FAA AD Differences

Note: This AD differs from the MCAI and/or service information as follows: No differences.

Other FAA AD Provisions

(g) The following provisions also apply to this AD:

(1) *Alternative Methods of Compliance (AMOCs):* The Manager, New York Aircraft Certification Office (ACO), FAA, has the authority to approve AMOCs for this AD, if requested using the procedures found in 14 CFR 39.19. Send information to ATTN: Ezra Sasson, Aerospace Engineer; New York ACO, FAA, 1600 Stewart Avenue, Suite 410, Westbury, New York 11590; telephone (516) 228–7320; fax (516) 794–5531. Before using any approved AMOC on any airplane to which the AMOC applies, notify your appropriate principal inspector (PI) in the FAA Flight Standards District Office (FSDO), or lacking a PI, your local FSDO.

(2) *Airworthy Product:* For any requirement in this AD to obtain corrective actions from a manufacturer or other source, use these actions if they are FAA-approved. Corrective actions are considered FAA-approved if they are approved by the State of Design Authority (or their delegated agent). You are required to assure the product is airworthy before it is returned to service.

(3) *Reporting Requirements:* For any reporting requirement in this AD, under the provisions of the Paperwork Reduction Act, the Office of Management and Budget (OMB) has approved the information collection requirements and has assigned OMB Control Number 2120–0056.

Related Information

(h) Refer to MCAI Canadian Airworthiness Directive CF–2006–13, dated June 6, 2006; Bombardier Service Bulletin 8–27–89, Revision "E," dated January 27, 2005; and Bombardier Service Bulletin 8–27–103, Revision "B," dated January 24, 2007; for related information.

Issued in Renton, Washington, on June 1, 2007.

Ali Bahrami,

Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. E7–11199 Filed 6–8–07; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 2

[Docket No. 2006N–0454]

RIN 0910–AF93

Use of Ozone-Depleting Substances; Removal of Essential-Use Designations

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA), after consultation with the Environmental Protection Agency (EPA), is proposing to amend FDA's regulation on the use of ozone-depleting substances (ODSs) in self-pressurized containers to remove the essential-use designations for oral pressurized metered-dose inhalers (MDIs) containing flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil. Under the Clean Air Act, FDA, in consultation with the EPA, is required to determine whether an FDA-regulated product that releases an ODS is an essential use of the ODS. Therapeutic alternatives that do not use an ODS are currently marketed and appear to provide all of the important public health benefits of the listed drugs. If the applicable essential-use designations are removed, flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil MDIs containing an ODS could not be marketed after a suitable transition period. We will hold an open public meeting on removing these essential-use designations in the near future.

DATES: Submit written or electronic comments by August 10, 2007.

ADDRESSES: You may submit comments, identified by Docket No. 2006N–0454, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD–ROM submissions]: Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted directly to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the Electronic Submissions portion of this paragraph.

Instructions: All submissions received must include the agency name and Docket No(s). and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents, comments, a transcript of, and material submitted for, the Pulmonary-Allergy Advisory Committee meeting held on June 10, 2005, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number(s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Wayne H. Mitchell or Martha Nguyen, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

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I. Background

A. CFCs

Chlorofluorocarbons (CFCs) are organic compounds that contain carbon, chlorine, and fluorine atoms. CFCs were first used commercially in the early 1930s as a replacement for hazardous materials then used in refrigeration, such as sulfur dioxide and ammonia. Subsequently, CFCs were found to have a large number of uses, including as solvents and as propellants in self-pressurized aerosol products, such as MDIs.

CFCs are very stable in the troposphere, the lowest part of the atmosphere. They move to the stratosphere, a region that begins about 10 to 16 kilometers (km) (6 to 10 miles) above the Earth's surface and extends up to about 50 km (31 miles) altitude. Within the stratosphere, there is a zone about 15 to 40 km (10 to 25 miles) above the Earth's surface in which ozone is relatively highly concentrated. This zone in the stratosphere is generally called the ozone layer. Once in the stratosphere, CFCs are gradually broken down by strong ultraviolet light, releasing chlorine atoms that then deplete stratospheric ozone. Depletion of stratospheric ozone by CFCs and other ODSs allows more ultraviolet-B (UV-B) radiation to reach the Earth's surface, where it increases skin cancers and cataracts, and damages some marine organisms, plants, and plastics.

B. Regulation of ODSs

The link between CFCs and the depletion of stratospheric ozone was discovered in the mid–1970s. Since 1978, the U.S. Government has pursued a vigorous and consistent policy, through the enactment of laws and regulations, of limiting the production, use, and importation of ODSs, including CFCs.

1. The 1978 Rules

In the **Federal Register** of March 17, 1978 (43 FR 11301 at 11318), FDA and EPA published rules banning, with a few exceptions, the use of CFCs as propellants in aerosol containers. These rules were issued under authority of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321 *et seq.*) and the Toxic Substances Control Act (15 U.S.C. 2601 *et seq.*), respectively. FDA's rule (the 1978 rule) was codified as § 2.125 (21 CFR 2.125). These rules issued by FDA and EPA had been preceded by rules issued by FDA and the Consumer Product Safety Commission requiring products that contain CFC propellants to bear environmental warning statements on their labeling (42 FR 22018, April 29, 1977; 42 FR 42780, August 24, 1977).

The 1978 rule prohibited the use of CFCs as propellants in self-pressurized containers in any food, drug, medical device, or cosmetic. As originally published, the rule listed five essential uses that were exempt from the ban. The second listed essential use was for "[m]etered-dose steroid human drugs for oral inhalation," and the third listed essential use was for "[m]etered-dose adrenergic bronchodilator human drugs for oral inhalation." These provisions describe flunisolide, triamcinolone, and pirbuterol MDIs, so the list of essential uses did not have to be amended when these products were approved by FDA.[1]

The 1978 rule provided criteria for adding new essential uses, and several uses were added to the list, the last one in 1996. The 1978 rule did not provide any mechanism for removing essential uses from the list as alternative products were developed or CFC-containing products were removed from the market. The absence of a removal procedure came to be viewed as a deficiency in the 1978 rule, and was addressed in a later rulemaking, discussed in section II.C.5 of this document.

2. The Montreal Protocol

On January 1, 1989, the United States became a party to the Montreal Protocol on Substances that Deplete the Ozone Layer (Montreal Protocol) (September 16, 1987, 26 I.L.M. 1541 (1987)), available at *http://www.unep.org/ozone/pdfs/Montreal-Protocol2000.pdf*.[2] The United States played a leading role in the negotiation of the Montreal Protocol, believing that internationally coordinated control of ozone-depleting substances would best protect both the U.S. and global public health and the environment from potential adverse effects of depletion of stratospheric ozone. Currently, there are 191 Parties to this treaty.[3] When it joined the treaty, the United States committed to reducing its production and consumption of certain CFCs to 50 percent of 1986 levels by 1998 (Article 2(4) of the Montreal Protocol). It also agreed to accept an "adjustment" procedure, by which, following assessment of the existing control measures, the Parties could adjust the scope, amount, and timing of those control measures for substances already subject to the Montreal Protocol. As the evidence regarding the impact of ODSs on the ozone layer became stronger, the Parties used this adjustment procedure to accelerate the phase-out of ODSs. At the fourth meeting of the Parties to the Montreal Protocol, held at Copenhagen in November 1992, the Parties adjusted Article 2 of the Montreal Protocol to eliminate the production and importation of CFCs by January 1, 1996, by Parties that are developed countries (Decision IV/2).[4] The adjustment also indicated that it would apply, "save to the extent that the Parties decide to permit the level of production or consumption that is necessary to satisfy uses agreed by them to be essential" (Article 2A(4)).

To produce or import CFCs for an essential use under the Montreal Protocol, a Party must request and obtain approval for an exemption at a meeting of the Parties. One of the most important essential uses of CFCs under the Montreal Protocol is their use in MDIs for the treatment of asthma and chronic obstructive pulmonary disease (COPD). The decision on whether the use of CFCs in MDIs is "essential" for purposes of the Montreal Protocol turns on whether: "(1) It is necessary for the

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[1] A metaproterenol MDI (Alupent MDI) was approved July 31, 1973, before the 1978 rule.

[2] FDA has verified all Web site addresses cited in this document, but FDA is not responsible for any subsequent changes to the Web sites after this document has published in the **Federal Register**.

[3] The summary descriptions of the Montreal Protocol and decisions of Parties to the Montreal Protocol contained in this document are presented here to help you understand the background of the action we are taking. These descriptions are not intended to be formal statements of policy regarding the Montreal Protocol. Decisions by the Parties to the Montreal Protocol are cited in this document in the conventional format of "Decision IV/2," which refers to the second decision recorded in the Report of the Fourth Meeting of the Parties to the Montreal Protocol on Substances That Deplete the Ozone Layer. Reports of meetings of the Parties to the Montreal Protocol may be found on the United Nations Environment Programme's Web site at *http://ozone.unep.org/Meeting_Documents/mop/index.asp*.

[4] Production of CFCs in economically less-developed countries is being phased out and is scheduled to end by January 1, 2010. See Article 2A of the Montreal Protocol.

health, safety, or is critical for the functioning of society (encompassing cultural and intellectual aspects) and (2) there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health; * * * (Decision IV/25)."

Since 1994 the United States and some 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 (see, among others, Decisions VI/9 and VII/28). The exemptions have been consistent with the criteria established by the Parties, which make the grant of an exemption contingent on a finding that the use for which the exemption is being requested is essential for health, safety, or the functioning of society, and that there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of health or the environment (Decision IV/25).

Several decisions of the Parties have dealt with the transition to CFC-free MDIs, including the following decisions:

- Decision VIII/10 stated that the Parties that are developed countries would take various actions to promote industry's participation in a smooth and efficient transition away from CFC-based MDIs (San Jose, Costa Rica, 1996).
- Decision IX/19 required the Parties that are developed countries to present an initial national or regional transition strategy by January 31, 1999 (Montreal, Canada, 1997).
- Decision XII/2 elaborated on the content of national or regional transition strategies required under Decision IX/19 and indicated that any MDI for the treatment of asthma or COPD approved for marketing after 2000 would not be an "essential use," unless it met the criteria laid out by the Parties for essential uses (Ouagadougou, Burkina Faso, 2000).
- Decision XIV/5 requested that each Party report annually the quantities of CFC and non-CFC MDIs and dry-powder inhalers (DPIs) sold or distributed within its borders and the approval and marketing status of non-CFC MDIs and DPIs. Decision XIV/5 also noted "with concern the slow transition to CFC-free metered-dose inhalers in some Parties" (Rome, Italy, 2002).
- Decision XV/5 states that, at the 17th meeting of the Parties (in December 2005) or thereafter, no essential uses of CFCs will be authorized for Parties that are developed countries, unless the Party requesting the essential-use allocation has submitted an action plan for MDIs for which the sole active ingredient is albuterol. Among other items, the action plan should include a specific date by which the Party plans to cease requesting essential-use allocations of CFCs for albuterol MDIs to be sold or distributed in developed countries[5] (Nairobi, Kenya, 2003).
- Decision XVII/5 states that Parties that are developed countries should provide a date to the Ozone Secretariat[6] before the 18th meeting of the Parties (October 30 to November 3, 2006) by which time a regulation or regulations will have been proposed to determine whether MDIs, other than those that have albuterol as the only active ingredient, are non-essential (Dakar, Senegal, 2005).

3. The 1990 Amendments to the Clean Air Act

In 1990, Congress amended the Clean Air Act to, among other things, better protect stratospheric ozone (Public Law No. 101–549, November 15, 1990) (the 1990 amendments). The 1990 amendments were drafted to complement, and be consistent with, our obligations under the Montreal Protocol (see section 614 of the Clean Air Act (42 U.S.C. 7671m)). Section 614(b) of the Clean Air Act provides that, in the case of a conflict between any provision of the Clean Air Act and any provision of the Montreal Protocol, the more stringent provision will govern. Section 604 of the Clean Air Act required the phase-out of the production of CFCs by 2000 (42 U.S.C. 7671c),[7] while section 610 of the Clean Air Act (42 U.S.C. 7671i) required EPA to issue regulations banning the sale or distribution in interstate commerce of nonessential products containing CFCs. Sections 604 and 610 provide exceptions for "medical devices." Section 601(8) (42 U.S.C. 7671(8)) of the Clean Air Act defines "medical device" as

> any device (as defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321)), diagnostic product, drug (as defined in the Federal Food, Drug, and Cosmetic Act), or drug delivery system—
>
> (A) if such device, product, drug, or drug delivery system utilizes a class I or class II substance for which no safe and effective alternative has been developed, and where necessary, approved by the Commissioner [of Food and Drugs]; and
>
> (B) if such device, product, drug, or drug delivery system, has, after notice and opportunity for public comment, been approved and determined to be essential by the Commissioner [of Food and Drugs] in consultation with the Administrator [of EPA].

4. EPA's Implementing Regulations

EPA regulations implementing the Montreal Protocol and the stratospheric ozone protection provisions of the 1990 amendments are codified in part 82 of title 40 of the Code of Federal Regulations (40 CFR part 82). (See 40 CFR 82.1 for a statement of intent.) Like the 1990 amendments, EPA's implementing regulations contain two separate prohibitions, one on the production and import of CFCs (subpart A of 40 CFR part 82) and the other on the sale or distribution of products containing CFCs (40 CFR 82.66).

The prohibition on production and import of CFCs contains an exception for essential uses and, more specifically, for essential MDIs. The definition of essential MDI at 40 CFR 82.3 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 regulations at 21 CFR 2.125.

The prohibition on the sale of products containing CFCs includes a specific prohibition on aerosol products and other pressurized dispensers. The aerosol product ban contains an exception for medical devices listed in § 2.125(e). The term "medical device" is used with the same meaning it was given in the 1990 amendments and includes drugs as well as medical devices.

5. FDA's 2002 Regulation

In the 1990s, we decided that § 2.125 required revision to better reflect our obligations under the Montreal Protocol, the 1990 amendments, and EPA's

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[5] Our obligation under XV/5 was met by our final rule eliminating the essential-use status of albuterol, effective December 31, 2008 (70 FR 17168, April 4, 2005).

[6] The Ozone Secretariat is the Secretariat for the Montreal Protocol and the Vienna Convention for the Protection of the Ozone Layer (the Vienna Convention) (March 22, 1985, 26 I.L.M. 1529 (1985)), available at *http://hq.unep.org/ozone/pdfs/viennaconvention2002.pdf.*

Based at the United Nations Environment Programme (UNEP) offices in Nairobi, Kenya, the Secretariat functions in accordance with Article 7 of the Vienna Convention and Article 12 of the Montreal Protocol. The main duties of the Secretariat include: Arranging for and servicing the Conference of the Parties, meetings of the Parties, their committees, the bureaus, working groups, and assessment panels; Arranging for the implementation of decisions resulting from these meetings; Monitoring the implementation of the Vienna Convention and the Montreal Protocol; Reporting to the meetings of the Parties and to the Implementation Committee; Representing the Convention and the Protocol; and Receiving and analyzing data and information from the Parties on the production and consumption of ODSs.

[7] In conformance with the adjustment contained in Decision IV/2, EPA issued regulations accelerating the complete phase-out of CFCs, with exceptions for essential uses, to January 1, 1996 (58 FR 65018, December 10, 1993).

regulations, and to encourage the development of ozone-friendly alternatives to medical products containing CFCs. In particular, as acceptable alternatives that did not contain CFCs or other ODSs came on the market, there was a need to provide a mechanism for removing essential uses from the list in § 2.125(e). In the **Federal Register** of March 6, 1997 (62 FR 10242), we published an advance notice of proposed rulemaking (the 1997 ANPRM) in which we outlined our then-current thinking on the content of an appropriate rule regarding ODSs in products FDA regulates. We received almost 10,000 comments on the 1997 ANPRM. In response to the comments, we revised our approach and drafted a proposed rule published in the **Federal Register** of September 1, 1999 (64 FR 47719) (the 1999 proposed rule). We received 22 comments on the 1999 proposed rule. After minor revisions in response to these comments, we published a final rule in the **Federal Register** of July 24, 2002 (67 FR 48370) (the 2002 final rule) (corrected in 67 FR 49396, July 30, 2002, and 67 FR 58678, September 17, 2002). The 2002 final rule listed as a separate essential use each active moiety[8] marketed under the 1978 rule as essential uses for metered-dose steroid human drugs for oral inhalation and metered-dose adrenergic bronchodilator human drugs for oral inhalation; eliminated the essential-use designations in § 2.125(e) for metered-dose steroid human drugs for nasal inhalation and for products that were no longer marketed; set new standards to determine when a new essential-use designation should be added to § 2.125; and set standards to determine whether the use of an ODS in a medical product remains essential.

This rulemaking fulfills our obligation under § 2.125, as well as the Clean Air Act, the Montreal Protocol, and our general duty to protect the public health, by removing ODS products from the marketplace when those products are no longer essential.

II. Criteria

Among other changes, the 2002 final rule, in revised § 2.125(g)(2), establishes a standard for removing an essential-use designation for any drug after January 1, 2005, that would apply to a drug where there are no acceptable non-ODS alternatives with the same active moiety. This standard provides an incentive for manufacturers to reformulate their products in a timely manner. There are no acceptable non-ODS alternatives available that have the same active moieties as the products marketed under the essential uses that are the subject of this proposed rule; therefore, we are proceeding with this rulemaking under the provisions of § 2.125(g)(2). The process for removing the essential use designation under § 2.125(g)(2) includes a consultation with a relevant advisory committee and an open public meeting, in addition to a proposed rule and a final rule. The criterion established for removing the essential use in such circumstances is that it no longer meets the criteria specified in revised § 2.125(f) for adding a new essential use (§ 2.125(g)(2)). The criteria in § 2.125(f) for adding an essential use are:

(i) Substantial technical barriers exist to formulating the product without ODSs;

(ii) The product will provide an unavailable important public health benefit; and

(iii) 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.

Because the three criteria in § 2.125(f) are linked by the word "and," failure to meet any single criterion results in a determination that the use is not essential.

We discussed these criteria in the preamble to the 1999 proposed rule. A key point in our discussion of technical barriers was: "Generally, FDA intends the term 'technical barriers' to refer to difficulties encountered in chemistry and manufacturing. A petitioner would have to establish that it evaluated all available alternative technologies and explain in detail why each alternative was deemed to be unusable to demonstrate that substantial technical barriers exist." (1999 proposed rule at 47721.)

In applying the "technical barriers" criteria, we look at the results of reformulation efforts for similar products as well as statements made about the manufacturer's particular efforts to reformulate their product.

Similarly, in discussing what is "an unavailable important public health benefit," we said: "The agency intends to give the phrase 'unavailable important public health benefit' a markedly different construction from the [phrase used in the 1978 rule] 'substantial health benefit.' A petitioner should show that the use of an ODS would save lives, significantly reduce or prevent an important morbidity, or significantly increase patient quality of life to support a claim of important public health benefit." (1999 proposed rule at 47722.)

One key point to note here is that we raised the hurdle for the public health benefit that needs to be shown. A use that was shown to have a "substantial health benefit" under the 1978 rule (all essential uses were established under the 1978 rule), will not necessarily be able to clear the higher hurdle of the 2002 final rule's "unavailable important public health benefit."

In determining if a drug product provides an otherwise unavailable important public health benefit, our primary focus is on the availability of non-ODS products that provide equivalent therapeutic benefits for patients who are currently using the CFC MDIs. If therapeutic alternatives exist for all patients using the CFC MDI, we would then determine that the CFC MDI does not provide an otherwise unavailable important public health benefit.

Under the third criterion, the essential use must be eliminated unless we find that use of the product does not release cumulatively significant amounts of ODSs into the atmosphere, or that the release, although cumulatively significant, is warranted in view of the otherwise unavailable important public health benefit that the use of the drug product provides. In evaluating whether continuing the essential-use designation of these MDIs would result in the products releasing significant quantities of ODSs, in light of past policy statements (2002 final rule p. 48380) and the current state of the phase-out of ODSs, we tentatively conclude that the release of CFCs from MDIs containing flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil would be significant. The reasons for this tentative conclusion are discussed in the following paragraphs.

The United States evaluated the environmental effect of eliminating the use of all CFCs in an environmental impact statement in the 1970s (see 43 FR 11301). As part of that evaluation, FDA concluded that the continued use

[8] Section 314.108(a) of the act (21 CFR 314.108(a)) defines "active moiety" as the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance. When describing the various essential uses, we will generally refer to the active moiety, for example, cromolyn, as opposed to the active ingredient, which, using the same example, would be cromolyn sodium. When discussing particular indications and other material from the approved labeling of a drug product, we will generally use the brand name of the product, which, using the same example, would be INTAL MDI. In describing material from treatises, journals, and other non-FDA approved publications, we will generally follow the usage in the original publication.

of CFCs in medical products posed an unreasonable risk of long-term biological and climatic impacts (see Docket No. 1996N–0057 (formerly 96N–0057)). Congress later enacted provisions of the Clean Air Act that codified the decision to fully phase out the use of CFCs over time (see 42 U.S.C. 7671 *et seq.* (enacted November 15, 1990)). We note that the environmental impact of individual uses of nonessential CFCs must not be evaluated independently, but rather must be evaluated in the context of the overall use of CFCs. Cumulative impacts can result from individually minor but collectively significant actions taking place over a period of time (40 CFR 1508.7). Significance cannot be avoided by breaking an action down into small components (40 CFR 1508.27(b)(7)). Currently, MDIs for the treatment of asthma and COPD are the only legal use of newly produced or imported CFCs (see EPA 2006 Allocation rule). Although it may appear to some that the CFCs released from MDIs represent insignificant quantities of ODSs, and therefore should be exempted, the elimination of CFC use in MDIs is one of the final steps in the overall phase-out of CFC use. The release of ODSs from some of the MDIs may be relatively small compared to total quantities that were released 2 or 3 decades ago, but if each use that resulted in the release of relatively small quantities of ODSs were provided an exemption, the cumulative effect would be to prevent the elimination of ODS releasing products. This would prevent the full phase-out envisioned by the Clean Air Act and the Montreal Protocol. Therefore, we tentatively conclude that the release of ODSs from these MDIs is cumulatively significant.

Given this proposed finding, the essential use for each product must be eliminated under § 2.25(f)(1)(iii) unless we also find that the product provides an otherwise unavailable important health benefit which warrants the cumulatively significant release of the ODS.

As noted previously, because the three criteria in § 2.25(f)(1) are linked by the word "and," failure to meet any single criterion results in a determination that the use is not essential. Accordingly, if we find that any product fails to provide an otherwise unavailable important health benefit (criterion two), we would be required to find that the use of the product is not essential, and we would not need to reach the last step under the third criteria (balancing the important health benefit against the release of the ODS to determine if the release is warranted). Assuming, however that the first and second criteria in § 2.125(f) are met, because of our tentative conclusion that the release of ODSs from these MDIs is cumulatively significant, we would then need to conduct the balancing inquiry under the third criterion for that product.

The criteria in § 2.125(f)(1) we are using in this rulemaking, as cross-referenced in § 2.125(g)(2), are different from those in § 2.125(g)(3) and (g)(4). Section 2.125(g)(2) specifically addresses the situation where there is no other marketed product containing the same active moiety in a non-ODS formulation, while § 2.125(g)(3) and (4)[9] apply to situations where there is at least one other product marketed with the same active moiety in a non-ODS formulation. When we removed the essential-use designation for albuterol (70 FR 17168, April 4, 2005) we used the criteria found in § 2.125(g)(4) because there were more than one albuterol CFC MDI being marketed and there were two acceptable alternatives containing albuterol (Proventil HFA and Ventolin HFA) to the albuterol CFC MDIs. This contrasts to § 2.125(g)(2), which permits FDA to remove an essential use even if there are no alternatives available with the same active moiety, provided that sufficient alternative products with different active moieties exist to meet the needs of patients, because the essential use would then no longer provide an otherwise unavailable important health benefit. Therefore, the analyses we use here are not identical to the analyses we used under § 2.125(g)(4) in the albuterol rulemaking. In both the albuterol rulemaking and this rulemaking, the primary focus is on determining whether acceptable alternatives exist for the products that are marketed under the essential use, but with this rulemaking we are able to consider alternatives with different active moieties. Therefore, our analyses are similar, and we have found it useful to borrow concepts from the more specific provisions of § 2.125(g)(3) and (g)(4) to help give more structure to our analysis under the broader language of § 2.125(f)(1). In general, as explained in the preamble to the 1999 proposed rule, "FDA is requiring the existence of feasible alternatives that are acceptable from a health standpoint before it will find any CFC–MDI no longer essential." (1999 proposed rule at 47736.) Thus, we request comment on whether the available alternatives for each of the seven moieties are acceptable from a public health perspective.

[9] The text of § 2.125(g)(3) and (4) is as follows:

(3) For individual active moieties marketed as ODS products and represented by one new drug application (NDA):

(i) At least one non-ODS product with the same active moiety is marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the ODS product containing that active moiety;

(ii) Supplies and production capacity for the non-ODS product(s) exist or will exist at levels sufficient to meet patient need;

(iii) Adequate U.S. postmarketing use data is available for the non-ODS product(s); and

(iv) Patients who medically required the ODS product are adequately served by the non-ODS product(s) containing that active moiety and other available products; or

(4) For individual active moieties marketed as ODS products and represented by two or more NDAs:

(i) At least two non-ODS products that contain the same active moiety are being marketed with the same route of delivery, for the same indication, and with approximately the same level of convenience of use as the ODS products; and

(ii) The requirements of paragraphs (g)(3)(ii), (g)(3)(iii), and (g)(3)(iv) of this section are met.

There are noteworthy procedural differences between § 2.125(g)(2) and § 2.125(g)(3) and (4). A rulemaking under § 2.125(g) (3) or (4) could have been started before January 1, 2005, and there is no requirement for either an advisory committee meeting or public meeting. The proposed rule for the removal of the essential-use designation for albuterol was published in the **Federal Register** of June 16, 2004 (69 FR 33602) and although the matter was discussed at a public meeting of the Pulmonary-Allergy Drug Advisory Committee on June 10, 2004, no separate public meeting on the matter was held.

III. Effective Date

We are proposing that any rule finalizing the removal of an essential use proposed in this document have an effective date of December 31, 2009. In determining the appropriate effective date or dates for this rulemaking, we will consider not only whether therapeutic alternatives are on the market but also whether adequate production capacity and supplies are available to meet the new, presumably increased, demand for the therapeutic alternatives once products marketed under the old essential use are no longer sold. Depending on the data presented to us in the course of the rulemaking, we may determine that it is appropriate to have different effective dates for different uses.

In determining an appropriate effective date, we have kept in mind that albuterol HFA[10] MDIs are primary therapeutic alternatives to drugs produced under three of the essential uses described in this rule. Sales of the products marketed under those essential uses have totaled approximately 14

[10] These albuterol inhalers use the non-ozone-depleting hydrofluoroalkane HFA-134a (usually referred to as HFA) as a propellant.

[11] Current information indicates that production of albuterol HFA MDIs will be adequate to meet the current demand for albuterol MDIs much earlier than December 31, 2008.

million MDIs a year. We are confident there will be adequate supplies of albuterol HFA MDIs to meet the needs of all current users of albuterol CFC MDIs by December 31, 2008 (the date on which albuterol MDIs will no longer be designated an essential use).[11] Although we have limited data on production increases above current demand for 2009 and later, we believe that, by December 31, 2009, albuterol HFA production will be able to meet any increased demand caused by this rulemaking. We specifically invite comments from manufacturers of albuterol HFA MDIs on this issue.

We also believe that a December 31, 2009 effective date is more than sufficient to allow patients to consult their health care providers and obtain prescriptions for therapeutic alternatives in an orderly fashion.

In proposing a December 31, 2009, effective date, we expect that 2009 would be a transition year characterized by declining production of the CFC MDIs that are the subject of this rule. If a December 31, 2009 effective date is established by this rulemaking, we anticipate that other administrative actions taken by EPA and FDA would reflect the concept of 2009 being a transition year.

The sale of remaining stocks of CFC MDIs by manufacturers, wholesalers, and retailers was a consideration in setting the effective date of the albuterol rule (70 FR 17168 and 17179). We believe that this consideration also is appropriate for this rulemaking. In evaluating the period of time that is needed to sell remaining stocks of the CFC MDIs that are the subject of this rulemaking, a factor that must be considered is the expiration dating for the relevant products. One product has an expiration date set at 18 months after manufacture, five products have dates set at 24 months, and three products' expiration dates are 30 months or more after production.[12] Prescription drug products, particularly those for chronic diseases such as asthma and COPD, are generally dispensed well before the expiration date, allowing the patients a significant amount of time to use the drugs before they reach their expiration dates. Therefore, we believe that all of the products with 18-month and 24-month expiration dates manufactured prior to publication of a final rule based on this proposal will have passed their expiration dates and been dispensed or destroyed by December 31, 2009. We invite comments on the relationship between expiration dates and the distribution and dispensing of the products that are the subject of the rulemaking.

IV. 2005 PADAC Meeting

As required by § 2.125(g)(2), we consulted an advisory committee before drafting this proposed rule. We consulted with FDA's Pulmonary and Allergy Drugs Advisory Committee (PADAC) at their July 14, 2005, meeting (2005 meeting) on the essential-use status of MDIs containing flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil. The opinions expressed by the PADAC members about each of these essential uses will be discussed below.[13]

This PADAC meeting should not be confused with the open public meeting that we will be holding in the near future on the essential-use status of these MDIs. We will publish a notice for the public meeting in the **Federal Register** shortly.

V. Drugs We Are Proposing as Nonessential

A. Flunisolide and Triamcinolone

We are proposing to remove the essential-use designations for MDIs containing flunisolide (AEROBID) and triamcinolone (AZMACORT). AEROBID and AZMACORT are orally inhaled corticosteroids. AZMACORT is the only currently marketed drug product that provides orally inhaled triamcinolone. AEROBID and AZMACORT are the only two orally inhaled corticosteroids marketed that contain ODSs. Both drugs are indicated for the maintenance treatment and prophylaxis of asthma in patients as young as 6 and both are prescription drugs. Flunisolide and triamcinolone, as well as other corticosteroids, are not indicated for relief of acute bronchospasm. Inflammation is an important component in the development of asthma. The anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma. Though effective for the treatment of asthma, corticosteroids do not appreciably affect asthma symptoms immediately. Individual patients experience a variable time to onset and degree of symptom relief. Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. AEROBID was approved on April 23, 1982, and AZMACORT was approved on August 17, 1984. Their use was considered essential under the 1978 rule, which stated that "[m]etered-dose steroid human drugs for oral inhalation" were essential. Flunisolide and triamcinolone were designated as essential as different active moieties in the 2002 rule. In addition to the ODS-containing AEROBID, AEROSPAN, a flunisolide HFA MDI, was approved January 27, 2006, but has not yet been introduced onto the market.

We have tentatively concluded that the following orally inhaled corticosteroid drug products, which do not contain ODSs, collectively provide adequate therapeutic alternatives to AEROBID and AZMACORT:

- Beclomethasone dipropionate MDI (QVAR),
- Budesonide DPI (PULMICORT TURBUHALER),
- Fluticasone propionate MDI (FLOVENT HFA), and
- Mometasone furoate DPI (ASMANEX TWISTHALER).

All of these drugs are indicated for the maintenance treatment and prophylaxis of asthma. All of the therapeutic alternatives have adequate safety profiles similar to those of AEROBID and AZMACORT. Our tentative conclusion that these four drugs collectively provide adequate therapeutic alternatives does not mean that each can be freely substituted for AEROBID and AZMACORT, or freely substituted one for another. Rather, we believe that at least one of those drugs should be an adequate therapeutic alternative for every patient currently using AEROBID or AZMACORT. There are significant differences among these drugs, for example FLOVENT HFA and ASMANEX TWISTHALER are both indicated for patients 12 and older, compared to AEROBID and AZMACORT, which are indicated for patients 6 and older. However, QVAR and PULMICORT TURBUHALER are indicated for patients as young as 5 and 6, respectively. With these two drugs, younger pediatric patients who used AEROBID and AZMACORT should be more than adequately served. There are other notable differences: ASMANEX TWISTHALER contains lactose; there is clinical data on the use of inhaled budesonide by pregnant women in labeling for PULMICORT TURBUHALER; QVAR and FLOVENT HFA are MDIs; ASMANEX TWISTHALER and PULMICORT TURBUHALER are different types of DPIs. All of these elements, and more, may factor into a decision on which drug product to substitute for AEROBID

[12] Nine different products, including two sizes of COMBIVENT and two flavors (plain and menthol) of AEROBID, are produced under the seven essential uses that are the subject of this rule.

[13] A transcript of the meeting and other meeting material is available on the Web at *http://www.fda.gov/ohrms/dockets/ac/cder05.html#PulmonaryAllergy*.

and AZMACORT for any individual patient.

A therapeutic alternative to AEROBID and AZMACORT, primarily for patients who are using both salmeterol and either AEROBID or AZMACORT, is the ADVAIR DPI which contains fluticasone propionate and another asthma drug salmeterol, in combination, which is available in various strengths. .

FDA has recently approved SYMBICORT, an HFA MDI combining budesonide and formoterol, a long-acting beta-agonist. This drug product is expected to enter the U.S. market in mid-2007 and would be a logical first option for patients using both formoterol (FORADIL) and either AEROBID or AZMACORT. However, the lack of postmarketing data and the unavailability of information on future production capacity and supplies for SYMBICORT means that we cannot consider at this time the expected availability of SYMBICORT as grounds for eliminating the essential use of flunisolide under § 2.125(g)(2). The expected availability of SYMBICORT was not considered a material issue in our tentative determination that flunisolide MDIs are not an essential use of ODSs: there are more than a sufficient number of therapeutic alternatives to AEROBID and AZMACORT without considering SYMBICORT.

We realize that inhaled corticosteroids are widely considered the drugs of choice, used in conjunction with other drugs, for treatment of severe persistent, moderate persistent, and mild persistent asthma in adults and children (Ref. 1, app. A–1).[14] However certain health care providers and patients, particularly in cases of mild persistent asthma, may decide to switch from AEROBID and AZMACORT to drugs other than inhaled corticosteroids. If these other drugs do not release ODSs, such as leukotriene modifiers and theophylline, then they also provide alternative therapies.

The recently approved AEROSPAN (flunisolide HFA MDI) may also be a therapeutic alternative to AEROBID and AZMACORT. However, as previously noted with SYMBICORT, the lack of postmarketing data and the unavailability of information on future production capacity and supplies for AEROSPAN mean that we cannot consider at this time the availability of AEROSPAN as grounds for eliminating the essential use of flunisolide under § 2.125(g)(3). The availability of AEROSPAN was not considered a material issue in our tentative determination that flunisolide MDIs are not an essential use of ODSs: there are more than a sufficient number of therapeutic alternatives to AEROBID and AZMACORT without considering AEROSPAN. However, we do solicit comments on postmarketing data for AEROSPAN and its suitability as an alternative to AEROBID and AZMACORT.

PADAC members expressed the opinion, without dissent, that flunisolide and triamcinolone were no longer essential uses of ODSs.

We have tentatively come to the following conclusion:

- The pharmaceutical industry has had success in formulating other orally inhaled corticosteroids without ODSs. In particular, the AEROSPAN flunisolide HFA MDI was approved by FDA. We have no evidence to suggest that the ODS containing triamcionolone or flunisolide oral inhalation drug products pose unique technical challenges to formulation without ODSs. Therefore, we tentatively conclude that no substantial technical barriers exist to formulating triamcinolone or flunisolide oral inhalation drug products without ODSs.
- Flunisolide and triamcinolone MDIs do not provide an otherwise unavailable important public health benefit because of the available therapeutic alternatives.
- The release of ODSs into the atmosphere from flunisolide and triamcinolone MDIs is cumulatively significant and is not warranted because they do not provide an otherwise unavailable important public health benefit.

We, therefore, tentatively conclude that oral pressurized MDIs containing flunisolide and triamcinolone are no longer essential uses of ODSs and should be removed from the list of essential uses in § 2.125(e).

B. Metaproterenol and Pirbuterol

We are proposing to remove the essential-use designations for MDIs containing metaproterenol (ALUPENT MDI) and pirbuterol (MAXAIR). Metaproterenol and pirbuterol are short-acting beta$_2$-adrenergic agonists used in the treatment of bronchospasm associated with asthma and COPD. They act as bronchodilators. Pirbuterol is only available in a CFC MDI, while metaproterenol is also available as a syrup, as tablets, and as an inhalation solution for use in nebulizers. This rulemaking will not affect any dosage form of metaproterenol other than the ALUPENT MDI which contains CFCs. ALUPENT MDI and MAXAIR are the only beta$_2$-adrenergic agonist MDIs currently marketed containing CFCs (other than albuterol, whose essential use status will end December 31, 2008). ALUPENT MDI and MAXAIR are prescription drugs. Their use was considered essential under the 1978 rule, which stated that "[m]etered-dose adrenergic bronchodilator human drugs for oral inhalation" were essential. Metaproterenol and pirbuterol were designated as essential as different active moieties in the 2002 rule. ALUPENT MDI was approved on July 31, 1973, and MAXAIR was approved on November 30, 1992.

We have tentatively concluded that the following beta$_2$-adrenergic agonist MDIs, which use HFA-134a (1,1,1,2, tetrafluoroethane) as a propellant instead of ODSs, collectively provide adequate therapeutic alternatives to ALUPENT MDI and MAXAIR:

- Albuterol sulfate MDI (PROAIR HFA),
- Albuterol sulfate MDI (PROVENTIL HFA),
- Albuterol sulfate MDI (VENTOLIN HFA),
- Levalbuterol tartrate MDI (XOPONEX HFA).

ALUPENT MDI, MAXAIR, and the therapeutic alternatives are all very similar drugs. They are all indicated for the relief of bronchospasms associated with asthma and COPD (although the labeled indications may be worded differently), have very similar safety profiles,[15] and have similar dosing regimens. When we say that these 4 drugs collectively provide adequate therapeutic alternatives, we are not saying that each can be freely substituted for ALUPENT MDI and MAXAIR, or freely substituted one for another. Rather, we are saying that one of those drugs should be an adequate therapeutic alternative for every patient currently using ALUPENT MDI or MAXAIR. ALUPENT MDI and MAXAIR are indicated for children as young as 12, while the therapeutic alternatives are indicated for children as young as 4. The albuterol sulfate products are indicated for prevention of exercise-induced asthma, while ALUPENT MDI, MAXAIR, and Xopenex are not. MAXAIR includes one product form that incorporates an "autohaler" device. This mechanism senses patient effort and delivers the dose in relationship to inhalation by the patient. While this

[14] References to outside publications or any other statements of fact or opinion in this document concerning a drug product are not intended to be equivalent to statements in labeling approved under section 505 of the act (21 U.S.C. 355) and part 314 of our regulations (21 CFR part 314).

[15] Metaproterenol, because it is less selective than pirputerol, albuterol, levalbuterol, and some other beta$_2$-agonists, may present greater potential for excessive cardiac stimulation (Ref. 2, p. 64; Ref. 1, Appendix A–2).

mechanism is believed to lessen issues with coordinating inhalation to actuation, there are no data to adequately document that this feature leads to improvements in therapy. However, the use of spacer devices with other alternative products may provide options for individuals who have difficulties in coordinating inhalation with MDI operation, allowing them to more satisfactorily use MDIs that do not have a breath-actuated mechanism.

PADAC members gave their opinion, without dissent, that metaproterenol and pirbuterol were no longer essential uses of ODSs.

We have tentatively come to the following conclusions:

- The pharmaceutical industry has had success in formulating other orally inhaled $beta_2$-adrenergic bronchodilators without ODSs. We have no evidence to suggest that the ODS containing metaproterenol or pirbuterol oral inhalation drug products pose unique technical challenges to formulation without ODSs Therefore, we tentatively conclude that no substantial technical barriers exist to formulating metaproterenol and pirbuterol oral inhalation drug products without ODSs.
- Metaproterenol and pirbuterol MDIs do not provide an otherwise unavailable important public health benefit because of the available therapeutic alternatives.
- The release of ODSs into the atmosphere from metaproterenol and pirbuterol MDIs is cumulatively significant and is not warranted because they do not provide an otherwise unavailable important public health benefit.

We, therefore, tentatively conclude that oral pressurized MDIs containing metaproterenol and pirbuterol are no longer essential uses of ODSs and should be removed from the list of essential uses in § 2.125(e).

C. Cromolyn and Nedocromil

Cromolyn sodium and nedocromil sodium are members of the class of drugs called "cromones." Although it is not entirely clear how cromones exert their clinical effect, cromones are thought to inhibit antigen-induced bronchospasm as well as the release of histamine and other autacoids from sensitized mast cells. Cromolyn is also available for use in treating asthma as an inhalation solution for use in a nebulizer. Both cromolyn and nedocromil are also used in ophthalmic products, and cromolyn is available for oral administration for an enteric indication. None of these formulations would be affected by this proposed action.

The only cromolyn MDI (INTAL MDI) was approved for marketing on December 5, 1985. The essential-use designation for "[m]etered-dose cromolyn sodium human drugs administered by oral inhalation" was added to § 2.125(e) on February 6, 1986 (51 FR 5190).

The only nedocromil MDI (TILADE) was approved for marketing December 30, 1992. The essential-use designation for "[m]etered-dose nedocromil sodium human drugs administered by oral inhalation" was added to § 2.125(e) on January 26, 1993 (58 FR 6086).

No other cromone drug is marketed in an MDI or other dosage form.

Both INTAL MDI and TILADE are indicated for the management of asthma in patients as young as 5 and 6, respectively. Both are prescription drugs. Neither drug is indicated for the relief of acute bronchospasm.

We have tentatively concluded that the following orally inhaled corticosteroid drug products, which do not contain ODSs, collectively provide adequate therapeutic alternatives to INTAL MDI and TILADE:

- Beclomethasone dipropionate MDI (QVAR),
- Budesonide DPI (PULMICORT TURBUHALER),
- Fluticasone propionate MDI (FLOVENT HFA), and
- Mometasone furoate DPI (ASMANEX TWISTHALER).

Inhaled corticosteroids are generally considered the preferred treatment for mild but persistent asthma, while cromolyn and nedocromil are considered to be alternative, or secondary, treatments (Ref. 1, appendix A–1, and p. 23). Cromolyn and nedocromil are generally regarded as having an excellent safety profile, but their clinical usefulness has been questioned, particularly when compared to inhaled corticosteroids (Ref. 1., p. 23; Ref. 2;). The clinical evidence of better effectiveness outweighs any minor concerns we may have about the slight differences that may exist between the safety profiles of the cromones (cromolyn and nedocromil) and the inhaled corticosteroids. QVAR, and PULMICORT TURBUHALER, as discussed in part V.A of this document, provide more than adequate therapeutic alternatives for younger pediatric patients. While low-dose inhaled corticosteroids are generally considered the drugs of choice for mild but persistent asthma in adults and children, health care providers and patients, particularly in cases of patients who do not tolerate corticosteroids, may decide to switch from INTAL MDI and TILADE to drugs other than inhaled corticosteroids. Also, there are non-inhaled asthma medications, such as leukotriene modifiers and theophylline, which also provide alternative therapies. Leukotriene modifiers and theophylline (as well as cromolyn and nedocromil) have been suggested as alternative medications for moderate but persistent asthma in children older than 5 and in adults (Ref. 1, app. A–1)

Although we believe that patients using INTAL MDIs and TILADE will be adequately served by the inhaled corticosteroids and other therapeutic alternatives described previously, another therapeutic alternative may be the use of cromolyn inhalation solution in a portable nebulizer. We bring up this issue here because of the absence of MDIs and DPIs containing a cromone, and the availability of cromolyn in an inhalation solution. In the past we have downplayed, but never categorically rejected, the suitability of portable nebulizers as therapeutic alternatives to ODS-containing MDIs (see the 1999 Proposed Rule at 47226, and the 2002 Final Rule at 48377). We invite comment on the suitability of portable nebulizers as therapeutic alternatives to INTAL MDIs and TILADE, and whether use of a portable nebulizer would be necessary to serve all patients who are currently using INTAL MDIs and TILADE.

PADAC members were closely divided at the 2005 meeting on whether cromolyn is essential. Several members questioned the drug's effectiveness with some concluding that the drug was no longer essential, while others felt that the drug was preferable for treating some "niche" patient populations, even though inhaled corticosteroids were more generally effective. The two niche patient populations identified were patients who could not tolerate $beta_2$-adrenergic agonists who experience exercised-induced bronchospasm, and patients who need prophylaxis for a specific allergy-induced bronchospasm, such as might happen when an allergic patient visits a house with a cat in it. One member said that for the small group of patients that have no other alternative than to use cromolyn, nebulizers, while somewhat inconvenient, may provide a therapeutic alternative for situations involving planned and known exposures to allergens. Another member disagreed with this opinion, responding that nebulizers are too inconvenient to provide a therapeutic alternative to MDIs.

A consensus quickly developed among the PADAC members at the 2005 meeting that nedocromil was not essential. One member questioned

whether TILADE was still on the market and another stated that he had assumed it was off the market. One member said that his view on nedocromil, which he viewed as very comparable to cromolyn (a view well supported by available literature), was influenced by the supposition that a cromolyn product would still be on the market.

The issue of exercise-induced bronchospasm in determining the essential-use status of cromolyn and nedocromil is a difficult subject to address. Beta$_2$-adrenergic agonists are generally regarded as the treatment of choice for prophylaxis of exercise induced bronchospasm (Ref. 3, p. 100). The labeling for PROVENTIL HFA, VENTOLIN HFA, PROAIR HFA, formoterol fumarate inhalation powder (FORADIL), and SEREVENT DISKUS includes indications for exercise induced bronchospasm. As stated at the 2005 PADAC meeting, the primary issue then becomes one of prophylaxis of exercise induced bronchospasm in patients who do not tolerate beta$_2$-adrenergic agonists. The size of this patient population is not well documented. Studies of albuterol in HFA MDIs show rates of adverse events that are not significantly different from the rates with a placebo, indicating that this is a very well-tolerated drug.[16] If a patient population that cannot tolerate beta$_2$-adrenergic agonists exists, it would seem to be very small. However, there appear to be therapeutic alternatives for INTAL MDIs and TILADE for this population. Long-term control therapy using corticosteroids may provide an appropriate therapeutic alternative for prophylaxis of exercise induced bronchospasm. Long-term control therapy, including corticosteroids and montelukasts (SINGULAIR), may decrease the bronchial hyperresponsiveness and therefore significantly lessen the need for immediate prophylaxis of exercise induced bronchospasm with a shorter-acting drug, such as cromolyn, nedocromil, or albuterol. (Ref. 3, p. 100; Ref. 4; Ref. 5; Ref. 6). Portable nebulizers using cromolyn may provide an attractive therapeutic alternative for this patient population as well. A nebulizer too large to carry in a pocket or purse might be easily carried in a gym bag. Larger nebulizers using cromolyn may also provide an acceptable therapeutic alternative for prophylaxis of exercise induced bronchospasm, because exercise can be scheduled so that access to a nebulizer is available before the exercise.

The issue of INTAL MDI and TILADE patients who needed prophylaxis for a specific allergy-induced bronchospasm, such as might occur when an allergic patient visits a house with a cat in it, is less well defined than the prophylaxis of exercise induced bronchospasm. We believe that our discussion of alternatives to INTAL MDIs and TILADE in regard to exercise induced bronchospasm would be equally relevant to this issue.

We agree with the PADAC member that cromolyn and nedocromil are very comparable drugs (see Ref. 7 (cromolyn and nedocromil administered by MDI provide similar protection against exercise induced bronchospasm in children)). We request comment as to whether there is a medically sound rationale for treating them differently. It would seemingly make little sense to remove the essential use of one and retain the other without such a rationale. There would be no net decrease in the amount of ODSs released into the atmosphere if everyone currently using INTAL MDI switched to TILADE, or vice versa. Therefore, our analysis has treated the two drugs together.

We have tentatively come to the following conclusion:

- The pharmaceutical industry has had success in formulating other orally inhaled drugs with similar physical properties to cromolyn and nedocromil without ODSs, including the development of cromolyn and nedocromil HFA MDIs overseas. We have no evidence to suggest that the ODS containing cromolyn or nedocromil oral inhalation drug products pose unique technical challenges to formulation without ODSs. Therefore, we tentatively conclude that no substantial technical barriers exist to formulating cromolyn and nedocromil oral inhalation drug products without ODSs.
- Cromolyn and nedocromil MDIs do not provide an otherwise unavailable important public health benefit because of the available therapeutic alternatives. However, given the issues raised during the discussion at the PADAC meeting, we request comment on our tentative conclusion.
- The release of ODSs into the atmosphere from cromolyn and nedocromil MDIs is cumulatively significant and is not warranted, because they do not provide an otherwise unavailable important public health benefit.

We, therefore, tentatively conclude that oral pressurized MDIs containing cromolyn sodium and nedocromil sodium are no longer essential uses of ODSs and should be removed from the list of essential uses in § 2.125(e).

D. Albuterol and Ipratropium in Combination

We are proposing to remove the essential-use designations for MDIs containing albuterol sulfate and ipratropium bromide in combination (COMBIVENT).[17] COMBIVENT is a prescription drug. Albuterol is a beta$_2$-adrenergic bronchodilator and ipratropium is an anticholinergic bronchodilator. Both are used in the treatment of bronchospasm associated with COPD. Albuterol is somewhat faster acting than ipratropium, while ipratropium is somewhat longer acting than albuterol. The primary advantage of using the two drugs in combination is that, by using two distinctly different mechanisms of action, the two drugs in combination should produce greater bronchodilator effect than using either drug alone. The essential use for MDIs containing albuterol sulfate and ipratropium bromide in combination was added to § 2.125(e) in the **Federal Register** of April 9, 1996 (61 FR 15700). Albuterol and ipratropium, in combination, are also sold as an inhalation solution (DUONEB) for use in a nebulizer. Nebulizers do not use CFCs. This current rulemaking will not affect the regulatory status of DUONEB.

We have tentatively determined that an ipratropium bromide MDI (ATROVENT HFA) used with an albuterol sulfate HFA MDI (PROAIR HFA, PROVENTIL HFA, OR VENTOLIN HFA) will provide an acceptable therapeutic alternative to COMBIVENT. Using the two MDIs together will deliver the same dose of ipratropium (18 mcg per inhalation) and essentially the same dose of albuterol (108 mcg versus 103 mcg per inhalation). While the acceptability as a therapeutic alternative of the same two drugs delivered by two separate MDIs rather than by one may seem obvious, this opinion is not universally shared. A Boehringer

[16] Other beta$_2$-adrenergic bronchodilators, particularly older, less selective beta$_2$-adrenergic bronchodilators, may not be as well tolerated. Salmeterol has specific safety concerns (see the boxed warning on the approved labeling of Serevent Diskus). However, albuterol is the most widely used beta$_2$-adrenergic bronchodilator, and it is indicated for prophylaxis of exercise induced bronchospasm, so we feel comfortable in focusing our discussion on this single member of the class.

[17] We have received a citizen petition from Boehringer Ingelheim Pharmaceuticals, Inc. (BI) (Docket No. 2006P-0428/CP1). The petition asks us to refrain from taking any action to remove the essential-use designation for COMBIVENT. We have not had adequate time to evaluate this lengthy petition and its 52 references. We will treat the petition as a comment on this proposal. The contents of this petition do not need to be resubmitted, but BI is free to submit any additional information or analysis they feel is relevant.

Ingelheim Pharmaceuticals, Inc. (BI), employee commented at the 2005 PADAC meeting that having patients use albuterol and ipratropium in a single combination MDI resulted in higher patient compliance with the prescribed regimen of medication than having the patient use two separate MDIs. Several PADAC members agreed with BI that higher compliance rates among patients was a significant factor that justified continuing the essential-use status of albuterol and ipratropium in combination. Other PADAC members stated that combining the two drugs was more of a convenience than an essentiality. One member noted that the hospital at which he practiced did not have COMBIVENT on its formulary, and albuterol and ipratropium are prescribed in separate MDIs. He concluded that providing the two drugs together in a combination MDI was not essential. One PADAC member pointed out that the increasing popularity of the tiotropium bromide DPI (SPIRIVA HANDIHALER) would decrease demand for COMBIVENT, because ipratropium cannot be used in conjunction with tiotropium. One PADAC member stated that the combination should remain essential for the time being because of the unnecessary anxiety that removing COMBIVENT from the market could cause. Opinion on whether the combination should retain its essential-use status was evenly divided.

We are aware of one health economics survey suggesting that a single inhaler containing both albuterol and ipratropium might increase compliance and decrease risk of emergency department visits and mean length of hospital stays compared to the effects achieved with separate inhalers for these two moieties (Ref. 8). However, we have not fully evaluated this survey. A patient's failure to use albuterol and ipratropium as prescribed would be expected to lead to increased symptoms, but it would not affect the permanent underlying state of the patient's lungs (Ref. 9). When the patient resumes using albuterol and ipratropium as prescribed (which he or she would have a major incentive to do), the symptoms should be relieved, with no significant changes in the patient's health compared to the period before the patient stopped using the MDIs as prescribed. We welcome any reports of studies on these subjects. We request comment on whether increased compliance and increased quality of life would be compelling reasons for continuing the essential-use designation for albuterol and ipratropium in combination. We do not currently have sufficient information to say that continuing the essential use will significantly increase patient quality of life to support a claim of important public health benefit.

Continuing the essential-use status of albuterol and ipratropium in combination is no longer supported by one of the rationales that BI proposed in their citizen petition requesting that MDIs containing albuterol sulfate and ipratropium bromide in combination be listed as essential in § 2.125(e). BI said that use of the COMBIVENT MDI could reduce the release of CFCs into the atmosphere, because patients would be using one CFC MDI for both albuterol and ipratropium, instead of two separate CFC MDIs (neither albuterol nor ipratropium was available in a non-ODS MDI at the time) (Citizen Petition, dated October 19, 1992, Docket No. 1992P–0403/CP1 (formerly 92P–0403)). We adopted this rationale in our rulemaking to add the essential use to § 2.125(e) (60 FR 53725, October 17, 1995; 61 FR 15699, April 9, 1996). Now, however, with ATROVENT HFA and albuterol sulfate HFA MDIs on the market, this rationale is no longer valid.

We have tentatively come to the following conclusion:

- Although a BI employee said at the 2005 PADAC meeting that there were substantial technical barriers to formulating albuterol and ipratropium in combination without ODSs, we have not been supplied with any information to support this conclusion and we cannot make an initial determination on whether substantial technical barriers exist.
- Albuterol and ipratropium in combination CFC MDIs do not provide an otherwise unavailable important public health benefit. However, given the issues raised during the discussion at the PADAC meeting, we request comment on our tentative conclusion.
- The release of ODSs into the atmosphere from albuterol and ipratropium in combination MDIs is cumulatively significant and is not warranted, because they do not provide an otherwise unavailable important public health benefit.

We, therefore, tentatively conclude that metered-dose ipratropium bromide and albuterol sulfate, in combination, administered by oral inhalation for human use is no longer an essential use of ODSs and should be removed from the list of essential uses in § 2.125(e). We would be able to reach this conclusion without reaching a conclusion about whether substantial technical barriers exist to formulating an ipratropium bromide and albuterol sulfate combination without ODSs because a CFC ODS product must meet all three criteria to remain designated as an essential use (see § 2.125(g)(2)).

VI. Environmental Impact

We have carefully considered the potential environmental effects of this action. We have tentatively concluded that the action will not have a significant adverse impact on the human environment, and that an environmental impact statement is not required. Our initial finding of no significant impact and the evidence supporting that finding, contained in a draft environmental assessment, may be seen in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday. We invite comments on the draft environmental assessment. Comments on the draft environmental assessment may be submitted in the same way as comments on this document (see **DATES**).

VII. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is a significant regulatory action as defined by the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The agency does not believe that this proposed rule would have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $118 million, using the most current (2004) Implicit Price Deflator for the Gross

Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

The Congressional Review Act requires that regulations that have been identified as being major must be submitted to Congress before taking effect. This rule is major under the Congressional Review Act.

Limitations in the available data prevent us from estimating quantitatively the anticipated costs and benefits to society, so we focus instead on proxy measures. The costs of this proposed rule include the benefits lost by consumers who would have bought MDIs at current prices, but would not buy them at higher prices. Consumers of flunisolide MDIs (AEROBID) and MDIs delivering albuterol and ipratropium in combination (COMBIVENT) will face higher prices because available substitutes cost more. In contrast, users of triamcinilone MDIs (AZMACORT), metaproterenol MDIs (ALUPENT), pirbuterol MDIs (MAXAIR), cromolyn sodium MDIs (INTAL), and nedocromil sodium MDIs (TILADE) will be able to switch to less expensive alternatives. Consumers of these products may benefit as they are made aware of less expensive, therapeutically adequate alternatives to the MDIs they currently use.

Net spending by consumers and third-party payers, including Federal and State Governments, will increase as patients switch to more expensive therapeutic alternatives; the potential for spending reductions by users of AZMACORT, ALUPENT, MAXAIR, INTAL, and TILADE is not enough to offset expected increases in spending by users of AEROBID and COMBIVENT. These spending increases, however, overstate social costs because, to some extent, they represent resources transferred from drug buyers (consumers and third-party payers) to drug sellers (drug manufacturers, wholesalers, pharmacies). We estimate that, when it occurs, the introduction of generic albuterol HFA MDIs to the market will eliminate price and spending increases resulting from this proposed rule. The benefits of this rule include the value of improvements in the environment and public health that may result from reduced emissions of ODSs (for example, the reduced future incidence of skin cancers and cataracts). The benefits also include improved expected returns on investments in environmentally friendly technologies and greater international cooperation and goodwill to comply with the Montreal Protocol.

Estimated spending increases (summarized in tables 1 and 2 of this document) cannot be attributed solely to this rule. These increases result from COMBIVENT users switching to ATROVENT HFA and albuterol HFA MDIs. The increased spending from this switch, in turn, is driven by the switch from inexpensive generic albuterol CFC MDIs to more expensive albuterol HFA MDIs, which was mandated in earlier rulemaking (70 FR 17168). These estimated spending increases may also be attributed to the withdrawal of albuterol CFC MDIs (including all of the less-expensive generic albuterol MDIs) from the market (see 70 FR 17168). The rightmost column in table 1 of this document shows estimates of the amount of increased spending attributable to this proposed rule if COMBIVENT prices were to increase dramatically, as discussed in section VII.C.6 of this document, even in the absence of this proposed rule. These remaining costs would be attributable to this proposed rule until a mandatory phase-out of all CFCs under the Montreal Protocol.

TABLE 1.—SUMMARY OF ANNUAL QUANTIFIABLE EFFECTS OF THE PROPOSED RULE

Patient Days of Therapy Affected	Increased MDI Expenditures, in 2005 dollars	Possible Reduction in Days of Therapy Used (millions)	Reduced CFC Emissions from Phase-out (tonnes)	Increased MDI Expenditures Attributable to this Proposed Rule Without Increase in Expenditures by COMBIVENT Users
440 million	$200–$400 million	0.7–11	310–365	-$70 to $70 million

TABLE 2.—SUMMARY OF INCREASES IN IMPACTS RELATIVE TO HFA PATENT EXPIRATION

Date of HFA Patent Expiration	Possible Decreases in Use of Asthma and COPD Therapy (million days of therapy)	Discount Rate	Increases in Expenditures on CFC-based MDIS, Present Value in 2006 (billions)
2010	.68–11	3%	$.19–$.38
		7%	$.17–$.35
2017	5.4–88	3%	$1.3–$2.7
		7%	$1.1–$2.2

The decreased use of MDIs may adversely affect some patients, but we currently lack data that would allow us to characterize such effects quantitatively. We also are unable to estimate quantitatively the reductions in skin cancers, cataracts, and environmental harm that may result from the reduction in CFC emissions by 310 to 365 tonnes during these years. Although we cannot estimate quantitatively the public health effects of the phase-out, based on a qualitative assessment, the agency concludes that the benefits of this regulation justify its costs.

We state the need for the regulation and its objective in section VII.B of this document. Section VII.C of this document provides background on CFC depletion of stratospheric ozone, the Montreal Protocol, the albuterol MDI market, and the health conditions that albuterol is used to treat. We analyze the benefits and costs of the rule, including effects on government outlays, in section VII.D of this document. We assess alternative dates in section VII.E of this document, and discuss sensitivity analysis in section VII.F of this document. We present an analysis of the effects on small business in a regulatory flexibility analysis in section VII.G of this document. We discuss our conclusions in section VII.H of this document.

B. Need for Regulation and the Objective of this Rule

This proposed regulation responds to U.S. obligations under the Montreal Protocol and the Clean Air Act. The Montreal Protocol itself recognizes that the regulation of ozone-depleting substances is necessary because private markets are very unlikely to preserve levels of stratospheric ozone sufficient to protect the public health. Individual users of CFC MDIs have no significant private incentive to switch to non-ozone-depleting products because, under current regulations, the environmental and health costs of ozone-depleting products are external to end users. Moreover, should MDI users voluntarily internalize these costs by switching to alternative products, they would not receive the benefits of their actions. Each user would bear all of the costs and virtually none of the benefits of such a switch, as the environmental and health benefits would tend to be distributed globally and occur decades in the future. Thus, the outcome of a private market would likely be continued use of CFC MDIs, even if the social value of reducing emissions were clearly much greater than the price premium for non-ozone-depleting therapies and the possible adverse affects on some patients due to the decreased use of MDIs.

The objective of this proposed rule is to respond to the Clean Air Act and the Montreal Protocol's requirements that the United States, and other nations, reduce atmospheric emissions of ODSs, specifically CFCs. CFCs and other ODSs deplete the stratospheric ozone that protects the Earth from ultraviolet solar radiation. We are proposing to end the essential-use designation for ODSs used in MDIs containing triamcinilone, metaproterenol, pibuterol, cromolyn sodium, nedocromil sodium, flunisolide, and albuterol and ipratropium in combination, because we tentatively conclude that adequate therapeutic alternatives are available. Removing this essential-use designation will comply with obligations under the Montreal Protocol and the Clean Air Act, thereby reducing emissions that deplete stratospheric ozone.

C. Background

1. CFCs and Stratospheric Ozone

During the 1970s, scientists became aware of a relationship between the level of stratospheric ozone and industrial use of CFCs. Ozone (O_3), which causes respiratory problems when it occurs in elevated concentrations near the ground, shields the Earth from potentially harmful solar radiation when it is in the stratosphere. Excessive exposure to solar radiation is associated with adverse health effects such as skin cancer and cataracts, as well as adverse environmental effects. Emissions of CFCs and other ODSs reduce stratospheric ozone concentrations through a catalytic reaction, thereby allowing more solar radiation to reach the Earth's surface. Because of this effect and its consequences, environmental scientists from the United States and other countries advocate ending all uses of these chemicals.

2. The Montreal Protocol

The international effort to craft a coordinated response to the global environmental problem of stratospheric ozone depletion culminated in the Montreal Protocol, an international agreement to regulate and reduce production of ODSs. The Montreal Protocol is described in section I.B.2 of this document. One hundred and eighty-eight countries have now ratified the Montreal Protocol, and the overall usage of CFCs has been dramatically reduced. In 1986, global consumption of CFCs totaled about 1.1 million tonnes annually, and by 2004, total annual production had been reduced to 70,000 tonnes (Ref. 10). This decline amounts to more than a 90-percent decrease in production and is a key measure of the success of the Montreal Protocol. Within the United States, use of ODSs, and CFCs in particular, has fallen sharply—production and importation of CFCs is less than 1 percent of 1989 production and importation (Ref. 10).

A relevant aspect of the Montreal Protocol is that production of CFCs in any year by any country is generally banned after the phase-out date unless the Parties to the Montreal Protocol agree to designate the use for which the CFCs are produced as "essential" and approve a quantity of new production for that use.

Each year, each Party nominates the amount of CFCs needed for each essential use and provides the reason why such use is essential. Agreement on both the essentiality and the amount of CFCs needed for each nominated use is reached at the annual Meeting of the Parties.

3. Benefits of the Montreal Protocol

EPA has generated a series of estimates of the environmental and public health benefits of the Montreal Protocol (Ref. 11). The benefits include reductions of hundreds of millions of nonfatal skin cancers, 6 million fewer fatalities due to skin cancer, and 27.5 million cataracts avoided between 1990 and 2165 if the Montreal Protocol were fully implemented. EPA estimates the value of these and related benefits to equal $4.3 trillion in present value when discounted at 2 percent over the period of 175 years. This amount is equivalent to about $6 trillion after adjusting for inflation between 1990 and 2004. This estimate includes all benefits of total global ODS emission reductions expected from the Montreal Protocol and is based on reductions from a baseline scenario in which ODS emissions would continue to grow for decades but for the Montreal Protocol.

4. Characteristics of COPD

The seven CFC MDI products that are the subject of this proposed rule, and COMBIVENT in particular, may be used to treat COPD. While there is some overlap between asthma patients and COPD patients, COPD encompasses a group of diseases characterized by relatively fixed airway obstruction associated with breathing-related symptoms (for example, chronic coughing, expectoration, and wheezing). COPD is generally associated with cigarette smoking and is extremely rare in persons younger than 25.

According to the National Health Interview Survey (NHIS), an estimated 10 million adults in the United Sates carried the diagnosis of COPD in 2000 (table 1 of Ref. 12). The underlying surveys depend on patient-reported diagnoses and many affected individuals have not been formally diagnosed. Data from the National Health and Nutrition Examination Survey (table 3 of Ref. 12), which was not based on patient self-reporting, suggests that as many as 24 million Americans may actually be affected by the illness. The proportion of the U.S. population with mild or moderate COPD has declined over the last quarter century, although the rate of COPD in females increased relative to males between 1980 and 2000. Among smokers, the most effective intervention in modifying the course of COPD is smoking cessation. Symptoms such as coughing, wheezing, and sputum production are treated with medication.

5. Characteristics of Asthma

These seven CFC MDIs, with the exception of COMBIVENT, may be used to treat asthma, a chronic respiratory disease characterized by episodes or attacks of bronchospasm on top of chronic airway inflammation. These attacks can vary from mild to life-threatening and involve shortness of breath, wheezing, coughing, or a combination of symptoms. Many factors, including allergens, exercise,

viral infections, and others, may trigger an asthma attack.

According to the NHIS, approximately 21 million patients in the United States reported they had asthma in 2004 (table 7 of Ref. 13). The prevalence of asthma decreases with age, with the prevalence being 84.7 per 1,000 children ages 0-17 (6.2 million children) compared to 63.9 per 1,000 among adults ages 18-44 (7.1 million), 69.4 per 1,000 among adults ages 45-64 (4.9 million), and 70.2 per 1,000 among adults age 65 and over (2.4 million) (table 7 of Ref. 13).

The NHIS reported that, during 2004, about 12 million patients reported experiencing an asthma attack in the course of the previous year (table 10 of Ref. 13). According to the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, in 2004 there were 14 million outpatient asthma visits to physician offices and hospital clinics and 1.8 million emergency room visits (table 19 of Ref. 13). According to the National Center for Health Statistics' National Hospital Discharge Survey, there were 497,000 hospital admissions for asthma in 2004 (table 17 of Ref. 13) and 4,099 mortalities in 2003 (table 1 of Ref. 13). The direct medical cost of asthma (hospital services, physician care, and medications) was estimated as $11.5 billion for 2004 (table 20 of Ref. 13).

While the prevalence of asthma has been increasing in recent years, the Centers for Disease Control and Prevention (CDC) reports that the patients reported experiencing an asthma attack in the course of the previous year has remained fairly constant since 1997 (Ref. 14). Non-Hispanic Blacks, children under 17 years old, and females have higher incidence rates than the general population and also have higher attack prevalence. The CDC notes that, although increases have occurred in the numbers and rates of physician office visits, hospital outpatient visits, and emergency room visits, these increases are accounted for by the increase in prevalence. CDC also reported declines in hospitalization for asthma and mortality. The declines may indicate early successes by asthma intervention programs that include access to medications.

6. Current U.S. Market for CFC MDIs

In the 2005 calendar year, we estimate that sales of these seven CFC MDIs provided roughly 440 million days of therapy, sufficient to treat roughly 1.2 million COPD and asthma patients for a full year. We focus on days of therapy as a common metric because these MDIs vary in the number of inhalations provided, and the number of inhalations that the average user would use each day. We calculate the number of days of therapy provided by each MDI as equal to the number of MDIs sold multiplied by the number of inhalations contained by the MDI, divided by the recommended, or usual, daily inhalations described in the MDI's physician labeling: [(Days of Therapy) = (MDIs) x (Inhalations/MDI) ÷ (Inhalations/day)]. We calculate MDI sales for each of the seven products using data from IMS Health's National Sales Perspective (Ref. 15).

We calculate the average price per day of therapy for a CFC MDI as the total revenue derived from sales of that product in 2005, as reported by IMS Health's National Sales Perspective, divided by the number of days of therapy for that product: [(Price/Day of Therapy) = (Total Sales) ÷ (Total Days of Therapy)]. We use the same method to calculate the average price per day of therapy for the nine non-ozone-depleting products we consider the most medically appropriate alternatives to these seven CFC MDIs. We then estimate the price premium (or savings) associated with alternatives as the difference between price per day of the CFC product and the price per day of its most appropriate alternatives.

TABLE 3.—SUMMARY OF CFC MDIS, NON-ODS ALTERNATIVES, AND EXPECTED PRICE CHANGES PER DAY OF THERAPY (REF. 15)

CFC MDI	Non-ODS Alternatives	Price Premium per Day of Therapy	
		Maximum	Minimum
AEROBID AEROBID–M	QVAR PULMICORT TURBOHALER FLOVENT HFA ASMANEX TWISTHALER	$1.63	$0.27
AZMACORT	QVAR PULMICORT TURBOHALER FLOVENT HFA ASMANEX TWISTHALER	$0.35	-$1.01
ALUPENT	PROAIR HFA PROVENTIL HFA VENTOLIN HFA XOPENEX HFA	$0.07	-$0.14
MAXAIR	PROAIR HFA PROVENTIL HFA VENTOLIN HFA XOPENEX HFA	-$0.23	-$0.53
INTAL	QVAR PULMICORT TURBOHALER FLOVENT HFA ASMANEX TWISTHALER	-$0.33	-$1.69

TABLE 3.—SUMMARY OF CFC MDIS, NON-ODS ALTERNATIVES, AND EXPECTED PRICE CHANGES PER DAY OF THERAPY (REF. 15)—Continued

CFC MDI	Non-ODS Alternatives	Price Premium per Day of Therapy	
		Maximum	Minimum
TILADE	QVAR PULMICORT TURBOHALER FLOVENT HFA ASMANEX TWISTHALER	-$2.34	-$5.12
COMBIVENT	ATROVENT HFA + one of the following: PROAIR HFA PROVENTIL HFA VENTOLIN HFA XOPENEX HFA	$1.22	$0.92

Source: IMS Health, IMS National Sales Perspective (TM), 2005, extracted March 2006.

Table 3 of this document shows each of the CFC MDIs that would no longer be marketed, the therapeutic alternatives that users of these CFC MDIs would be expected to purchase, and the range of differences in price per day of therapy. For example, an AZMACORT user would be expected to switch to QVAR, PULMICORT TURBOHALER, FLOVENT HFA, or ASMANEX TWISTHALER. The most expensive of these alternatives would cost roughly 35 cents more per day of therapy, and the least would cost roughly $1 less per day of therapy. COMBIVENT users would be expected to switch to both ATROVENT HFA and one of four albuterol HFA MDIs currently marketed. We make no attempt to forecast future price changes, but note that, during the past year, changes in prices of CFC MDIs did not differ systematically from the changes in prices of the proposed alternatives.

We estimate that, on average, users of these seven CFC MDIs will pay 20 percent to 50 percent more per day of therapy. If all users switched to the least expensive alternative therapy, the average price for users of these seven CFC MDIs, weighted by the number of days of therapy sold for each product in 2005, would increase roughly 20 percent; if all users switch to the most expensive alternative therapy, the average price per day of therapy would increase roughly 50 percent. These prices represent average ex-manufacturer prices across all distribution channels, and do not incorporate retail markups or off-invoice discounts (Ref. 15).

These estimated price increases may also be attributed to the withdrawal of albuterol CFC MDIs (including all generic albuterol MDIs) from the market (see 70 FR 17168). These estimated price increases are driven almost entirely by the large population of COMBIVENT users switching to both the ipratropium MDI (ATROVENT HFA) and albuterol HFA MDIs which, together, are more expensive. Through 2003, the price for a day of therapy with COMBIVENT was roughly equal to the sum of a day of therapy with ATROVENT (the ipratropium CFC MDI which has been withdrawn from the market) and a day of therapy with a generic albuterol CFC MDI. Since 2003, the price of a day of COMBIVENT therapy has risen to be roughly equal to the sum of a day of therapy with ATROVENT HFA and a day of therapy with a generic albuterol CFC MDI, likely in anticipation of the withdrawal of ATROVENT from the market. One might predict that, with the withdrawal of albuterol CFC MDIs (including all generic albuterol MDIs) from the market (see 70 FR 17168), the price of a day COMBIVENT therapy would increase to the sum of a day of therapy with ATROVENT HFA and an albuterol HFA MDI. To the extent that this prediction is accurate, the price increases described previously, and the estimated spending increases derived from it, result not from this proposed rule, but from the earlier rule removing albuterol CFC MDIs from the market. Indeed, without the estimated increase in spending estimated for the price per day of COMBIVENT therapy, the expected average price per day of therapy would not increase; the midpoint of the range of spending changes shown in table 1 of this document, -$70 million to $70 million, is zero.

We estimate that these seven CFC MDIs are responsible for roughly 310 to 365 tonnes of CFC emissions annually. The CFC content of the seven CFC MDIs ranges from about 6 to 20.5 grams per MDI. Multiplying the total 2005 sales of each of the CFC MDIs by its CFC content, and allowing for an additional 10 percent loss in the production process, yields a total of 310 tonnes of CFC emissions annually, our low estimate. The CFC MDI manufacturers have requested roughly 365 tonnes of CFCs for production of the seven CFC MDIs in 2007, our high estimate.[18]

D. Benefits and Costs of the Proposed Rule

We estimate the benefits and costs of a government action relative to a baseline scenario that in this case is a description of the production, use, and access to these seven CFC MDIs in the absence of this rule. In this section, we first describe such a baseline and then present our analysis of the benefits of the proposed rule. We also present an analysis of the most plausible regulatory alternative, given the Montreal Protocol. Next we turn to the costs of the rule and to an analysis of the effects on the Medicare and Medicaid programs.

1. Baseline Conditions

We developed baseline estimates of future conditions to assess the economic effects of prohibiting marketing of these seven CFC MDIs after December 31, 2009. It is standard practice to use, as a baseline, the state of the world without the rule in question, or where this implements a legislative requirement, the world without the statute. For this proposed rule, the Montreal Protocol makes the baseline assumption of indefinite availability infeasible, but we can nevertheless use it as a point of reference. In addition to the baseline of indefinite availability, we also assess alternative phase-out dates for the final disappearance of CFC products.

[18] CFC MDI manufacturers disclose the CFC content of their MDIs to EPA as part of the process of requesting essential-use allocations; however, the CFC content of any particular MDI is considered a trade secret and may not be disclosed without the manufacturer's consent.

Throughout this analysis, we assume that sufficient inventories of CFCs are available to meet demand for these seven CFC MDIs through December 31, 2009, and that there will be sufficient therapeutic alternatives to meet demand after December 31, 2009.

However, in the absence of this proposed rule, the parties to the Montreal Protocol are likely to consider restrictions on access to the CFCs needed to produce these seven CFC MDI products. These likely restrictions imply the costs detailed in section 3 of this document may very well accrue regardless of whether this proposed rule is made final. The cost-benefit analysis presented here would then reflect the withdrawal of the CFC-containing products from the market, rather than the specific effects of this rulemaking.

2. Benefits of the Proposed Rule

The benefits of the proposed rule include environmental and public health improvements from protecting stratospheric ozone by reducing CFC emissions. Benefits also include expectations of increased returns on investments in environmentally friendly technology, and continued international cooperation and goodwill to comply with the spirit of the Montreal Protocol, thereby potentially reducing future emissions of ODSs throughout the world.

Failure to promulgate the requirements proposed in this proposed rule would likely lead the parties to the Montreal Protocol to consider restricting access to the CFCs required to manufacture these seven CFC MDI products, leading to a risk of unexpected disruptions of supplies of drug products which are still being used by patients with asthma and COPD. These disruptions could potentially harm the public health of the United States by preventing a smooth transition from CFC MDIs to non-CFC products.

a. *Reduced CFC emissions.* Market withdrawal of these seven CFC MDIs will reduce emissions by approximately 310 to 365 tonnes of CFCs per year. Current CFC inventories are substantial. Nominations for new CFC production are generally approved by the Parties to the Montreal Protocol 2 years in advance. The proposed rule would ban marketing of these seven CFC MDIs after December 31, 2009. There is some uncertainty with respect to the amount of inventory that will be available in the future, but we anticipate that existing inventory will allow EPA, in consultation with FDA, to avoid allocating any CFCs for 2009. Therefore, we estimate the proposed regulation will reduce CFC use by 310 to 365 tonnes per year after the end of 2009, a benefit that will continue beyond the evaluation period.

In an evaluation of its program to administer the Clean Air Act, EPA has estimated that the benefits of controlling ODSs under the Montreal Protocol are the equivalent of $6 trillion in 2004 dollars. However, EPA's report provides no information on the total quantities of reduced emissions or the incremental value per tonne of reduced emissions. EPA derived its benefits estimates from a baseline that included continued increases in emissions in the absence of the Montreal Protocol. We have searched for authoritative scientific research that quantifies the marginal economic benefit of incremental emission reductions under the Montreal Protocol, but have found none conducted during the last 10 years. As a result, we are unable to quantify the environmental and human health benefits of reduced emissions from this regulation. Such benefits, in any event, were included in EPA's earlier estimate of benefits.

As a share of total global emissions, the reduction associated with the elimination of the seven CFC MDIs represents only a fraction of 1 percent. Current allocations of CFCs for the seven MDIs account for less than 0.1 percent of the total 1986 global production of CFCs (Ref. 10). Furthermore, current U.S. CFC emissions from MDIs represent a much smaller, but unknown, share of the total emissions reduction associated with EPA's estimate of $6 trillion in benefits because that estimate reflects future emissions growth that has not occurred.

Although the direct benefits of this regulation are small relative to the overall benefits of the Montreal Protocol, the reduced exposure to UV–B radiation that will result from these reduced emissions will help protect public health. The proposed rule will account for some small part of the benefits estimated by EPA. However, we are unable to assess or quantify specific reductions in future skin cancers and cataracts associated with these reduced emissions.

b. *Returns on investment in environmentally-friendly technology.* Establishing a phase-out date prior to the expiration of patents on HFA MDI technology not only rewards the developers of the HFA technology, but also serves as a signal to other potential developers of ozone-safe technologies. In particular, such a phase-out date would preserve expectations that the government protects incentives to research and develop ozone-safe technologies.

Newly developed technologies to avoid ODS emissions have resulted in more environmentally "friendly" air conditioners, refrigerants, solvents, and propellants, but only after significant private-sector investments. Several manufacturers have claimed development costs that total between $250 million and $400 million to develop HFA MDIs and new propellant-free devices for the global market (Ref. 16).

These investments have resulted in several innovative products in addition to HFA MDIs. For example, breath-activated delivery systems, dose counters, DPIs, and mini-nebulizers have also been successfully marketed.

c. *International cooperation.* The advantages of selecting a date that maintains international cooperation are substantial because the Montreal Protocol, like most international environmental treaties, relies primarily on a system of national self-enforcement, although it also includes a mechanism to address noncompliance. In addition, compliance with its directives is subject to differences in national implementation procedures. Economically less-developed nations, which have slower phase-out schedules than developed nations, have emphasized that progress in eliminating ODSs in developing nations is affected by observed progress by developed nations, such as the United States. If we propose to adopt a later phase-out date, other Parties could attempt to delay their own control measures.

3. Costs of the Proposed Rule

The proposed rule would increase spending for needed medicines used to treat asthma and COPD. The social costs of the proposed rule include the benefits lost through decreased use of medicines that may result from increased prices. We discuss the increased spending and then the social costs in turn. We are unable to quantify the economic costs of reducing the variety of marketed products from which consumers, and their doctors, can choose, but we note that these costs may be substantial. Because we lack data that would enable us to measure the effects of a decreased number of products from which to choose, in this analysis we only quantify the effects on spending.

In the absence of this regulation, we would expect 440 million days of therapy of these seven CFC MDIs to be sold annually. With this regulation, patients who would have used any of these seven CFC MDIs are expected to switch to one of several other products as described in table 3 of this document. Depending on whether asthma and

COPD patients use the most or least expensive of alternatives, once this proposed rule becomes final and goes into effect, private, third-party and public expenditures on inhaled medicines would increase by roughly $200 million to $400 million per year. These expenditure increases will be driven almost exclusively by COMBIVENT users changing to both ATROVENT HFA and one of four available albuterol HFA products. With most—perhaps all—of this increase coming from estimated increased spending on albuterol HFA MDIs, what happens to the prices of albuterol MDIs will largely determine the change in overall spending. As discussed in section VII.C.6, it is possible that, in response to earlier rulemaking removing generic CFC albuterol MDIs from the market, COMBIVENT prices would increase dramatically even in the absence of this proposed rule. If, even in the absence of this proposed rule, the cost of a day of COMBIVENT therapy were to increase to the sum of a day of albuterol HFA MDI and ATROVENT HFA therapy, this proposed rule would change private, third-party and public expenditures on inhaled medicines by roughly -$70 million to $70 million per year. This increased expenditure would continue until lower-priced non-ODS substitutes appear on the market. For many of these products it is difficult to predict when this might occur. With the exception of albuterol CFC MDIs, generic versions of prescription MDIs and DPIs for treatment of asthma and COPD have not been introduced, despite the expiration of the patents on many of the innovator products. However, the market for albuterol MDIs has a clear history of generic competition. A prior rulemaking (70 FR 17168) will remove albuterol CFC MDIs, including generic albuterol CFC MDIs, from the market by December 31, 2008. If these cheaper generic albuterol MDIs were somehow to remain on the market, the expected cost of switching from COMBIVENT to both ATROVENT HFA and an albuterol HFA MDI would be essentially eliminated. Because expenditure increases resulting from this proposed rule stem almost exclusively from the transition away from COMBIVENT, such increases would most likely be eliminated with the introduction of generic albuterol HFA MDIs to the market. Patents listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for albuterol HFA MDIs expire in 2010 and 2017, making those possible dates for generic entry. Of course, unforeseen introduction of alternative therapies could reduce these expected increases in expenditures.

These increased expenditures represent, to some extent, transfers from consumers and third-party payers, including State and Federal Governments, to pharmaceutical manufacturers, patent holders, and other residual claimants. However, to some extent, increased expenditures represent purchases of products that are more costly to manufacture and bring to market. We are unable to estimate the fraction of the increased expenditures that constitute societal costs.

We expect that price increases resulting from market withdrawal of less expensive CFC MDIs could reduce use of inhaled therapy by 0.7 to 11 million days annually, equivalent to roughly 2 to 30 thousand patient years of therapy. The impact of this reduction on health outcomes is too uncertain to quantify given available data, and we invite comments on this issue. We also invite comments on changes in copayments (resulting in higher out-of-pocket costs for insured consumers) and potential effect on therapy days.

A recent article found that "copayment increases led to increased use of emergency department visits and hospital days for the sentinel conditions of diabetes, asthma, and gastric acid disorder: predicted annual emergency department visits increased by 17 percent and hospital days by 10 percent when copayments doubled." (Ref. 17). However, the article proceeds to characterize these results as "not definitive." This finding suggests that increased prices for medicines may lead to some adverse public health effects among the users of these seven CFC MDIs. This evidence is insufficient to permit us to quantify any adverse public health effects. We use expected reductions in days of therapy purchased as a surrogate measure of the impact.

Our approach to estimating the effects of this proposed rule assumes that the primary effect of an elimination of these seven CFC MDIs from the market would be an increase in the average price of MDI and DPI therapy. Given the price increase expected, we have projected how the quantity of MDI and DPI therapy consumed may decline as a result of this rule. We assume that the reduction in the use of MDI and DPI therapy attributable to this rule can be calculated as the product of the sensitivity of use with respect to the price increase, the baseline use of these seven CFC MDIs among price-sensitive patients, and the price increase in percentage terms. We discuss these in turn.

We have no information about how consumers react to increases in the price of these seven forms of CFC MDIs in particular, much less to what amounts to a compulsory switch to different, more expensive drugs. Economists have, however, researched the response of consumers to higher insurance copayments for drugs in general. Goldman et al. estimate price elasticities in the range of -0.33 (for all antiasthmatic drugs) to -0.22 (for antiasthmatic drugs among patients with chronic asthma), implying that a 10 percent increase in insurance copayments apparently leads to a reduction in use of between 2.2 and 3.3 percent (Ref. 17), but the authors report that there is wide variance based on the availability of over-the-counter substitutes. For example, for drugs with no over-the-counter substitutes—a set that includes all seven of these CFC MDIs—the reported price elasticity was -0.15 (Ref. 17, p. 2348). Drugs included as antiasthmatics in this study include anticholinergics, anti-inflammatory asthma agents, leukotriene modulators, oral steroids, steroid inhalers, sympathomimetics, and xanthines. We have used price elasticities of between -0.15 and -0.33 to estimate the potential effect of price increases on demand.

To derive an estimate of the quantity of medicines not sold as a result of this rule, we need an estimate of the baseline use of these seven CFC MDIs by price-sensitive consumers. Based on IMS data, we estimate that asthma and COPD patients receive roughly 440 million days of therapy each year in the form of these seven CFC MDIs (Ref. 15). If users of these products are uninsured in proportion to the share of uninsured in the overall U.S. population (15.7 percent) (Ref. 18), then uninsured asthma and COPD patients receive roughly 69 million days of therapy [(440 million) x (15.7 percent)] in the form of these seven CFC MDIs, equivalent to roughly 188 thousand patient years. However, increases in the price of therapy will fall disproportionately on COMBIVENT users with COPD. In 1995, more than two-thirds of COPD patients were over the age of 65 (Ref. 19); these individuals would therefore be covered, at least in part, by Medicare. If the remaining, under-65 third of the COPD patients are uninsured in proportion to the uninsured share of the population, then only 23 million days of therapy [(440 million) x (15.7 percent) ÷ 3] are used by uninsured COPD patients each year. We are unable to estimate the extent to which Medicare's Part D benefit will cover the increased costs to those patients over age 65. Because most

of those over age 65 have insurance, 15.7% likely understates the true percentage of individuals under 65 without insurance. To the extent this is true, these estimates will understate the true impact of this proposed rule. Finally we estimate that users of these seven CFC MDIs face an average price increases of between 20 and 50 percent per day of therapy, depending on whether asthma and COPD patients switch to the most or least expensive of the proposed alternatives detailed in table 3 of this document. We calculate the low and high estimates as the average percentage price change of the least and most expensive alternatives to each of the seven CFC MDIs, weighted by the number of days of therapy of CFC MDIs sold in 2005. Excluding COMBIVENT, users of the other six CFC MDIs would face prices somewhere between 30 percent higher and 30 percent lower.

We combine different measures of price elasticities (-0.15 to -0.33), the size of the uninsured CFC MDI market (23 to 69 million days of therapy), and estimated price increases (20 percent to 50 percent) to estimate the impact of price increases on use. For example, assuming a price elasticity of -0.15 and 23 million days of therapy sold to the uninsured annually, a 20 percent price increase would reduce demand for inhaled therapy by the uninsured by roughly 700,000 days of therapy annually. By contrast, assuming a price elasticity of -0.33 and 69 million days of therapy sold to the uninsured annually, a 50 percent price increase would reduce uninsured demand by roughly 11 million days of therapy [(69 million days) x (-0.33 elasticity) x (50 percent price increase) = 11 million days of therapy]. We recognize that, because of varying measures of the size of the CFC MDI market for the uninsured, uncertainty about the magnitude of price increases, and consumer response, the true impact of the rule could fall outside this range.

When we exclude COMBIVENT from the calculation, we get a much smaller effect. The expected price change of 30 percent higher to 30 percent lower implies a -4.5 percent to 4.5 percent change in days of therapy if the price elasticity is -0.15 and a -10 percent to 10 percent change in days of therapy if the price elasticity is -0.33. The expected change in days of therapy would be zero, the midpoint of the range.

4. Effects on Medicaid and Medicare

Based on 2005 Medicaid utilization data, we estimate this proposed rule would reduce Federal Medicaid spending by $40 million to $60 million annually. Based on Medicare Current Beneficiary Survey estimates of the Medicare population and estimates of the price difference between CFC MDIs and HFA MDIs, we estimate Federal spending on Medicare beneficiaries, as well as by Medicare beneficiaries themselves, will increase from $190 million to $450 million annually. We recognize these estimates of increased Medicare spending suggest a broader range of potential spending increases than estimates of the overall impact of the proposed rule introduced in table 1 of this document. We discuss data limitations that cause this in section VII.D.3.b of this document.

a. *Medicaid*. Based on aggregated state Medicaid utilization data for 2005,[19] we estimate this proposed rule will reduce Medicaid reimbursements by roughly $40 million annually, because Medicaid reimbursement rates for CFC MDI products are, on average, higher than reimbursement rates for the proposed HFA MDI alternatives. First, we estimate total days of therapy reimbursed by Medicaid in 2005 for each of the seven CFC MDIs and calculate the average reimbursement per day of therapy. Second, we estimate the average reimbursement per day of therapy for each alternative therapy. If all Medicaid beneficiaries using CFC MDIs switch to the most expensive of available alternatives and reimbursement rates remain unchanged, total reimbursements would decrease by approximately $40 million; if they all switch to the least expensive of available alternatives, total reimbursements would decrease by roughly $60 million. Because these estimates are based on 2005 data, they do not take into account decreases in Medicaid reimbursements that will occur as those individuals eligible for both Medicaid and Medicare, and who were covered by Medicaid in 2005, receive their 2006 coverage through Medicare.

TABLE 4.—ESTIMATED IMPACT ON MEDICAID REIMBURSEMENTS BASED ON 2005 DATA

CFC MDIs	Total Days of Therapy	Total Expenditure	Reimbursement per Day of Therapy	Expenditure Premium		Expenditure Change	
				Maximum	Minimum	Maximum	Minimum
MAXAIR	7,248,876	$12,320,046	$1.70	-$0.36	-$0.36	-$2,581,185	-$2,581,185
AEROBID	1,513,499	$4,506,603	$2.98	$1.77	-$1.42	$2,679,966	-$2,149,445
AZMACORT	6,519,580	$19,408,252	$2.98	$1.77	-$1.42	$11,548,769	-$9,254,506
COMBIVENT	47,888,737	$138,485,222	$2.89	-$1.15	-$0.93	-$54,987,774	-$44,318,563
INTAL	550,246	$1,801,310	$3.27	$1.47	-$1.72	$811,434	-$944,343
TILADE	27,497	$151,039	$5.49	-$0.74	-$3.94	-$20,474	-$108,214
ALUPENT	0	$0	$0	$0	$0	$0	$0
Total						-$42,549,264	-$59,356,256

b. *Medicare*. Based on 2003 data from the Medicare Current Beneficiary Survey and price estimates introduced in table 3 of this document, we estimate Federal Medicare spending, together with private expenditure by Medicare beneficiaries, will increase roughly $190 million to $450 million. We estimate roughly 1.2 million beneficiaries used

[19] Our estimate uses State drug utilization data for outpatient drugs paid for by State Medicaid agencies as part of the Medicaid Drug Rebate Program. The data is available at: *http://www.cms.hhs.gov/MedicaidDrugRebateProgram/SDUD/list.asp#TopOfPage*.

these seven CFC MDIs in 2003. Excluding COMBIVENT, we estimate that this spending could increase by as much as $75 million or decrease by as much as $90 million.

TABLE 5.—INCREASED SPENDING ON MEDICARE BENEFICIARIES

	Number of Full-year Medicare users	Price Premium		Cost Per day		Cost Per Year	
		Max	Min	Max	Min	Max	Min
Aerobid	112,259	$1.63	$0.27	$183,219.05	$30,151.89	$66,874,952.64	$11,005,440.65
Azmacort	185,035	$0.35	-$1.01	$65,250.68	-$187,047.39	$23,816,497.79	-$68,272,296.85
Alupent	10,415	$0.07	-$0.14	$752.26	-$1,505.96	$274,574.93	-$549,676.92
Maxair	26,909	-$0.23	-$0.53	-$6,109.49	-$14,387.81	-$2,229,962.64	-$5,251,551.32
Intal	9,950	-$0.33	-$1.69	-$3,273.69	-$16,840.06	-$1,194,895.82	-$6,146,620.75
Tilade	15,108	-$2.34	-$3.70	-$35,296.79	-$55,896.24	-$12,883,326.74	-$20,402,126.86
Combivent	833,103	$1.22	$0.92	$1,019,601.26	$763,304.20	$372,154,460.78	$278,606,034.58
Total	1,192,779					$446,812,300.95	$188,989,202.52

The 1.2 million figure for the number of Medicare users presented previously includes people enrolled as of January 2002 who lived in a community setting during 2003 and who filled a prescription for at least one of these MDIs in 2003. It excludes an additional 102,000 users of these MDIs who were enrolled as of January 2002, lived in a facility for some or all of 2003, and filled at least one prescription. This 1.2 million figure also counts each individual who used more than one of these MDI products one time for each kind of MDI used. An individual using more than one of these products will therefore be counted as a full year user of each product. These estimates exclude individuals who enrolled after January 2002.

Based on the price per day of therapy of each of these products and of their alternatives, we estimate annual Federal spending on Medicare beneficiaries and private spending by Medicare beneficiaries will increase by $190 million to $450 million, depending on whether beneficiaries switch to the least, or most, expensive of available alternatives. This calculation assumes that full-year beneficiaries that use each of these products use a full 365 days of therapy per year, and therefore likely overestimates spending increases, particularly in the case where an individual switched from one to another MDI in the course of a year. These estimates also combine estimates of the Medicare population with price estimates (introduced in table 3 of this document) based on the entire market. Actual prices paid by Medicare beneficiaries are likely to differ systematically from the market as a whole, though it is not clear that the relevant price premiums do.

We are unable to estimate the extent to which these price increases will be paid by Medicare beneficiaries themselves or by the Federal Government. Whether individuals or the Federal Government will pay depends on beneficiaries' aggregate drug spending in a given year and the plan they choose. Data from the Medicare Part D benefit, which would give us better estimates of prices paid and the public and private shares of the burden, are not yet available.

E. Alternative Phase-out Dates

We consider the impacts of the alternative phase-out date of December 31, 2010, in table 6 of this document. A phase-out date set too far in the future would be incompatible with the timetable set by the Montreal Protocol. An earlier phase-out date would be impractical due to the time necessary to complete the regulatory process and to the risk of MDI shortages if the market has insufficient time to switch from CFC to HFA MDIs. This leaves a narrow window for consideration.

TABLE 6.—SUMMARY OF IMPACTS OF A DECEMBER 31, 2010 PHASE-OUT RELATIVE TO HFA PATENT EXPIRATION

Date of HFA Patent Expiration	Possible Decreases in Use of Asthma and COPD Therapy (million days of therapy)	Discount Rate	Increases in Expenditures on CFC-based MDIS, Present Value in 2006 (billions)
2010	0	3%	$0
		7%	$0
2017	4.9–77	3%	$1.2–$2.4
		7%	$0.9–$1.8

Table 6 of this document shows the effect of different expiration dates for HFA MDI patents on the impact of the proposed rule. Listed HFA MDI patents expire in 2010 and 2017. We assume albuterol HFA MDIs are not inherently more costly to produce than albuterol CFC MDIs. Once the relevant patents have expired, generic competition should drive the price of albuterol HFA MDIs down to the current level of generic albuterol CFC MDIs. If generic albuterol HFA MDIs become available in 2010, we estimate COMBIVENT users would not pay more to switch to both

albuterol HFA MDIs and ATROVENT HFA, due to lower prices of generic albuterol HFA MDIs. Therefore, current CFC MDI users would not, on average, pay more for MDIs as a result of this proposed rule. If current CFC MDI users would not pay more on average, they would not reduce their use of these products solely in response to higher prices.

If, however, relevant HFA MDI patents do not expire until 2017, this proposed rule will cause current CFC MDI users to pay more for their MDIs until then, and to reduce their use of these MDIs in response to higher prices.

F. Sensitivity Analyses

The estimated impacts of this proposed rule summarized in table 1 of this document incorporate a range of estimates about the price increases consumers and other payers will face, the size of the affected market and how consumers will respond to price increases. This range represents the full uncertainty range for the estimated effects of this proposed rule. The full range incorporates the ranges of estimates for the individual uncertain variables in the analysis.

In each section of the document, we show the ranges associated with each major uncertain variable. To estimate reduced use of inhaled medications, we estimate 23 million to 69 million days of therapy are used by uninsured individuals annually. We estimate that these consumers will face price increases in switching from CFC to HFA MDIs from 20 to 50 percent per day of therapy, depending on whether they switch to the most expensive or least expensive of the available alternatives. We use price elasticities ranging from -0.15 to -0.33 to estimate how consumers will reduce their MDI use in response to price increases.

Similarly, estimates of the impact of the proposed rule on public and private spending depend on the overall size of the CFC MDI market and how much prices increase. We estimate the consumers purchase roughly 440 million days of therapy in the form of CFC MDIs annually, and that prices will increase 20 to 50 percent depending on whether they switch to the most expensive or least expensive of available alternatives. If we exclude COMBIVENT from the calculation, the expected price effects range from a 30 percent increase to a 30 percent decrease, depending on whether they switch to the most expensive or least expensive of available alternatives.

G. Conclusion

Limits in available data prevent us from quantifying the costs and benefits of the proposed rule and weighing them in comparable terms. The benefits of international cooperation to reduce ozone emissions are potentially enormous but difficult to attribute to any of the small steps, such as this proposed rule, that make such cooperation effective. As discussed previously in detail, the benefits of the proposed rule include environmental and public health improvements from protecting stratospheric ozone by reducing CFC emissions. Benefits also include expectations of increased returns on investments in environmentally friendly technology, reduced risk of unexpected disruption of supply of CFC MDIs, and continued international cooperation to comply with the spirit of the Montreal Protocol, thereby potentially reducing future emissions of ODSs throughout the world.

This proposed rule could potentially cost public and private consumers of CFC MDIs hundreds of millions of dollars annually, but it is difficult to link these costs to adverse public health outcomes.

VIII. Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. FDA requests comment on this issue. This rule may have a significant impact on firms that manufacture the seven CFC MDIs, including firms that distribute CFC MDIs that are manufactured under contract for them. According to the U.S. Small Business Administration, "pharmaceutical preparation manufacturers" (North American Industrial Classification System (NAICS) code 325412) are considered small entities if they employ fewer than 750 people, and "drug and druggists' sundries merchant wholesalers" (NAICS code 424210) are small entities if they employ fewer than 100 people. None of the firms that manufacture the seven CFC MDIs, including firms that distribute CFC MDIs that are manufactured under contract for them, employ fewer than 750 people and therefore none are small entities.

We do not expect that premiums paid by small businesses or other small entities for employees' prescription drug benefit plans will increase significantly as a result of this rulemaking. Accordingly, the agency does not believe that this proposed rule would have a significant economic impact on a substantial number of small entities.

IX. The Paperwork Reduction Act of 1995

This proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. While this rule may result in States increasing spending for albuterol MDIs in programs such as Medicaid, the increased spending is not a substantial direct compliance cost, as the term is used in Executive Order 13132. Accordingly, we have concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XI. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this proposal. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

An upcoming public meeting on the essential-use status of MDIs containing flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil will provide an additional opportunity for public comment. We will provide details on the meeting in a notice published in the **Federal Register** in the near future.

XII. References

The following references have been placed on display in the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. FDA has verified the

Web site addresses, but we are not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.

1. National Heart, Lung, and Blood Institute, *Expert Panel Report: Update on Selected Topics 2002: Guidelines for the Diagnosis and Management of Asthma*, NIH publication No. 02–5074, June 2003.

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9. Anthonisen, N. R. et al., "Hospitalizations and Mortality in the Lung Health Study" *American Journal of Respiratory and Critical Care Medicine*, 166:333–339, 2002.

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11. U.S. Environmental Protection Agency, "The Benefits and Costs of the Clean Air Act: 1990–2010" (*http://www.epa.gov/air/sect812/copy99.html*) (November 1999).

12. Mannino, D. M. et al., "Chronic Obstructive Pulmonary Disease Surveillance—United States, 1971–2000," *Morbidity and Mortality Weekly Report*, 51(SS06):1–16, August 2, 2002.

13. American Lung Association, "Trends in Asthma Morbidity and Mortality," Epidemiology & Statistics Unit, Research and Program Services, July 2006.

14. Mannino, D. M. et al., "Surveillance for Asthma—United States, 1980–1999," *Morbidity and Mortality Weekly Report*, 51(SS01):1–13, March 29, 2002.

15. Analysis completed by FDA based on information provided by IMS Health, IMS National Sales Perspective (TM), 2005, extracted March 2006. These data are available for purchase from IMS Health. Please send all inquiries to: IMS Health, Attn: Brian Palumbo, Account Manager, 660 West Germantown Pike, Plymouth Meeting, PA 19462.

16. Rozek, R. P., and E. R. Bishko, "Economics Issues Raised in the FDA's Proposed Rule on Removing the Essential-Use Designation for Albuterol MDIs," National Economic Research Associates, August 13, 2004 (FDA Docket No. 2003P–0029/C25).

17. Goldman, D. P. et al., "Pharmacy Benefits and the Use of Drugs by the Chronically Ill," *JAMA: The Journal of the American Medical Association*, 291:2344–2350, May 19, 2004.

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List of Subjects in 21 CFR Part 2

Administrative practice and procedure, Cosmetics, Drugs, Foods.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Clean Air Act and under authority delegated to the Commissioner of Food and Drugs, after consultation with the Administrator of the Environmental Protection Agency, it is proposed that 21 CFR part 2 be amended as follows:

PART 2—GENERAL ADMINISTRATIVE RULINGS AND DECISIONS

1. The authority citation for 21 CFR part 2 continues to read as follows:

Authority: 15 U.S.C. 402, 409; 21 U.S.C. 321, 331, 335, 342, 343, 346a, 348, 351, 352, 355, 360b, 361, 362, 371, 372, 374; 42 U.S.C. 7671 *et seq.*

§ 2.125 [Amended]

2. Section 2.125 is amended by removing and reserving paragraphs (e)(1)(iii), (e)(1)(v), (e)(2)(iii), (e)(2)(iv), (e)(4)(iv), (e)(4)(vii), and (e)(4)(viii).

Dated: June 4, 2007.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 07–2883 Filed 6–6–07; 1:35 pm]

BILLING CODE 4160–01–S

DEPARTMENT OF THE INTERIOR

Office of Surface Mining Reclamation and Enforcement

30 CFR Part 943

[Docket No. TX–057–FOR]

Texas Regulatory Program and Abandoned Mine Land Reclamation Plan

AGENCY: Office of Surface Mining Reclamation and Enforcement, Interior.

ACTION: Proposed rule; reopening and extension of public comment period on proposed amendment.

SUMMARY: We, the Office of Surface Mining Reclamation and Enforcement (OSM), are announcing receipt of revisions to a previously proposed amendment to the Texas regulatory program (Texas program) and the Texas abandoned mine land plan (Texas plan) under the Surface Mining Control and Reclamation Act of 1977 (SMCRA or the Act). The revisions concern "determination of amount of penalty" in the Texas regulations and "administrative penalties for violation of permit conditions" in the Texas statute. Texas intends to improve operational efficiency.

This document gives the times and locations that the Texas program and Texas plan and proposed amendments to that program and plan are available for your inspection and the comment period during which you may submit written comments on the revisions to the amendment.

DATES: We will accept written comments until 4 p.m., c.t., June 26, 2007.

ADDRESSES: You may submit comments, identified by Docket No. TX–057–FOR, by any of the following methods:

- *E-mail: athomas@osmre.gov.* Include "Docket No. TX–057–FOR" in the subject line of the message.
- *Mail/Hand Delivery:* A. Dwight Thomas, Acting Director, Tulsa Field Office, Office of Surface Mining Reclamation and Enforcement, 1645 South 101st East Avenue, Suite 145, Tulsa, Oklahoma 74128.
- *Fax:* (918) 581–6419.
- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments.

Instructions: All submissions received must include the agency name and docket number for this rulemaking. For detailed instructions on submitting comments and additional information on the rulemaking process, see the "Public Comment Procedures" heading