

A United States regulator's perspective on the ongoing chlorofluorocarbon transition

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The Food and Drug Administration (FDA) put in place a general ban on the use of chlorofluorocarbons for the products it regulates (medical devices, drugs, and foods) in 1978, exempting those products where chlorofluorocarbon use was determined to be essential for the public health. In the intervening years, as the international commitment to a full transition away from all chlorofluorocarbon use took shape under the Montreal Protocol, the FDA has worked with industry to facilitate the development and testing of alternative technologies and products for inhalation drug products. As these alternative products begin to move from testing through the approval process and into marketing, the FDA is working collaboratively with the Environmental Protection Agency, other governmental agencies, and nongovernmental stakeholders to develop a transition policy for the United States. The transition policy for metered dose inhalers must be one that achieves the dual aims of first protecting the patients who rely on these vital medical products, while also achieving the public health need of protecting the ozone layer. As a part of developing such a transition strategy, the FDA published an advance notice of proposed rulemaking (ANPRM) in March 1997. The ANPRM proposed mechanisms by which the FDA could determine when chlorofluorocarbon use in a drug product could no longer be considered essential. The ANPRM resulted in a large amount of valuable public debate and input. The FDA is now working to incorporate the knowledge gained from these public comments as it continues the rule-making process. (*J Allergy Clin Immunol* 1999;104:S236-8.)

Key words: *Chlorofluorocarbons, metered dose inhalers, phase-out, FDA*

This discussion is intended to present a United States regulator's opinion of the ongoing transition from chlorofluorocarbon-propelled metered dose inhalers (MDIs) to alternative products. It will briefly review the past actions of the United States Food and Drug Administration (FDA) on the chlorofluorocarbon issue, the current

Abbreviations used

ANPRM: Advance Notice of Proposed Rule-Making
FDA: US Food and Drug Administration
MDI: Metered dose inhalers

state of FDA regulations on chlorofluorocarbons, the current state of the transition in the United States, and the future of the chlorofluorocarbon transition within the United States.

PAST FDA ACTIONS

Through decades of use, chlorofluorocarbons proved to be ideal compounds for many purposes, including use as propellants in MDIs beginning in the 1950s. Chlorofluorocarbons gained acceptance as propellants in MDIs because of a number of desirable attributes, being largely nontoxic, noncorrosive, nonflammable, and unreactive with most other substances, yet having good solvent capabilities.

In 1974, scientists first implicated chlorofluorocarbons as a threat to the ozone layer. By 1976, there was a public call for the US government to place limitations on the use of these chemicals. The US government responded by generally banning the sale of aerosol cans containing CFCs. As a part of these efforts, the FDA finalized a new regulation (21 CFR 2.125) in 1978 banning the use of chlorofluorocarbons in all FDA-regulated products, except where medically essential. Uses deemed essential were listed under 21 CFR 2.125(e), generally in broad classes (eg, "metered-dose steroid human drugs for oral inhalation"). A process for petitioning to add new, individual essential uses was laid out in the regulation. The determination of "essentiality" contained in this regulation was to be based on the lack of a technically feasible alternative, showing that the product would provide a substantial health, public, or environmental benefit and that the release of chlorofluorocarbons was small or justified given the benefit. Although the preamble discussion accompanying this final regulation foresaw that these essential-use listings would likely become obsolete in the future as technologies evolved, no formal mechanism for removing essential-use listings was contained in the final regulation itself.

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0091-6749/99 \$8.00 + 0 1/0/102783

In the intervening years, the Division of Pulmonary Drug Products and the Center for Drug Evaluation and Research within the FDA worked with the pharmaceutical industry to help the industry in identifying acceptable, safe alternative propellants for MDIs and to develop products using these alternatives. These cooperative efforts by the FDA included agreements with industry consortia (IPACT I for HFA-134a, and IPACT II for HFA-227ea) on the animal toxicology testing programs needed for the new propellants. Because of the long-term use of MDIs and because of the high proportion of the formulation made up of propellant, this toxicology testing was extensive, as extensive as that done to support new drug substances. The Division of Pulmonary Drug Products also outlined the required pharmacology/toxicology testing to support the use of these propellants in new products. This testing was based on streamlined "bridging studies" that were significantly less extensive than that needed to support a wholly new product, but sufficient to answer toxicologic concerns related to new formulations. Additionally, the Division of Pulmonary Drug Products wrote and published a "Points to Consider" in 1994 outlining recommended abbreviated clinical programs for reformulated products that focused on clinical comparisons to approved chlorofluorocarbon products. The Division also has had substantial ongoing involvement with industry to assist in the design of their clinical programs to support these reformulated MDIs.

CURRENT US REGULATORY SITUATION

A general ban on the production or importation of chlorofluorocarbons in major industrialized countries, including the United States, went into effect in January 1996 through the Montreal Protocol. This ban allows for the temporary exemption of chlorofluorocarbons for use in MDIs for the treatment of asthma and chronic obstructive lung diseases. When this general ban went into effect and the first new drug applications for alternatively propelled MDIs were submitted, the FDA began a process to amend its regulations so that products currently listed in 21 CFR 2.125(e) could be removed from the list of essential-use products, as medically acceptable alternatives were introduced and proved to be adequate replacements to the existing chlorofluorocarbon-based products.

As the first step in amending the FDA's regulations, the Agency published an initial draft proposal (advance notice of proposed rule-making [ANPRM]) on March 7, 1997. In this ANPRM, the Agency proposed ways in which it would define acceptable alternatives to chlorofluorocarbon-based MDIs (eg, alternate propellant MDIs and potentially multidose dry powder inhalers) and how it would monitor availability of alternatives for each drug product/class. It also proposed criteria that would have to be met to make determinations that existing chlorofluorocarbon products could no longer be considered as "essential" uses of chlorofluorocarbons. The ANPRM proposed a framework by which the FDA

could, in the future, modify its existing regulations that confer essentiality on chlorofluorocarbon products to allow for an appropriate determination of nonessentiality when adequate and acceptable alternatives existed to a given listed essential product. Final implementation of the ANPRM as proposed would not have eliminated from essential use status any MDI for the treatment of asthma or chronic obstructive pulmonary disease. Rather, the ANPRM proposed to amend the current chlorofluorocarbon-related regulations (21 CFR 2.125) to include a procedure and criteria for the future removal of drugs from the listing of essential uses, as nonchlorofluorocarbon-based products are approved and shown to be acceptable alternatives.

CURRENT STATE OF THE US TRANSITION*

There remains only one approved alternative-propellant MDI in the United States, Proventil HFA, an albuterol sulfate MDI marketed by Key Pharmaceuticals. Several multidose dry powder inhalers have also recently been approved and marketed, Pulmicort (budesonide) Turbuhaler marketed by AstraZeneca and Serevent (salmeterol) Diskus and Flovent (fluticasone) Rotadisk both marketed by Glaxo Wellcome. Other alternative-propellant MDI products and multidose dry powder inhaler products are in the late stages of development and will likely come to the US market in the not-too-distant future. The FDA is committed to assuring that all approved inhalation drug products, including the alternatives under development, are quality products that are reliable, safe, and effective. However, even after approval and marketing, there will need to be experience gained in the general population to better assess whether the new products can be considered as adequate replacements to an existing chlorofluorocarbon-based product. It is clear that the transition to chlorofluorocarbon-free inhalers will continue in the United States into the next decade. Like other industrialized MDI-producing countries, the United States continues to apply for essential-use exemptions through the Montreal Protocol process. The United States currently has exemptions approved through the year 2000 and has submitted a request for the year 2001.

THE FDA'S CURRENT AND FUTURE ROLE IN THE US TRANSITION

The FDA is currently working to draft the proposed rule to amend 21 CFR 2.125, appropriately accounting for the public commentary received on the ANPRM. The US Congress called for the Agency to publish the proposed rule by September 1999.[†] After the publication of the proposed rule, the FDA intends to conduct public

*As of August 5, 1999.

[†]This proposed rule was published in the Federal Register on September 1, 1999 and is available at <http://www.fda.gov/cder/mdi>.

forums and meetings to clearly communicate the contents of the proposed rule to the public and to gain further valuable public input on the revised proposal. The FDA continues to work with the Environmental Protection Agency, the National Heart, Lung, and Blood Institute, and other governmental and nongovernmental concerns to educate the public and monitor the continuing transition. The FDA is committed to interacting with industry, governmental agencies, professional societies, patient groups, and the general public to develop a feasible, accepted transition process for the United States that is consistent with fully protecting patient health, that is consistent with industry capability, and that conforms

with the international obligations of the United States. As the transition transpires, the FDA will monitor the transition and will be ready to respond to any unexpected developments.

To summarize, the FDA is working to achieve a balanced US transition process, one that fully protects the health of the millions of patients with asthma and chronic obstructive pulmonary disease within the United States, while also working towards the eventual elimination of chlorofluorocarbon use in MDIs as called for by international treaties and US law.

For more information, please see: <http://www.fda.gov/cder/mdi>.