI, on April 19, 2001 and it was introduced into the U.S. market in February 2002. Both of these products use the hydrofluoroalkane HFA-134a as a replacement for CFCs. HFA-134a does not affect stratospheric ozone. Given that we now have two albuterol non-CFC MDIs in the U.S. market, FDA is undertaking a public discussion of whether the albuterol CFC MDIs (including generic albuterol) should be removed as essential uses of CFCs under FDA’s criteria as contained in 21 CFR 2.125, as listed above.

Of note, related to these criteria, branded albuterol products (CFC or HFA) are currently approximately \$37 retail, with the CFC generic ranging from \$14 - \$25. In the preamble to 21 CFR 2.125 when its revisions were finalized, FDA had stated that it would consider costs to patients among its consideration of whether the alternatives adequately serve patient's needs.

In 2003, the FDA received a "Citizen Petition" from the American Lung Association on behalf of a group of involved patient and professional organizations asking FDA to initiate rule making to remove the essential use designation for albuterol. While this advisory committee and public meeting on June 10th is not directly responsive to that petition, this petition and the public comments to the petition are relevant to this meeting and therefore are included in the background materials for this meeting. Particularly, there are submissions from GlaxoSmithKline addressing the criteria for removing an essential use designation, including the issues of affordability and manufacturing capacity.

It is important to also understand the global context of albuterol (called salbutamol in much of the rest of the world). Due to the widespread availability of HFA alternatives, albuterol MDIs are no longer considered an essential use of CFCs in many developed countries, including Canada, Australia, Japan and much of the European Union. There has been increasing pressure on the remaining developed countries who participate in the Montreal Protocol to act expeditiously to declare albuterol to no longer be an essential use of CFCs. However, the United States, unlike other developed countries, does not have a health care system where drug prices are set by the government. The resulting higher prices that U. S. payors face for albuterol HFA MDIs complicate the considerations of essentiality. It is clear that the United States cannot hope for the Parties to indefinitely approve our essential use requests for CFCs for albuterol MDIs indefinitely.

We thank you in advance for your time and consideration in this important matter. We expect that there will be considerable public input and interest in this meeting and we feel that a full consideration of this input by the PADAC will be of great value to the FDA in deciding on whether to remove the essential use designation for albuterol CFC MDIs.