The Rule

This action amends Title 14 Code of Federal Regulations (14 CFR) part 71 by adding additional Class E airspace 700 and 1,200 feet above the surface for Point Mugu NAS, Oxnard, CA, to accommodate the vectoring of aircraft flying en route, in and out of the Los Angeles ARTCC's airspace area. This action enhances the safety and management of aircraft operations in Los Angeles ARTCC's airspace. This action also changes the name from Point Mugu NAWS, to Point Mugu NAS, and updates the geographic coordinates of Point Mugu NAS, Oxnard, CA.

The FAA has determined this regulation only involves an established body of technical regulations for which frequent and routine amendments are necessary to keep them operationally current. Therefore, this regulation: (1) Is not a "significant regulatory action" under Executive Order 12866; (2) is not a "significant rule" under DOT Regulatory Policies and Procedures (44 FR 11034; February 26, 1979); and (3) does not warrant preparation of a regulatory evaluation as the anticipated impact is so minimal. Since this is a routine matter that will only affect air traffic procedures and air navigation, it is certified this rule, when promulgated, will not have a significant economic impact on a substantial number of small entities under the criteria of the Regulatory Flexibility Act. The FAA's authority to issue rules regarding aviation safety is found in Title 49 of the U.S. Code. Subtitle 1, Section 106 discusses the authority of the FAA Administrator. Subtitle VII, Aviation Programs, describes in more detail the scope of the agency's authority. This rulemaking is promulgated under the authority described in Subtitle VII, Part A, Subpart I, Section 40103. Under that section, the FAA is charged with prescribing regulations to assign the use of airspace necessary to ensure the safety of aircraft and the efficient use of airspace. This regulation is within the scope of that authority as it establishes additional controlled airspace at Point Mugu NAS, Oxnard, CA.

List of Subjects in 14 CFR Part 71

Airspace, Incorporation by reference, Navigation (air).

Adoption of the Amendment

■ In consideration of the foregoing, the Federal Aviation Administration amends 14 CFR part 71 as follows:

PART 71—DESIGNATION OF CLASS A, B, C, D AND E AIRSPACE AREAS; AIR TRAFFIC SERVICE ROUTES; AND REPORTING POINTS

■ 1. The authority citation for 14 CFR part 71 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40103, 40113, 40120; E. O. 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389.

§ 71.1 [Amended]

■ 2. The incorporation by reference in 14 CFR 71.1 of the Federal Aviation Administration Order 7400.9T, Airspace Designations and Reporting Points, signed August 27, 2009, and effective September 15, 2009, is amended as follows:

Paragraph 6005 Class E airspace areas extending upward from 700 feet or more above the surface of the earth.

* * * * *

AWP CA E5 Oxnard, CA

Point Mugu NAS (Naval Base Ventura Co), CA
(Lat. 34°07′09″N., long. 119°07′10″W.)

That airspace extending upward from 700 feet above the surface beginning at lat. 34°01′56″N., long. 119°01′44″W.; to lat. 34°02′30″N., long. 118°53′33″W.; to lat. 34°19′30″N., long. 118°53′03″W.; to lat. 34°19′30″N., long. 119°29′53″W.; thence 3 miles west of and parallel to the shoreline to lat. 34°14′50″N., long. 119°22′03″W.; to lat. 34°14′45″N., long. 119°23′33″W.; to lat. 34°06′55″N., long. 119°22′33″W.; to lat. 34°07′41″N., long. 119°15′40″W., thence via a 7-mile radius of Point Mugu NAS to the point of beginning. That airspace extending upward from 1,200 feet above the surface bounded by a line beginning at lat. 34°30′00″N., long. 118°50′03″W.; to lat. 34°00′00″N., long. 118°50′03″W.; to lat. 34°00′00″N., long. 119°05′00″W.; to lat. 33°52′03″N., long. 119°06′59″W.; to lat. 33°28′30″N., long. 119°07′03″W.; to lat. 33°28′30″N., long. 118°47′00″W.; to lat. 33°19′30″N., long. 118°37′03″W.; to lat. 32°53′00″N., long. 119°13′00″W.; to lat. 33°05′00″N., long. 119°45′07″W.; to lat. 33°53′00″N., long. 120°38′00″W.; lat. 33°54′00″N., long. 120°00′03″W.; to lat. 34°20′00″N., long. 120°00′04″W.; to lat. 34°20′00″N., long. 119°30′03″W.; to lat. 34°30′00″N., long. 119°30′03″W., thence to the point of beginning, excluding that airspace more than 12 nautical miles from the shoreline. That airspace extending upward from 5,000 feet MSL bounded by a line beginning at lat. 34°08′00″N., long. 120°00′03″W.; to lat. 33°54′00″N., long. 120°00′03″W.; to lat. 33°53′00″N., long. 120°38′00″W.; to lat. 33°55′00″N., long. 120°40′00″W.; lat. 34°00′00″N., long. 120°43′00″W.; to lat. 34°06′15″N., long. 120°30′04″ W.; to lat. 34°08′00″N., long. 120°26′04″W., thence to the point of beginning, excluding that airspace more than 12 nautical miles from the shoreline.

Issued in Seattle, Washington, on March 31, 2010.

Robert E. Henry,

Acting Manager, Operations Support Group, Western Service Center .

[FR Doc. 2010–8407 Filed 4–13–10; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 2

[Docket No. FDA–2006–N–0304] (formerly Docket No. 2006N–0262)

RIN 0910–AF92

Use of Ozone-Depleting Substances; Removal of Essential-Use Designation (Flunisolide, etc.)

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA), after consultation with the Environmental Protection Agency (EPA), is amending FDA's regulation on the use of ozone-depleting substances (ODSs) in self-pressurized containers to remove the essential-use designations for flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil used in oral pressurized metered-dose inhalers (MDIs). The Clean Air Act requires FDA, in consultation with the EPA, to determine whether an FDA-regulated product that releases an ODS is an essential use of the ODS. FDA has concluded that there are no substantial technical barriers to formulating flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil as products that do not release ODSs, and therefore they will no longer be essential uses of ODSs as of the effective dates of this rule. MDIs for these active moieties containing an ODS may not be marketed after the relevant effective date.

DATES: Removal of § 2.125(e)(2)(iii) and § 2.125(e)(4)(vii) is effective June 14, 2010. Removal of § 2.125(e)(1)(v) and § 2.125(e)(4)(iv) is effective December 31, 2010. Removal of § 2.125(e)(1)(iii) is effective June 30, 2011. Removal of § 2.125(e)(2)(iv) and § 2.125(e)(4)(viii) is effective December 31, 2013.

ADDRESSES: For access to the docket to read background documents or comments received, go to *http://*

www.regulations.gov and insert the docket number, 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: Martha Nguyen, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6352, Silver Spring, MD 20993–0002, 301–796–3601.

SUPPLEMENTARY INFORMATION:

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I. Introduction and Highlights of the Rule

With this rule, FDA removes the last remaining essential-use designations for chlorofluorocarbons (CFCs) used in MDIs for the treatment of asthma and chronic obstructive pulmonary disease (COPD). This regulatory action is the culmination of many years of efforts to protect the environment by limiting the production and use of ODSs. It began with a rulemaking in 1978 and involved an international treaty, legislation, and rulemakings as described in the background section. After the effective date of this rule, there will remain only three essential uses of ODSs: (1) Anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application; (2) metered-dose atropine sulfate aerosol human drugs administered by oral inhalation; and (3) sterile aerosol talc administered intrapleurally by thoracoscopy for human use (21 CFR 2.125(e)(4)(iii), (vi), and (ix)).

On June 11, 2007, FDA published a proposed rule in the **Federal Register** (72 FR 32030) (the proposed rule), proposing to remove the essential-use designations for oral pressurized MDIs containing flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil. These MDIs containing chlorofluorocarbons (CFCs) or other ODSs may not be marketed without an essential-use designation. There are three criteria that must all be met for each of these MDIs to retain their essential-use designation. For each of these MDIs to retain its essential-use designation, we must find that:

1. Substantial technical barriers exist to formulating the product without ODSs;

2. The product will provide an unavailable important public health benefit; and

3. 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.

With respect to MDIs containing flunisolide, triamcinolone, metaproterenol, pirbuterol, cromolyn, and nedocromil, we tentatively found in the proposed rule that no substantial technical barriers exist to formulating them without ODSs, they do not provide an otherwise unavailable important public health benefit because of the availability of therapeutic alternatives, and the release of ODSs into the atmosphere from these MDIs is cumulatively significant and is not warranted because they do not provide an otherwise unavailable important public health benefit. In addition, we had proposed an effective date for this rule of December 31, 2009.

After considering the information received at the August 2, 2007, public meeting and written comments submitted in response to the proposal, FDA has concluded that there are no

substantial technical barriers to formulating flunisolide, triamcinolone, metaproterenol, pirbuterol, cromolyn, and nedocromil as products that do not release ODSs, and therefore flunisolide, triamcinolone, metaproterenol, pirbuterol, cromolyn, and nedocromil no longer meet the criteria to be an essential use of ODSs. We have also determined that the appropriate effective date for the removal of the essential-use designation for metaproterenol and nedocromil MDIs is June 14, 2010, the appropriate effective date for the removal of the essential-use designation for triamcinolone and cromolyn MDIs is December 31, 2010, and the appropriate effective date for the removal of the essential-use designation for flunisolide is June 30, 2011. In addition, we have determined that the appropriate effective date for pirbuterol is December 31, 2013, because this date provides over 3 years for Maxair Autohaler (pirbuterol acetate inhalation aerosol) users who are accustomed to a breath-actuated device to consult with their health care providers, evaluate options, and transition to appropriate therapeutic alternatives. We will discuss our determinations on the criteria and the effective date in section IV of this document, "Comments on the 2007 Proposed Rule."

With respect to MDIs containing albuterol and ipratropium in combination, we were unable to determine initially whether substantial technical barriers exist to formulating them without ODSs. In the proposed rule, we tentatively found that these MDIs do not provide an otherwise unavailable important public health benefit and the release of ODSs into the atmosphere from these MDIs is cumulatively significant and is not warranted because they do not provide an otherwise unavailable important public health benefit. Again, we proposed an effective date for this rule of December 31, 2009.

After considering the information received at the August 2, 2007, public meeting and written comments submitted in response to the proposal, FDA has concluded that there are no substantial technical barriers to formulating albuterol and ipratropium bromide in combination as a product that does not release ODSs, and therefore albuterol and ipratropium bromide in combination no longer meets the criteria to be an essential use of ODSs. We have determined that the appropriate effective date for the removal of the essential-use designation for albuterol and ipratropium bromide in combination is December 31, 2013, because this date provides over 3 years to disseminate information about the transition to Combivent Inhalation Aerosol users who may have multiple health conditions that may make the transition to therapeutic alternatives more difficult. The transition period allows these individuals time to consult with their health care providers, evaluate options, and transition to appropriate therapeutic alternatives. We will discuss our determinations on the criteria and the effective date in section IV of this document "Comments on the 2007 Proposed Rule."

II. 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 stratospheric 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), 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 exempt from the ban. The second listed essential use was for "[m]etered-dose steroid bronchodilator human drugs for oral inhalation." This use describes flunisolide MDIs and triamcinolone MDIs. The third listed essential use was for "[m]etered-dose adrenergic bronchodilator human drugs for oral inhalation." This use describes metaproterenol MDIs and pirbuterol MDIs.[1]

The 1978 rule provided criteria for adding new essential uses, and several uses were added to the list using these criteria, 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.B.5 of this document.

2. The Montreal Protocol

On April 21, 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)),

[1] 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 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). The essential-use designation for "[m]etered-dose ipratropium bromide and albuterol sulfate, in combination, administered by oral inhalation" was added on April 9, 1996 (61 FR 15700).

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 ODSs 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 196 Parties to this treaty.[3] When it joined the treaty, the United States committed to reducing production and consumption of certain CFCs to 50 percent of 1986 levels by 1998–99 (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)). Under the treaty's rules of procedure, an essential-use decision requires a two-thirds majority vote by the Parties to the treaty, although, to date, all such decisions have been made by consensus. 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 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 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).

Each request and any subsequent exemption is for only 1 year's duration (Decision V/18). 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).

Phasing out the use of CFCs in MDIs for the treatment of asthma and COPD has been an issue of particular interest to the Parties to the Montreal Protocol. 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 developed country Parties that submitted essential-use nominations for CFC-propelled MDIs 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. 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 counties 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 nonessential (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

[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*.

[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.

[5] Our obligation under XV/5 was met by our final rule eliminating the essential-use status of albuterol (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://ozone.unep.org/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 the following:

- Arranging for and servicing the Conference of the Parties, Meetings of the Parties, their Committees, the Bureaux, 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.

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 requires 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 § 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 FDA regulations have interpreted the term "medical device" to refer to any product that contains an active moiety that appears on the essential-use list found in § 2.125.

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 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.

III. Criteria

The 2002 final rule revised 21 CFR § 2.125(g)(2) to establish a standard for removing an essential-use designation after January 1, 2005, for any drug for which there is no acceptable non-ODS alternative with the same active moiety. As explained in the proposed rule, we have reviewed the essential-use designation for flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil under that authority. The process for removing the essential-use designation under § 2.125(g)(2) includes 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 the use no longer meets the criteria specified in revised § 2.125(f) for adding a new essential use (21 CFR § 2.125(g)(2)). The criteria in § 2.125(f) 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."

The three criteria in § 2.25(f)(1) are linked by the word "and." Because the three criteria are linked by "and" (as

[7] In conformance with 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).

[8] Section 314.108(a) (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, pirbuterol, as opposed to the active ingredient, which, using the same example, would be pirbuterol acetate. 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 Maxair. In describing material from treatises, journals, and other non-FDA approved publications, we will generally follow the usage in the original publication.

opposed to "or"), failure to meet any single criterion results in a determination that the use is not essential.

As noted in the 2002 proposed rule, we intend the term "technical barriers" to refer to difficulties encountered in chemistry and manufacturing. To demonstrate that substantial technical barriers exist, it would have to be established that all available alternative technologies have been evaluated and that each alternative is unusable (67 FR 48370 at 48373). In applying the "technical barriers" criterion, we look at the results of reformulation efforts for similar products, as well as statements made about the manufacturer's particular efforts to reformulate its product or products.

In discussing what is "an unavailable important public health benefit," we have 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." One key point to note here is that the 2002 final rule (67 FR 48370) 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." A petitioner seeking to add an essential-use designation should show that the use of an ODS-containing MDI 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 (64 FR 47719 at 47722).

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

The third criterion in § 2.125(f)(1) provides that the essential use must be eliminated unless we find either: (a) The use of the product does not release cumulatively significant amounts of ODSs into the atmosphere; or (b) 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.

Based on an extensive record dating back to the 1970s, we reached a tentative conclusion in the proposed rule that the release of ODSs into the atmosphere from the MDIs that are the subject of this rulemaking is cumulatively significant. We noted that the use of CFCs in MDIs for the treatment of asthma and COPD is the only legal use in the United States of newly produced or imported CFCs; all other uses of newly produced or imported CFCs are prohibited by the Montreal Protocol. We noted 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 that take place over a period of time (40 CFR 1508.7).

The criteria in § 2.125(g)(2) (which refers to those found in § 2.125(f)(1)) that we are using in this rulemaking 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 marketed non-ODS product containing the active moiety listed as an essential use, while § 2.125(g)(3) and (g)(4) apply to situations where there is at least one marketed non-ODS product with the listed active moiety. Section 2.125(g)(2) permits FDA to remove an essential use even if a current essential-use active moiety is not reformulated, provided that sufficient alternative products exist to meet the needs of patients, because the essential use would no longer provide an otherwise unavailable important health benefit. As we explained in the proposed rule, the analysis we use here is different from the analysis we used under § 2.125(g)(4) in the rulemaking to remove the essential use for albuterol (70 FR 17168, April 4, 2005). However, the basic concern of protecting the public health underlies all of the criteria. 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).

Section 2.125(g)(2) requires that we consult an advisory committee and hold an open public meeting before we remove an essential-use designation when there is no non-ODS product with the same active moiety. Prior to publishing the proposed rule, on July 14, 2005, we consulted with FDA's Pulmonary and Allergy Drugs Advisory Committee (PADAC) on the essential-use status of MDIs containing flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil (PADAC meeting) (see 70 FR 24605, May 10, 2005).[9]

On August 2, 2007, following publication of the proposed rule, we held the required open public meeting to discuss the issues involved in removing the essential-use designations for flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil MDIs (see the **Federal Register** of July 9, 2007 (72 FR 37137)). Input from the open public meeting is considered and discussed in section IV of this document together with the written comments that were submitted in response to the proposed rule.

IV. Comments on the 2007 Proposed Rule

We received over 4,000 comments in response to the proposed rule. They were submitted by consumers, health care providers, patient advocacy groups, professional groups, manufacturers, a Congressional caucus, and industry organizations. The speakers who participated in the open public meeting on August 2, 2007, also submitted written comments. In the discussion that follows, we address the oral presentations and written comments submitted at or following the open public meeting, and the written and electronic comments submitted to the docket in response to the 2007 proposed rule.

To make it easier to identify comments and our responses, the word "Comment," in parentheses, appears before the comment's description, and the word "Response," in parentheses, appears before our response. We have numbered each comment to help distinguish between different comments. Similar comments are grouped together under the same comment number. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which it was received.

In reviewing these comments we are particularly focused on our proposed findings relating to the criteria in § 2.125(f) of our regulations. As discussed above, we must remove the

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

essential-use designation for a CFC-containing drug product unless we find that all of the following are met: (1) Substantial technical barriers exist to formulating the product without ODSs; (2) the product provides an unavailable important public health benefit; and (3) use of the product does not release cumulatively significant amounts of ODSs into the atmosphere or, if the release is significant, it is warranted in view of the unavailable important public health benefit. As discussed in the proposed rule, the failure to meet any one of these criteria results in our determination that the use is not essential.

A. Flunisolide, Triamcinolone, Metaproterenol

We are removing the essential-use designations for MDIs containing flunisolide (Aerobid Inhaler System) and triamcinolone (Azmacort Inhalation Aerosol). Aerobid and Azmacort are orally inhaled corticosteroids. Azmacort is the only currently marketed drug product that provides orally inhaled triamcinolone. Both Aerobid and Aerospan Inhalation Aerosol provide orally inhaled flunisolide, but Aerobid is the only currently marketed flunisolide drug product that contains ODSs. 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 6 years of age and older, 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 Inhalation Aerosol, a new drug application (NDA) for a flunisolide HFA MDI, was approved January 27, 2006 (NDA 21–247), but has not yet been introduced onto the market.

We are also removing the essential-use designation for MDIs containing metaproterenol (Alupent Inhalation Aerosol). Metaproterenol is a short-acting $beta_2$–adrenergic agonist used in the treatment of bronchospasm associated with asthma and COPD. It acts as a bronchodilator. 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 Inhalation Aerosol which contains CFCs. Alupent Inhalation Aerosol is a prescription drug. Alupent Inhalation Aerosol's use was considered essential under the 1978 rule, which stated that "[m]etered-dose adrenergic bronchodilator human drugs for oral inhalation" were essential. Metaproterenol was designated as essential as an active moiety in the 2002 rule. Alupent Inhalation Aerosol was approved on July 31, 1973. Boehringer Ingelheim Pharmaceuticals, Inc., the manufacturer of Alupent Inhalation Aerosols, has informed us that they discontinued U.S. distribution of Alupent Inhalation Aerosols as of November 14, 2008.

In the proposed rule, we tentatively concluded that there are no technical barriers to formulating flunisolide, triamcinolone, and metaproterenol MDIs without ODSs (72 FR 32030 at 32036–37). We did not receive any substantive comments disagreeing with our tentative conclusion. Therefore, we conclude that that there are no technical barriers to formulating flunisolide, triamcinolone, and metaproterenol MDIs without ODSs. As stated earlier, flunisolide has been reformulated in an HFA MDI, but the product is not yet marketed. We also did not receive any substantive comments on the second and third criteria in § 2.125(f)(1).[10] As explained in section III of this document, because the three criteria are linked by the word "and," failure to meet any single criterion results in a determination that the use is not essential. Accordingly, because we have found in this rule that there are no substantial barriers to reformulating these products, we are required to find that the use of the products is not essential, and we do not need to reach a decision on the second or third criteria in § 2.125(f)(1).

[10] Abbott Laboratories, the NDA holder for Azmacort Inhalation Aerosol, submitted and later withdrew its comment. Therefore, we do not address the comment submitted by Abbot in response to the proposed rule.

B. 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 treatment of symptoms associated with mastocytosis. Only MDI formulations are affected by this rulemaking.

The only cromolyn MDI (Intal Inhaler) 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 Inhaler) was approved for marketing on 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). Intal Inhaler and Tilade Inhaler are indicated for the management of asthma in patients 5 years and older and 6 years and older, respectively. Both are prescription drugs. Neither drug is indicated for the relief of acute bronchospasm. On November 21, 2008, King Pharmaceuticals, Inc., the manufacturer of Tilade Inhaler, informed us that they had discontinued manufacturing of Tilade Inhaler in July 2008.

In the proposed rule, we tentatively concluded that there are no technical barriers to formulating cromolyn and nedocromil MDIs without ODSs (72 FR 32030 at 32038). We did not receive any substantive comments disagreeing with our tentative conclusion. Therefore, we conclude that there are no technical barriers to formulating cromolyn and nedocromil MDIs without ODSs. As explained in section III of this document, because the three criteria in § 2.125(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, because we have found in this rule that there are no substantial barriers to reformulating these products, we are required to find that the use of the products is not essential, and we do not need to reach a decision on the second or third criteria in § 2.125(f)(1).

However, we received several comments addressing the second and third criteria with respect to cromolyn and nedocromil, and we respond to these comments below.

(Comment 1) We received one comment arguing that there are no acceptable treatment alternatives for cromolyn and nedocromil.

(Response) In the proposed rule, we identified several orally inhaled corticosteroids that do not contain CFCs as therapeutic alternatives to Intal Inhalers and Tilade Inhalers, including beclomethasone dipropionate inhalers, budesonide inhalers, fluticasone propionate inhalers, and mometasone furoate inhalers (72 FR 32030 at 32037). We believe that most patients using Intal Inhalers and Tilade Inhalers as a controller medication should be adequately served by at least one of these currently marketed formulations. The comment did not provide explanation as to why the proposed alternatives are insufficient, so it is difficult to address this comment more fully. In addition to the active moieties described in the proposed rule, oral montelukast may be an appropriate therapeutic alternative. Also, cromolyn is available in a solution for use in nebulizers. For patients who use Intal Inhalers to treat exercise-induced bronchospasm, inhaled $beta_2$–agonists such as albuterol, salmeterol, and formoterol are considered suitable therapeutic alternates.

(Comment 2) One comment notes that Intal inhalers are safe for pregnant women and protect against pet allergen exposure.

(Response) Current FDA regulations on labeling for use during pregnancy require the classification of each drug product under one of five pregnancy categories (A, B, C, D, or X) on the basis of risk of reproductive and developmental adverse effects or, for certain categories, on the basis of such risk weighed against potential benefit. 21 CFR § 201.57(c)(9)(i)(A)(2). Intal Inhalers are classified as a Pregnancy Category B drug. Pregnancy Category B indicates that animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. In the proposed rule, we identified several non-CFC orally inhaled corticosteroids as therapeutic alternatives to cromolyn and nedocromil MDIs. One of these orally inhaled corticosteroids, budesonide inhalers (marketed as Pulmicort Turbuhaler and Pulmicort Flexhaler), is also classified as a Pregnancy Category B drug. We believe that budesonide inhalers are an appropriate non-CFC therapeutic alternative for pregnant women who are currently using Intal Inhalers.

We have no data to suggest that Intal is more effective than the therapeutic alternatives at preventing asthma symptoms triggered by pet allergens. Although we believe that current Intal and Tilade users will be adequately served by the inhaled corticosteroids identified above, we also note the availability of cromolyn sodium in a nebulized solution, which may provide a therapeutic alternative for situations involving planned and known exposures to allergens.

(Comment 3) One comment suggested that the amount of CFCs released from Intal and Tilade Inhalers is inconsequential.

(Response) As we have noted in previous rulemakings, the environmental impact of CFCs used in MDIs, including Intal and Tilade MDIs, 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, including Intal and Tilade, 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 Intal and Tilade 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, including Intal and Tilade, 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.

C. Pirbuterol

We are removing the essential-use designations for MDIs containing pirbuterol (Maxair Autohaler). Pirbuterol is a short-acting $beta_2$–adrenergic agonist used in the treatment of bronchospasm associated with asthma and COPD. Pirbuterol acts as a bronchodilator. Pirbuterol is only available in a CFC MDI. Maxair Autohaler is one of two $beta_2$–adrenergic agonist MDIs currently marketed as a prescription drug which contains CFCs. The other product, Alupent Inhalation Aerosol, is addressed in section IV.A of this document. Albuterol is also a $beta_2$–adrenergic agonist, but it is no longer marketed as a CFC MDI. Albuterol was addressed in a separate rulemaking, which removed its essential-use designation effective December 31, 2008. Maxair Autohaler is a prescription drug that was approved on November 30, 1992. Maxair Autohaler's use was considered essential under the 1978 rule, which stated that "[m]etered-dose adrenergic bronchodilator human drugs for oral inhalation" were essential. Pirbuterol was designated as essential as an active moiety in the 2002 rule. Maxair Autohaler has a breath-actuated delivery system.

1. Do Substantial Technical Barriers To Formulating Pirbuterol Products Without ODSs Exist?

We proposed a finding that there are no technical barriers to formulating pirbuterol MDIs without ODSs (72 FR 32030 at 32037).

(Comment 4) One comment, Graceway Pharmaceuticals, LLC (Graceway), the manufacturer of Maxair Autohaler, states that there are substantial barriers (chemistry, manufacturing, and engineering) to reformulating Maxair Autohaler without ODSs. Graceway also states these barriers are complicated by the breath-actuated system, which is more sensitive with respect to particle size and energy force.

(Response) When determining whether technical barriers to formulating pirbuterol MDIs without ODSs exist, we consider whether all available alternative technologies have been evaluated and whether each alternative is unusable (64 FR 47719 at 47721, September 1, 1999). In addition, we look at results of reformulation efforts for similar products, as well as statements made about the manufacturer's particular efforts to reformulate their product or products. Graceway has not demonstrated that the breath-actuated system is more sensitive with respect to particle size and energy force or explained how any such sensitivity poses a barrier to reformulating Maxair without ODSs. As noted in the proposed rule, the pharmaceutical industry has had success in formulating other orally inhaled $beta_2$–adrenergic bronchodilators without ODSs. At least nine different active moieties have been

formulated as HFA MDIs for the treatment of asthma and COPD in the United States and abroad.[11] HFA MDIs have been formulated with both suspensions and solutions. Pirbuterol is a close chemical analog to albuterol and levalbuterol. Given the chemical similarity between them and the success with reformulating albuterol (as albuterol sulfate in ProAir HFA Inhalation Aerosol, Proventil HFA Inhalation Aerosol, and Ventolin HFA Inhalation Aerosol) and levalbuterol (as levalbuterol tartrate in Xopenex HFA Inhalation Aerosol), there appears to be no technical reason why pirbuterol cannot be successfully reformulated into an HFA MDI.

Furthermore, Graceway has not demonstrated that it evaluated all available alternative technologies and found each alternative unusable—the standard described in section III of this document (64 FR 47719 at 47721, September 1, 1999). At the time the proposed rule published, we had no evidence to suggest that the ODS containing pirbuterol oral inhalation drug product posed unique technical challenges to formulation without ODSs. Since the time the proposed rule published, no data have been submitted to change that conclusion. Therefore, after consideration of the public comments on the issue, we conclude that there are no technical barriers to the development of a non-ODS pirbuterol product.

2. Do Pirbuterol MDIs Provide an Otherwise Unavailable Important Public Health Benefit?

In the proposed rule we tentatively found that pirbuterol MDIs do not provide an otherwise unavailable important public health benefit (72 FR 32030 at 32037). Because we have reached a conclusion that there are no substantial technical barriers to formulating pirbuterol into a non-ODS product, we do not believe it is necessary to reach a conclusion on the public health benefits of pirbuterol MDIs. However, we received a large number of comments in response to the proposed rule addressing the public health benefits of pirbuterol MDIs, and we believe it is appropriate to address the public health benefits in light of these comments.

[11] The nine moieties formulated as HFA MDIs are albuterol, beclomethasone, budesonide, fenoterol, fluticasone, flunisolide, formoterol, ipratropium, and salmeterol. While a salmeterol DPI (SEREVENT) has been approved in the United States, salmeterol HFA MDIs have only been approved overseas. There are no approved fenoterol or formoterol HFA products in the United States, but fenoterol HFA MDIs and formoterol HFA MDIs have been approved in several foreign countries.

a. *Does Pirbuterol provide a greater therapeutic benefit than similar adrenergic bronchodilators?* (Comment 5) In its comment in response to the proposed rule, Graceway claims that Maxair Autohaler provides important public health benefits that would otherwise be unavailable to substantial numbers of patients who have asthma or COPD. Graceway states that Maxair Autohaler is an alternative for those who do not tolerate or respond to albuterol and levalbuterol. Graceway bases this conclusion in part on the distinct chemical structure of pirbuterol, which Graceway claims is different from albuterol and levalbuterol, and also on variation among patients. In its comment, Graceway presents statements from physicians and patients claiming that many patients experience intolerance or allergic reaction to albuterol, but succeed on pirbuterol. In addition, we received many comments from pirbuterol users and physicians who prescribe pirbuterol, detailing experiences with pirbuterol and alternative MDIs, such as albuterol. The comments describe reactions to and intolerance experienced with albuterol and success with pirbuterol. Furthermore, many of the comments from the physicians and pirbuterol users claim that experience indicates that pirbuterol MDIs are more effective than albuterol MDIs.

(Response) Albuterol and pirbuterol are both short-acting beta$_2$–adrenergic bronchodilators. Bronchodilation occurs primarily through stimulation of the beta$_2$–adrenergic receptor. Albuterol MDIs are therapeutic alternatives to pirbuterol MDIs and are, by far, the most widely prescribed short-acting bronchodilators. We are not aware of any studies that support the comments' contentions that albuterol inhalers are not an appropriate alternative for pirbuterol inhalers. Moreover, we disagree with the contention that the pirbuterol MDIs provide any unique therapeutic or other advantage over the available alternatives. The labeling for Maxair Autohaler does not contain any superiority claims based on controlled clinical trials and we do not believe that anecdotal evidence is adequate to support such a conclusion.

Four prescription HFA MDIs with two different forms of albuterol are approved and currently available:

- ProAir HFA (albuterol sulfate) Inhalation Aerosol;
- Proventil HFA (albuterol sulfate) Inhalation Aerosol;
- Ventolin HFA (albuterol sulfate) Inhalation Aerosol; and
- Xopenex HFA (levalbuterol tartrate) Inhalation Aerosol.

These products use HFA, which does not affect stratospheric ozone as a replacement for ODSs. Maxair Autohaler 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, and have similar dosing regimens. At least one of the currently available albuterol drug products should be an adequate therapeutic alternative for patients currently using Maxair Autohaler.

We are not aware of any adequate and well-controlled studies which support the comments' views that individuals who do not respond to or tolerate albuterol and levalbuterol would find pirbuterol MDIs more effective or better tolerate pirbuterol, or that pirbuterol MDIs are more effective than other asthma MDIs, including albuterol HFA MDIs. The National Asthma Education and Prevention Program, Expert Panel Report 3 (NAEPP EPR–3) recommends that short-acting beta$_2$–adrenergic bronchodilators, in particular albuterol, levalbuterol, and pirbuterol, are the most effective medications for relieving acute bronchospasm. (Ref. 1) The NAEPP EPR–3 does not distinguish pirbuterol as providing any unique therapeutic or other advantage over the available alternatives.[12] Furthermore, the opinion of all PADAC members who voted on the issue was that pirbuterol is no longer an essential use of ODSs (72 FR 32030 at 32037). The studies and literature cited by Graceway in its comment provide cases of non-response or inadequate response to albuterol and levalbuterol. Graceway did not present studies comparing pirbuterol to albuterol or showing that pirbuterol would be more effective for those users who do not respond to or inadequately responded to albuterol. In fact, in its comment (Comment No. 4), Graceway stated that clinical studies have not been conducted to establish whether patients may respond differently to pirbuterol.

[12] In the United States, the generally recognized standard of care for asthma is set forth in the National Heart, Lung, and Blood Institute's National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR–3) (Ref. 2). The National Heart, Lung, and Blood Institute is one of the National Institutes of Health. In the 2007 update, we find the latest updates to the standard. The Guidelines represent best practices and are recognized as the clinical standard of care for treatment of asthma. See, e.g., *http://www.asthmanow.net/care.html*; *http://www.colorado.gov/bestpractices/index.html*; *http://www.doh.wa.gov/CFH/asthma/publications/plan/health-care.pdf*.

As stated previously, if therapeutic alternatives exist for users of the CFC MDI, we can determine that the CFC MDI does not provide an otherwise unavailable important public health benefit. We have carefully considered these comments asserting that Maxair Autohaler is a more effective alternative to other asthma MDIs. However, no data were submitted to the agency as part of this rulemaking, and the agency is not aware of any data that allow us to reach the conclusion that pirbuterol provides a greater therapeutic benefit than similar adrenergic bronchodilators. Thus, we believe that patients will be adequately served by alternative MDIs.

(Comment 6) Graceway also argues that pirbuterol is more likely than albuterol to select $beta_2$ receptors, which presents less risk of cardiac side effects.

(Response) As stated in response to the previous comment, albuterol and pirbuterol are both short-acting selective $beta_2$–adrenergic bronchodilators that achieve bronchodilation primarily through the $beta_2$–adrenergic receptor. Therefore, they both bind to the same receptor that causes bronchodilation. The studies Graceway submitted to support the conclusion that pirbuterol is more likely than albuterol to select $beta_2$–adrenergic receptors do not demonstrate that there is any difference in clinical efficacy or safety between the two drugs. Moreover, the Maxair Autohaler label warns of the same cardiovascular effects as other inhaled beta adrenergic agonists. The NAEPP EPR–3 states that albuterol, levalbuterol, and pirbuterol are all effective agonists and have few negative cardiovascular effects. Accordingly, we disagree that there is less risk of cardiac side effects with use of pirbuterol MDIs than with use of albuterol MDIs.

b. *Does the breath-actuated device associated with pirbuterol MDIs provide an important public health benefit?*

(Comment 7) Graceway, as well as many other comments, stresses the importance of Maxair Autohaler's breath-actuated device in providing an otherwise unavailable important public health benefit. Many people claim they cannot operate traditional press-and-breathe MDIs. They further claim that it is extremely inconvenient and more challenging to use a traditional press-and-breathe MDI with a spacer device to assist with coordination problems. Because spacers are bulky and less portable, people are less likely to carry them, and because they require additional maintenance, people are less likely to use them. The comments argue that Maxair Autohaler's ease of use, convenience, and portability allow for increased compliance. Graceway argues that the compliance obstacles will lead to an increase in morbidity, as well as an increase in missed school/work days and physician, hospital, and emergency department visits.

(Response) While some individuals or groups of people may have difficulty operating the alternative MDIs that use traditional press-and-breathe devices, and Maxair Autohaler's Autohaler device may be convenient, there are other options for these individuals and groups to treat their asthma or COPD. We understand the difficulties for certain groups of people, such as young children, older adults, and the physically or mentally disabled, of coordinating inhalation with MDI activation. Learning how to properly maintain medical devices and administer medication is a sometimes difficult, but necessary task for many patients with chronic diseases. It would certainly be more convenient to have available many different devices to meet the individual and distinct needs of every patient group. However, we do not believe that this type of patient convenience provides a basis to conclude that a product provides an otherwise unavailable health benefit. Because therapeutic alternatives exist, use of pirbuterol MDIs is not absolutely necessary to save lives, to reduce or prevent asthma morbidity, or to significantly increase patient quality of life.

The use of spacer devices with alternative products provides options for patient groups who have difficulties coordinating inhalation with MDI operation, allowing them to more satisfactorily use MDIs that do not have a breath-actuated delivery mechanism. A spacer is a device that adds space between the mouthpiece of an MDI and the patient's mouth and is used to increase the effectiveness of an MDI. Some have valves that result in the aerosol from the MDI being briefly held in a reservoir from which the patient subsequently inhales the aerosolized medication. Nebulizers provide another option for individuals or patient groups with coordination problems. Systematic reviews and meta-analyses have suggested that each of the aerosol delivery devices can work equally well in patients who can use them correctly. (Ref. 2) The availability of alternatives for those individuals or patient groups who are unable to operate traditional press-and-breathe devices supports a conclusion that any added convenience of a breath-actuated device for patients who have been prescribed drugs for the treatment of asthma or COPD does not provide an unavailable important public health benefit within the meaning of 21 CFR 2.125(f)(1)(ii).

Furthermore, we are not removing the breath-actuated delivery mechanism from the market; rather, as a result of this rule, the CFC-propelled pirbuterol may no longer be marketed. Graceway, or another company, may develop a breath-actuated delivery system with pirbuterol or other drugs of the class that do not use CFCs.

(Comment 8) Graceway also claims that it will be more costly to switch to one of the proposed alternatives. Increased costs include higher copayments for branded HFA MDIs, extra visits to health care providers to adjust treatment, purchase of spacers, and the cost of failing to adequately manage asthma or COPD. Graceway contends that the use of alternative MDIs is more costly because Maxair Autohaler contains 400 inhalations per MDI, twice the number of inhalations of alternative MDIs.

(Response) The bases Graceway identifies in support of its argument that it will be more costly to switch from Maxair Autohaler to an alternative MDI are largely invalid. First, Maxair Autohaler, the only marketed pirbuterol drug product, is a branded, rather than a generic, product. The therapeutic alternatives for Maxair Autohaler are also branded products. Therefore the purchase of an alternate branded HFA (hydrofluoroalkane HFA–134a) inhaler would require no greater copayment. Second, for most patients with asthma or COPD who use inhalers, regular doctor visits to adjust treatment plans are routine. There is no reason to believe that patients who use alternative HFA inhalers require any more adjustment in treatment than patients who use pirbuterol inhalers with a CFC propellant. Finally, no data have been presented to demonstrate that the cost of failing to adequately manage asthma or COPD is greater for individuals who use alternative HFA inhalers than for those who use Maxair Autohaler. As discussed in section VI of this rule, we anticipate the price per day of therapy to decrease after patients transition from Maxair to alternative therapies. Nevertheless, some individual patients might face higher costs, perhaps related to the costs of additional copayments associated with fewer numbers of inhalations provided by an alternative MDI.

We recognize that the pirbuterol breath-actuated MDIs may provide some public health benefits; however, nothing in this rulemaking suggests that continued use of these MDIs provides an unavailable important health benefit as previously defined. We do not

believe that we can conclude on the basis of the record in this rulemaking that continued use of Maxair Autohaler is necessary to save lives, to reduce or prevent asthma morbidity, or to significantly increase patient quality of life, particularly given the availability of albuterol MDIs as therapeutic alternatives, and the availability of spacers and nebulizers for use in lieu of breath-actuated MDIs.

In any case, given that we have already found no technical barriers to reformulation of pirbuterol MDIs under § 2.125(g)(2), a finding on the public health benefit issue is not necessary to this rulemaking, and we decline to make a specific finding on that issue in this final rule.

3. Does Use of Pirbuterol MDIs Release Cumulatively Significant Amounts of ODSs Into the Atmosphere and Is the Release Warranted Because These MDIs Provide an Otherwise Unavailable Important Public Health Benefit?

As explained in the proposed rule and above, because we have found in this rule that there are no substantial technical barriers to reformulating pirbuterol, we are required to find that the use of the product is not essential, and we do not need to reach a decision on the third criterion in § 2.125(f)(1). Nonetheless, based on the criteria described above and in the proposed rule, the quantity of CFCs used in pirbuterol MDIs is a significant portion of the total quantity of newly manufactured CFCs used, and therefore eventually released, in the United States. Accordingly, we tentatively concluded that any release of CFCs from pirbuterol MDIs is cumulatively significant (72 FR 32030 at 32033, 32034, and 32037). We received comments on the amount of CFCs released into the atmosphere from pirbuterol MDI use.

(Comment 9) Graceway asserts that the use of Maxair Autohaler does not release cumulatively significant amounts of ODSs into the atmosphere, and its de minimis release is warranted in view of the essential health benefits provided by the product. Graceway claims that Maxair Autohaler releases fewer CFCs than other MDIs because it releases fewer CFCs per puff than other MDIs and has a smaller market share. Graceway argues that without calculating the quantity of CFCs released from use of Maxair Autohaler alone, the agency admitted the quantity would, in any event, be minor. Graceway further argues that the agency has not shown how aggregate release of CFCs from all seven moieties has a significant impact on the environment.

(Response) Although we based our tentative conclusion that pirbuterol MDIs release cumulatively significant amounts of ODSs on previous policy statements about the environmental impact of CFCs, the basis for removing the essential-use designation for pirbuterol in this rulemaking is no significant barriers exist to reformulating pirbuterol MDIs without ODSs. We need not reach a conclusion that pirbuterol MDIs release cumulatively significant amounts of ODSs. Furthermore, as discussed previously, it is not necessary for us to reach a conclusion on the public health benefits of Maxair Autohaler, or to conduct the balancing test to reach a determination as to whether the release of CFC ODSs is warranted in view of the public health benefits. Regardless of outcome, the balancing test would not affect the ultimate finding in this rulemaking that, because there are no significant technical barriers to reformulation of the product, pirbuterol is no longer an essential use of ODSs and should be removed from the list of essential uses in § 2.125(e).

4. Additional Comments on Miscellaneous Issues

a. *Sufficiency of advisory committee and open public meetings.* (Comment 10) Graceway submitted a number of comments claiming insufficiencies of the two meetings held concerning the proposed rule to remove the essential-use designations of the seven moieties that are the subject of this final rule. Graceway asserts that the Pulmonary and Allergy Drugs Advisory Committee (PADAC) meeting held on July 14, 2005, did not fulfill the 21 CFR 2.125(g)(2) requirement for consultation with an advisory committee because the notice of the meeting did not identify the products and moieties at issue, state that the meeting was intended to fulfill requirements of 21 CFR 2.125(g)(2), or discuss the purpose and scope of the meeting. Therefore, informed views from independent experts could not be obtained because interested persons/companies either had no knowledge of the meeting or had insufficient time to adequately prepare for the meeting. Graceway also asserts that the background memorandum provided to the PADAC was inadequate and that committee members were confused. In addition, Graceway asserts that the agency did not properly consult with the committee members as to the health benefits of the moieties at issue and failed to consider the committee's advice or recognize issues raised by the committee members.

(Response) FDA may remove an essential-use designation under section 2.125(g)(2) if it no longer meets certain criteria after consultation with a relevant advisory committee and after holding an open public meeting. FDA made clear in the 1999 rule proposing criteria for removing essential-use designations that, before removing any essential-use designation, it would consult with an advisory committee and provide opportunity for public comment (64 FR 47719 at 47722). FDA published a notice in the **Federal Register** on May 10, 2005 (70 FR 24605), that the PADAC would be convening on July 14, 2005, to discuss the continued need for the essential-use designations of prescription drugs for the treatment of asthma and COPD. The notice further stated that interested persons could present data, information, or views, orally or in writing, on the issues pending before the committee. This notice provided sufficient time for those persons or companies with an interest in the essential-use designations of any moieties used in drugs that treat asthma or COPD to provide the committee members with any information they believed would be pertinent to the decision to remove a designation.

It was noted at the meeting that the committee was convened to determine whether changes in medical practice and the availability of alternatives render the products listed as essential no longer essential. The background memorandum provided to the PADAC described the regulatory criteria for removing essential uses and advised the committee to focus attention on the criterion related to the important public health benefits of the moieties. The background memorandum also listed those products containing CFCs that were still marketed and for which there were no current reformulations or direct alternative products, and products currently approved or marketed that do not contain CFCs. These lists were provided to assist the committee when considering whether adequate alternative therapy is available. The opportunity to ask clarifying questions was provided at the meeting, and presentations were made by an association representing manufacturers of MDIs, particular MDI manufacturers, and an interested person. Therefore, we disagree with the assertion that informed views from independent experts could not be or were not obtained.

After the presentations, the committee discussed the individual moieties, including pirbuterol, with regard to their essentiality. A majority of the members agreed that pirbuterol is

nonessential. The transcript of the meeting, available at *http://www.fda.gov/ohrms/dockets/ac/cder05.html#PulmonaryAllergy*, does not reveal any confusion on the part of the committee members. In the proposed rule, we stated that we consulted with the PADAC at their July 14, 2005, meeting on the essential-use status of MDIs containing, among other moieties, pirbuterol, and that the PADAC members gave their opinions, without dissent, that pirbuterol was no longer an essential use of ODSs (72 FR 32030 at 32035, 32037). Thus, FDA has taken full consideration of the opinions of the committee members.

(Comment 11) Graceway asserts that the agency failed to meet the spirit of the 21 CFR 2.125(g)(2) public meeting requirement to enrich notice-and-comment rulemaking. Graceway stated that scheduling the meeting with less than 3 weeks' notice, the lack of publicity, and the decision to hold a single meeting in one location were barriers to participation by patients, clinicians, and outside experts. Graceway also stated that the agency failed to solicit feedback on patients' experience with HFA alternatives and thus limited the scope of the administrative record.

(Response) FDA published a notice in the **Federal Register** on July 9, 2007 (72 FR 37137), that the public meeting would be held on August 2, 2007, at FDA's Center for Drug Evaluation and Research Advisory Committee conference room in Rockville, MD. The notice stated that the meeting was to solicit comments on the proposed rule amending the regulation on the use of ODSs to remove the essential-use designations for certain MDIs, and invited written or electronic comments for consideration at the meeting, as well as requests to speak at the meeting. We believe we provided sufficient notice of the meeting to allow for widespread participation and did not create barriers to participation by patients, clinicians, and outside experts. Accordingly, we disagree with Graceway's implication that the agency did not comply with the regulatory requirement for an open public meeting. Furthermore, in the proposed rule, we solicited any comments related to the removal of the essential-use designations for MDIs containing pirbuterol and other moieties, and in the notice of the public meeting we invited discussion of issues on which we asked for comments in the proposed rule. In fact, we received thousands of comments on patients' experiences with HFA alternatives to pirbuterol in particular. Therefore, we strongly disagree that the scope of the administrative record was limited in any way.

b. *Sufficiency of proposed rule.* (Comment 12) Graceway argues that FDA failed to publicize the proposed rule through a press release, public announcement, or on the Internet, and inhibited public participation in the rulemaking process.

(Response) Interested persons have had ample notice that FDA was considering removing the essential-use designation for pirbuterol and the six other drugs that are the subject of this rulemaking. This issue was first considered at the July 14, 2005, PADAC meeting (see 70 FR 24605). The trade press reported on this meeting, and minutes and a transcript of the meeting were placed on the Internet and are available at *http://www.fda.gov/OHRMS/DOCKETS/ac/cder05.html#PulmonaryAllergy*. We also announced our intention to publish a proposed rule in the unified agendas published in the **Federal Register** on December 11, 2006 (71 FR 73195 at 73223), and April 30, 2007 (72 FR 22489 at 22516). As stated previously, we published the proposed rule in the **Federal Register** on June 11, 2007 (72 FR 32030). These publications put the public on notice of our intent to remove the essential-use designations, and invited comments on our proposal. In addition, we held an open public meeting, as discussed previously, for which we solicited input from interested parties. Several companies, including Graceway, gave presentations at the open public meeting. Furthermore, our MDI Web site, *http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm063054.htm*, discusses the phase-out of all essential use designations and contains copies of all relevant documents, including the June 11, 2007, proposed rule. Our receipt of thousands of comments on the proposed rule further shows that the public was well aware of our intent to remove the essential-use designations and that public participation was not inhibited.

(Comment 13) Graceway also argues that FDA must give weight to the quality and quantity of comments submitted in response to the proposed rule because the number of comments is material where the degree of public interest is a legitimate factor for consideration. Graceway states that with regard to this rule, input from patients, physicians, and pharmacists is crucial because the decision-making involves weighing important and competing public policy considerations.

(Response) We have given due weight and full consideration to all comments submitted in response to the proposed rule. We have read each comment individually and provided responses to all unique comments submitted. When comments were duplicative in substance, we provided one response to all like comments. We fully understand the concern with removal of the essential-use designations and have weighed the public policy considerations, as discussed previously. After weighing the important and competing public policy considerations, and considering the nature and number of comments, we have concluded that the public is best served by the decision to remove the essential-use designations that are the subject of this rule.

(Comment 14) Graceway asserts that FDA's failure to create a confidential docket prevented companies from commenting on issues related to development of non-ODS formulations of pirbuterol.

(Response) There is no provision in our regulations for creating a confidential docket. As we commented previously with regard to technical barriers, the pharmaceutical industry has had success in formulating other orally inhaled beta$_2$–adrenergic bronchodilators without ODSs. Given the chemical similarity between the moieties used in these other bronchodilators and pirbuterol, and the success with reformulating albuterol and levalbuterol, there appears to be no technical reason why pirbuterol cannot be successfully reformulated into an HFA MDI or other non-ODS inhalation delivery system. Moreover, Graceway could have readily provided general comments related to development of a non-ODS delivery system.

(Comment 15) Graceway stated that FDA's concerns over the availability of CFCs beyond 2009 are more properly addressed through negotiation at Montreal Protocol meetings, rather than through removal of essential-use designations.

(Response) As a Party to the Montreal Protocol, the United States Government committed to eliminating all non-essential uses and reducing essential uses of CFCs. The Preamble to the Protocol states that the Parties are: "Determined to protect the ozone layer by taking precautionary measures to control equitably total global emissions of substances that deplete it, *with the ultimate objective of their elimination*" (Preamble to the Montreal Protocol (emphasis added.)). FDA's actions in this rulemaking are consistent with the United States' position in meetings regarding the Montreal Protocol. Discussion of the United States' position with regard to the Montreal Protocol is more appropriately directed to the

Department of State, which heads the United States delegation to meetings regarding the Montreal Protocol. If any company wants the United States to alter any of the positions taken with the Parties to the Protocol, it should present its views to appropriate officials in the State Department.

c. *Regulatory Flexibility Act.* (Comment 16) Graceway asserts that FDA erroneously concluded that none of the firms that manufacture the seven CFC MDIs is a small entity under the Regulatory Flexibility Act because none employs fewer than 750 people, and therefore the proposed rule would not have a significant economic impact on a substantial number of small entities. Graceway states that it is a small entity because it employs fewer than 750 people. It also claims that it constitutes a significant number of small entities because Graceway makes up more than 5 percent of the total number of affected entities (the five NDA holders for prescription CFC MDI products) and 100 percent of the affected small entities. Graceway also states that the rule would have a significant economic impact on it because Maxair comprises 15 percent of Graceway's U.S. revenues.

(Response) As explained in our Regulatory Flexibility Analysis (see section VII), for purposes of determining whether a substantial number of small entities are affected by this rule, the affected industry sector includes all manufacturers of pharmaceutical products in the United States. The effects of this final rule are not limited to the five NDA holders who are marketing the seven ODS drug products. Thus, the industry sector which will be directly affected by this rule includes all U.S. "pharmaceutical preparation manufacturers." The same industry sector was considered to be affected by the Albuterol final rule (70 FR 17191, April 4, 2005).

According to the U.S. Department of Commerce, the industry of "pharmaceutical preparation manufacturers" includes 901 establishments controlled by 723 companies (Ref. 3). Of these establishments, 822 have fewer than 500 employees. Only one of these companies, Graceway, has claimed that it is a small business and that the rule will cause it substantial economic harm. We do not need to determine if Graceway is in fact a small business, because even if it is, one single small affected entity among an industry of hundreds does not constitute a "substantial number" under the Regulatory Flexibility Act. Department of Health and Human Services Guidance[13] defines "substantial number" as 5 percent or more of the affected small entities within an identified industry. Graceway does not constitute 5 percent of the small entities in the "pharmaceutical preparation manufacturers" sector.

Because this rule would not affect a substantial number of small entities, we do not need to determine whether it would have a significant economic impact upon Graceway. Thus, we continue to believe that this rule would not have a significant economic impact on a substantial number of small entities and decline to reverse our previous determination under the Regulatory Flexibility Act.

d. *National Environmental Policy Act.* (Comment 17) Graceway asserts that FDA erroneously concluded that the rule would not have a significant adverse impact on the human environment. Graceway states that HFA alternatives to Maxair Autohaler and the overall shift of the market to HFA products have a significant global warming impact. Consequently, Graceway claims that FDA must provide evidence and analysis in support of its determination not to prepare an environmental impact statement. In particular, it maintains that FDA must discuss the impact of the proposed action and alternative approaches.

(Response) 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. These alternatives generally use HFC-134a (CH_2FCF_3), or, to a lesser degree, HFC-227ea (C_3HF_7) as a propellant. While HFC-134a and HFC-227ea are greenhouse gases (the global warming potentials (GWPs) are around 1300 GWP[14] and 2600 GWP, respectively),[15] the CFCs that were previously used are ozone disrupting compounds that have much higher global warming potentials of 5000 to 11,000.[16] In addition, considering the density of the HFC propellant is about 30 percent lower than for the CFC propellant, on a mass basis, the quantities emitted are reduced by 30 percent (Ref. 4).

Considering this data, we concluded that there will be an overall improvement in the levels of potent greenhouse gases released annually from the use of oral pressurized MDIs as a result of this action. Therefore, the removal of the essential-use designations results in a net improvement on the environmental effects of the use of these devices. Because there is no net negative environmental impact of this action, alternative actions will not be addressed. We encourage the development of new forms of propellants with even lower GWPs, as well as other delivery possibilities, but in the absence of such alternatives we reaffirm the removal of the essential-use designations for CFC-propelled MDIs as an environmentally sound action.

D. Albuterol and Ipratropium in Combination

We are removing the essential-use designations for MDIs containing albuterol sulfate and ipratropium bromide in combination (Combivent Inhalation Aerosol).[17] Combivent Inhalation Aerosol 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. 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 Inhalation Solution) for use in a nebulizer. Nebulizers do not use CFCs. This current rulemaking will not affect the regulatory status of DuoNeb Inhalation Solution.

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[13] Guidance on Proper Consideration of Small Entities in Rulemakings of the U.S. Department of Health and Human Services (May 2003).

[14] GWP: Global warming potential; represents how much a given mass of chemical contributes to global warming over a given time period compared with the same mass of carbon dioxide (GWP =1). It is defined as the ratio of the time-integrative radiative forcing from the instantaneous release of 1 kg of a trace substance relative to that of 1 kg of a reference gas (in most cases CO_2). All GWP values represent global warming potential over a 100-year time horizon.

[15] U.S. Environmental Protection Agency, Global Warming Potentials of ODS Substitutes: *http://www.epa.gov/Ozone/geninfo/gwps.html.* Accessed 5/21/2009.

[16] U.S. Environmental Protection Agency. Class I Ozone-depleting Substances: *http://www.epa.gov/Ozone/science/ods/classone.html.* Accessed 5/21/2009.

[17] As noted in the proposed rule, 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 Inhalation Aerosol. We have treated the petition as a comment on this proposal.

1. Do Substantial Technical Barriers to Formulating Products Containing Albuterol and Ipratropium in Combination Without ODSs Exist?

In the proposed rule, we noted that we had not been supplied with any information to support a conclusion that substantial technical barriers exist and could not make an initial determination on whether such barriers exist. We received several comments about technical barriers to reformulating Combivent Inhalation Aerosol without CFCs, one of which provided additional information about Combivent Inhalation Aerosol's reformulation efforts.

(Comment 18) In its comment in response to the proposed rule, Boehringer Ingelheim Pharmaceuticals, Inc. (BI), argues that substantial technical barriers have hampered the development of a CFC-free Combivent Inhalation Aerosol. Specifically, BI notes that Combivent Inhalation Aerosol's combination of two active ingredients with different physico-chemical properties presents unique challenges for formulating a Combivent HFA Inhalation Aerosol, including the development of different valves and materials for the HFA product. According to BI, significant problems arose during the clinical trial phase, including clogging and valve sticking. In addition, multiple formulations have been developed. BI also provides more detailed information on its current progress in developing a non-HFA CFC-free Combivent. Specifically, BI stated that it anticipated filing an NDA for Combivent Respimat at the end of 2008, permitting FDA review and approval to be completed by 2010 or 2011.

(Response) We have carefully reviewed the information provided by BI on its reformulation efforts. We have considered whether all available alternative technologies have been evaluated and whether each alternative is unusable. The information available to the agency suggests that viable alternatives exist or are in development. BI representatives stated at the Public Meeting in August 2007 and BI stated in its comment to the proposed rule that it is in the process of developing Combivent Respimat. BI's comments suggest that they anticipate being ready to commercially produce and legally distribute, and have the capacity to meet current market demand for, a non-CFC alternative Combivent product by 2011. In addition, BI's actions to date indicate that it has overcome difficulties in chemistry and manufacturing as it has developed and tested a Combivent Respimat product (see clinicaltrials.gov at Respimat Combivent Trial in Chronic Obstructive Pulmonary Disease (COPD), ClinicalTrials.gov identifier #NCT00400153 (completed April 2008)). We also note that both albuterol and ipratropium bromide have been successfully reformulated as non-CFC products. We believe that the success of BI's reformulation efforts to date demonstrates that although difficulties may have been encountered, they do not pose a substantial barrier to reformulating as described in section III of this document. Therefore, we conclude that substantial technical barriers to the development of a non-CFC combination albuterol and ipratropium product do not exist.

2. Do MDIs Containing Albuterol and Ipratropium in Combination Provide an Otherwise Unavailable Important Public Health Benefit?

In the proposed rule, we solicited comments on the public health benefits of Combivent Inhalation Aerosols (72 FR 32039). We tentatively concluded that Combivent Inhalation Aerosol does not provide an otherwise unavailable public health benefit and based this tentative conclusion on our tentative determination that an ipratropium bromide HFA MDI used with an albuterol sulfate HFA MDI would provide an acceptable therapeutic alternative to Combivent Inhalation Aerosol. Because we have reached a conclusion that there are no substantial technical barriers to formulating Combivent Inhalation Aerosol into a non-ODS product, we do not believe it is necessary to reach a conclusion on the public health benefits of Combivent Inhalation Aerosol. However, we sought and received multiple comments in response to the proposed rule addressing the public health benefits of Combivent Inhalation Aerosol, and we believe it is appropriate to address the public health benefits in light of these comments.

(Comment 19) For a number of reasons, BI disagrees with our tentative conclusion that Combivent Inhalation Aerosol does not provide an otherwise unavailable important public health benefit. BI claims that Combivent Inhalation Aerosol users are elderly and have COPD and co-morbid conditions, making them an especially vulnerable population. BI asserts that noncompliance is a significant problem among this population because many users have multiple medical conditions requiring multiple medications. According to BI, switching Combivent Inhalation Aerosol users to two separate inhalers would decrease compliance, increase medication errors due to incorrect administration, and increase treatment delays due to patient confusion over which inhaler to use. BI explains that compliance might decrease because ipratropium bromide has a longer onset of action, and patients may perceive a lack of efficacy if ipratropium bromide is administered separately from albuterol, which would lead patients to either overuse the product or not use it at all. BI also argues that some patients with COPD suffer from hyperinflation of the lungs, which makes it more difficult to take the deep breaths required for optimal dosing of medications, and doubling the number of inhalations to approximate the same therapeutic effect of Combivent Inhalation Aerosol would significantly increase the burden on the patient. We also received comments from patients who claim that using two inhalers would be too bulky. Several other comments raise similar concerns about compliance, and one comment raises these concerns with respect to patients with cystic fibrosis. Our response below addresses all such comments.

(Response) We believe that the ipratropium bromide HFA MDI and the albuterol sulfate HFA MDI, when used together, provide similar therapeutic benefits to Combivent Inhalation Aerosol. Using the two MDIs together will deliver the same dose of ipratropium (18 micrograms (mcg) per inhalation) and essentially the same dose of albuterol (108 mcg versus 103 mcg per inhalation) as the dose delivered by Combivent Inhalation Aerosol. As we noted in the proposed rule, the primary advantage of using the two drugs in combination is that by using two distinctly different mechanisms of action (albuterol is a $beta_2$–adrenergic bronchodilator while ipratropium bromide is an anticholinergic bronchodilator), the two drugs in combination should produce greater bronchodilator effect than using either drug alone. Combivent Inhalation Aerosol is a combination of convenience that is intended to facilitate patient use of the two drug products together.

Although it is not necessary for this rulemaking to evaluate whether the non-CFC therapeutic alternative has approximately the same level of convenience as the product it replaces, the analysis may be useful in light of the comments. As we stated in the 2002 rule, "in evaluating whether an alternative has approximately the same level of convenience of use compared to the ODS product containing the same active moiety, FDA will consider whether: (1) The product has approximately the same or better portability; (2) the product requires

approximately the same amount of or less preparation before use; and (3) the product does not require significantly greater physical effort or dexterity" (67 FR 48370 at 48374).

The proposed non-CFC alternatives to Combivent Inhalation Aerosol, an ipratropium bromide HFA MDI used with an albuterol sulfate HFA MDI, are MDIs like Combivent Inhalation Aerosol and are similarly portable. Both the CFC product and the HFA products require priming if they have not been used for a period of time, and therefore both products require approximately the same amount of preparation. We note that priming is only required when the product has not been used for a period of time. Because these inhalers are intended for daily use, we do not anticipate that regular priming would be necessary. And although twice as many puffs are required to deliver the dose of separate albuterol and ipratropium bromide into the lungs, the additional puffs do not require significantly greater physical effort or dexterity. In addition, we have not found any data to suggest that administering twice the number of puffs would be a significant burden for patients with hyperinflation. We acknowledge that carrying two inhalers is twice as bulky as carrying one, and some patients may find Combivent Inhalation Aerosol more convenient to use, but we believe that the therapeutic alternatives are only marginally less convenient, and any convenience provided by the availability of Combivent Inhalation Aerosol does not reach the level of essentiality.

We also acknowledge that some patients, particularly those with co-morbid conditions who are taking multiple medications, may be more compliant when using a Combivent Inhalation Aerosol than when using an ipratropium bromide HFA MDI with an albuterol sulfate HFA MDI. We believe that concerns about patient compliance can be appropriately addressed with patient outreach campaigns that provide education on how to use HFA MDIs correctly and the benefits of using both MDIs together. As we have stated elsewhere in this document, learning how to properly maintain and administer medications is a sometimes difficult, but necessary, task for many patients with chronic diseases. During the transition period, we intend to conduct this type of patient outreach campaign, and we encourage other stakeholders to work with us in educating Combivent Inhalation Aerosol users on the therapeutic alternatives. Because patient compliance may be greater with combination products such as Combivent Inhalation Aerosol, we intend to closely monitor the availability of any reformulated combination MDI product and the transition to the therapeutic alternatives identified in this rule, including albuterol and ipratropium delivered in single-ingredient MDIs, and modify the patient outreach efforts as appropriate.

(Comment 20) BI and other comments also argue that a decrease in compliance would lead to increased exacerbations and an increase in overall health care costs.

(Response) In one nonrandomized retrospective study comparing use of two separate inhalers to use of Combivent Inhalation Aerosol, Chrischilles et al. concluded that Combivent Inhalation Aerosol users were more compliant and had significantly lower average monthly health care costs compared to users of two separate inhalers (Ref. 5). Although the validity of the results depends on the authors' ability to control for important differences in the patient populations, we do not disagree with the conclusion that using two inhalers may be more expensive than using one combination inhaler, and we have identified and assessed those costs in our Analysis of Impacts.

(Comment 21) BI further argues that the proposed CFC-free therapeutic alternatives to Combivent Inhalation Aerosol (an ipratropium bromide HFA MDI used with an albuterol sulfate HFA MDI) have not been shown to provide similar therapeutic benefits. One comment claims that clinical studies have shown that a single inhaler of Combivent Inhalation Aerosol is more effective for the treatment of COPD than two separate inhalers. Several comments oppose the market removal of Combivent Inhalation Aerosol, arguing the combination of two medications that must be taken separately is not a substitute for the single product, Combivent Inhalation Aerosol.

(Response) As stated earlier, 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) as the dose delivered by Combivent Inhalation Aerosol. We are not aware of any data demonstrating that Combivent Inhalation Aerosol is clinically superior to an ipratropium bromide HFA MDI used with an albuterol sulfate HFA MDI. Other than the study by Chrischilles discussed earlier, most of the data cited by BI refers to older studies that did not study albuterol and ipratropium in combination inhalers. And as discussed earlier, we acknowledge that use of a combination inhaler may increase compliance, but we believe compliance can be increased with proper patient education, and we do not consider this factor to be determinative of public health benefit.

Neither the Chrischilles study nor any other study available to us or cited by BI demonstrates that Combivent Inhalation Aerosol is clinically superior to the two inhalers used together. We believe that the ipratropium bromide HFA MDI and the albuterol sulfate HFA MDI used together provide similar therapeutic benefits to the Combivent Inhalation Aerosol. We also note that albuterol and ipratropium bromide in combination are also available as an inhalation solution for use in a nebulizer (marketed as DuoNeb Inhalation Solution). DuoNeb Inhalation Solution is an option for patients who prefer a combination drug product. The availability of these therapeutic alternatives supports a conclusion that Combivent Inhalation Aerosol does not provide an otherwise unavailable important public health benefit.

3. Does Use of MDIs Containing Albuterol and Ipratropium in Combination Release Cumulatively Significant Amounts of ODSs Into the Atmosphere and Is the Release Warranted Because These MDIs Provide an Otherwise Unavailable Important Public Health Benefit?

As explained in the criteria in section III of this document, because we have found in this rule that there are no substantial technical barriers to reformulating Combivent Inhalation Aerosol, we are required to find that the use of Combivent Inhalation Aerosol is not essential, and we do not need to reach a decision on the third criterion in § 2.125(f)(1). However, we received several comments about this criterion, which we address below.

(Comment 22) BI argues that removing Combivent Inhalation Aerosol from the market would not significantly decrease the cumulative release of CFCs into the atmosphere and would have a negligible effect on the recovery of the stratospheric ozone layer. They also argue that any effect would not outweigh treatment disruption, health risks, and costs to Combivent Inhalation Aerosol users as a result of the market removal. According to BI, Combivent Inhalation Aerosol usage is expected to account for approximately 175 to 200 metric tons of annual CFC emissions in the coming years. Several comments assert that the amount of ODSs released from Combivent Inhalation Aerosol is insignificant, and eliminating their use would not provide a significant environmental benefit.

(Response) As we stated in the proposed rule and elsewhere in this document, the environmental impact of individual uses of nonessential CFCs must be evaluated in the context of the overall use of CFCs. The quantity of CFCs released from Combivent Inhalation Aerosol represents a significant portion of the total quantity of CFCs released from MDIs in the United States. FDA has not been assigned the task of determining what amount of environmental benefit would result from the removal of CFC-containing medical devices, diagnostic products, drugs, and drug delivery systems from the market. FDA is required to determine whether such products are essential uses of ODSs, and this rulemaking fulfills that obligation with respect to Combivent Inhalation Aerosol.

(Comment 23) BI argues that the proposed rule did not provide data or analysis demonstrating the amount of CFCs which constitutes a significant release. BI also comments that the criterion under the essential-use regulation was established to determine an individual product's release and its effect on the ozone layer, not whether it is significant relative to the release from other products. BI argues that our standard for determining whether a product releases significant amounts of ODSs into the atmosphere is not supported by science and should be developed in accordance with notice-and-comment rulemaking procedures.

(Response) We do not agree that the proposed rule did not provide data or analysis demonstrating the amount of CFCs which constitutes a significant release. We also disagree that our standard is not science-based or was developed without the opportunity for public comment. In reaching our tentative conclusion in the proposed rule that any release of CFCs from Combivent Inhalation Aerosol is cumulatively significant, we discussed our reasoning at length and cited multiple policy statements and other sources in support of our conclusion. We also solicited and received comments on our tentative conclusion. Through previous legislative and administrative actions, the United States has evaluated the environmental effect of eliminating the use of all CFCs and has made a decision to fully phase out the use of CFCs over time. Our conclusion that any release is cumulative is based on these legislative and administrative actions and reflects environmental science policies that have been developed over time through a public process.

(Comment 24) A few comments claim that CFCs used in Combivent Inhalation Aerosol do not have an adverse impact on the environment because the CFCs are inhaled rather than released into the environment.

(Response) As we have noted in previous rulemakings, nearly all of the CFCs inhaled into the lungs from an MDI are almost immediately exhaled into the environment (70 FR 17168 at 17179, April 4, 2005; 73 FR 69532 at 69540, November 19, 2008). The small amounts of CFCs absorbed into the body are later excreted and exhaled without being broken down. Essentially all of the CFCs released from an MDI end up in the atmosphere with resulting harm to the stratospheric ozone layer.

(Comment 25) One comment argues that the CFCs released from Combivent Inhalation Aerosol are less damaging to the ozone layer than the fumes from one diesel truck.

(Response) This comment appears to confuse CFCs with other greenhouse gases such as carbon dioxide and nitrous oxide. FDA's regulations at 21 CFR 2.125 reflect an international effort to reduce the production, importation, and use of substances that deplete the ozone layer. We are publishing this rule because the criteria in § 2.125 have been met, rather than because of any contribution CFCs may be making towards global warming.

(Comment 26) Another comment suggests FDA retain the essential-use designation for Combivent Inhalation Aerosol and instead remove other inhalants, such as aerosol hair sprays, spray paint, and perfumes.

(Response) The use of CFCs in cosmetics such as aerosol hair sprays, deodorant, shaving cream, and perfume was banned in 1978, along with the use of CFCs in spray paint, and household, food and automotive products.

4. Additional Comments on Miscellaneous Issues

a. *Criteria used in rulemaking.* (Comment 27) BI argues that the criteria in 21 CFR 2.125(g)(3)(ii), (g)(3)(iii), (g)(3)(iv), and (g)(4)(ii)[18] should be applied to any proposed CFC-free replacement. According to its comment, ignoring or failing to fully consider these criteria could result in patients being switched to "therapeutically inferior" alternatives. At a minimum, BI argues that this rulemaking should incorporate the analysis used in the albuterol rulemaking.

(Response) 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 the albuterol rulemaking. Although the analysis used here is not identical to that 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. Section 2.125(g)(2) 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. In the case of Combivent Inhalation Aerosol, both active moieties have been reformulated without CFCs, and FDA disagrees that the albuterol HFA MDI and the ipratropium bromide HFA MDI are therapeutically inferior to Combivent Inhalation Aerosol. As stated earlier, we find them to be therapeutically equivalent, and we believe the two MDIs used together will meet the needs of current Combivent Inhalation Aerosol users.

b. *Intent to reformulate.* (Comment 28) BI argues that removing Combivent Inhalation Aerosol's essential-use designation before a replacement can be developed preempts BI's good faith efforts to reformulate (a requirement under the Montreal Protocol).

(Response) Nothing about this decision precludes BI from reformulating. A reformulated product can be approved at any time after FDA has determined an NDA meets approval standards. Based on BI's assertions, it is possible a replacement will be available prior to the effective date of this rule for Combivent Inhalation Aerosol.

c. *Deadline for overall CFC phase-out.* (Comment 29) BI comments that the Montreal Protocol and the Clean Air Act do not set a firm deadline for the phase-out of CFC usage in MDIs, and FDA should exercise greater flexibility in its essential-use rulemakings.

[18] Included in 21 CFR 2.125(g)(3)(ii), (g)(3)(iii), and (g)(3)(iv) are some of the criteria for removing an essential-use designation for individual active moieties marketed as ODS products and represented by one new drug application. They require, among other criteria, that supplies and product capacity for the non-ODS product(s) exist or will exist at levels sufficient to meet patient need; adequate U.S. postmarketing data are available for the non-ODS product; and patients who medically require the ODS product are adequately served by the non-ODS product(s) containing that active moiety and other available products. Section 2.125(g)(4)(ii) incorporates these criteria by cross-reference and requires that they be met prior to removing the essential-use designation for individual active moieties marketed as ODS products that are represented by two or more NDAs.

(Response) As stated in the 2002 final rule, we reviewed the text of the Clean Air Act, its legislative history, the text of the Montreal Protocol, and decisions by the Parties to the Protocol. FDA also further discussed its understanding of the Clean Air Act and the Protocol with the EPA. The Clean Air Act does not state specifically whether such essential-use exemptions may continue indefinitely or must terminate at some future time. However, the legislative history for section 604(d)(2) of the Clean Air Act makes clear that the exemption is only permitted for a limited time. Specifically, the Senate Conference Report for this section of the Clean Air Act states: The centerpiece of the stratospheric ozone protection program established by this title is the phase-out of production and consumption of all ODSs (136 Cong. Rec. S16895 at 16946 and 16947 (daily ed. Oct. 27, 1990)). These statements are consistent with the Montreal Protocol. The Preamble to the Protocol states that the Parties are: Determined to protect the ozone layer by taking precautionary measures to control equitably total global emissions of substances that deplete it, *with the ultimate objective of their elimination* (Preamble to the Montreal Protocol (emphasis added)). Decision IV/25 of the Parties to the Protocol also indicates that essential-use exemptions are temporary. This decision asks the Technology and Economic Assessment Panel to determine an estimated duration for each essential use, the steps necessary to ensure alternatives are available as soon as possible, and whether previously qualified essential uses should no longer qualify as essential. Thus, although it is true that there is no set date for termination of essential-use exemptions, it is also clear that the exemptions were intended to be limited in number and duration and were not intended to exist forever.

d. *Sufficiency of advisory committee meeting.* (Comment 30) BI argues that little public notice was provided for the 2005 PADAC meeting and the notice contained little guidance on public participation and did not seek specific public input. BI also argues that the straw poll conducted at the PADAC meeting did not take into account the status of BI's CFC-free Combivent development programs. BI claims that had the PADAC members been provided a more complete record upon which to base their opinions, a majority would have recommended continuation of Combivent Inhalation Aerosol's essentiality and rejected the proposed therapeutic alternatives.

(Response) As stated earlier in this document, FDA, after consultation with a relevant advisory committee and after holding an open public meeting, may remove an essential-use designation under section 2.125(g)(2) if it no longer meets certain criteria. FDA made clear in the 1999 rule proposing criteria for removing essential-use designations that before removing any essential-use designation, it would consult with an advisory committee and provide opportunity for public comment (64 FR 47719 at 47722). FDA published a notice in the **Federal Register** on May 10, 2005 (70 FR 24605), that the PADAC would be convening on July 14, 2005, to discuss the continued need for the essential-use designations of prescription drugs for the treatment of asthma and COPD. The notice further stated that interested persons could present data, information, or views, orally or in writing, on the issues pending before the committee. This notice provided sufficient time for those persons or companies with an interest in the essential-use designations of any moieties used in drugs that treat asthma or COPD to provide the committee members with any information they believed would be pertinent to the decision to remove or continue a designation. Therefore, we disagree with the assertion that little public notice was provided for the 2005 PADAC meeting and the notice contained little guidance on public participation and did not seek specific public input.

We also disagree with the assertion that PADAC members were not provided a complete record upon which to base their opinions. At the PADAC meeting, an FDA representative made a detailed presentation to committee members on the Montreal Protocol and the essential-use process and rulemakings, including identification and description of the current essential uses and their therapeutic alternatives, as well as the criteria for removing the essential-use designations. After the FDA presentation, committee members had the opportunity to ask clarifying questions, and additional presentations were made by an association representing manufacturers of MDIs, specific MDI manufacturers, and an interested person. Committee members had additional time to discuss the individual moieties after these presentations were made. We believe that the record demonstrates the PADAC was provided ample information on which to render a vote.

E. Effective date

In the proposed rule, we proposed an effective date for removal of the essential-use designations for all seven moieties of December 31, 2009, and we solicited comments on this proposed effective date. We noted in the proposed rule that, depending on the data presented to us during the course of the rulemaking, we may determine that it is appropriate to have different effective dates for different uses.

We did not receive any substantive comments on the proposed effective date for metaproterenol and nedocromil. Alupent Inhalation Aerosol and Tilade Inhaler have been discontinued by BI and King Pharmaceuticals, Inc., respectively. BI has informed us that any Alupent Inhalation Aerosols that may be in retail or wholesale stocks will have passed their expiration date by December 2009. Accordingly, we have determined that the appropriate effective date for the removal of the essential-use designations for metaproterenol and nedocromil is June 14, 2010.

We did not receive any substantive comments on the proposed effective date for triamcinolone, and cromolyn. To allow an adequate length of time for patients to transition to the therapeutic alternatives identified in this rule, we have determined that December 31, 2010, is an appropriate effective date for removing the essential-use designations for triamcinolone and cromolyn. The additional period ensures more time to disseminate information about the phase-out to patients to ensure an orderly transition that is protective of public health.

We received one comment regarding the effective date for flunisolide from Forest Laboratories, Inc., the exclusive distributor for Aerobid (flunisolide) Inhaler System via a licensing agreement with Roche Palo Alto, the NDA holder for Aerobid. Forest requests an 18-month delay in the effective date of the rule. In its comment, Forest states that a June 30, 2011, effective date would allow time for Forest to commercially produce and market its non-CFC flunisolide formulation, Aerospan Inhalation Aerosol. We have considered this request and have determined that a June 30, 2011, effective date is appropriate for removing the essential-use designation for flunisolide. The June 30, 2011, effective date will provide sufficient time for current Aerobid Inhaler System users to transition to the therapeutic alternatives including Aerospan Inhalation Aerosol. We also note that the June 30, 2011, effective date provides sufficient time for Forest to prepare for commercial distribution of Aerospan Inhalation Aerosol.

We received several comments on the effective date for Combivent Inhalation Aerosol and Maxair Autohaler. After

considering the comments, we were persuaded that December 31, 2013, rather than December 31, 2009, as proposed, is a more appropriate effective date for removing the essential-use designations for Combivent Inhalation Aerosol and Maxair Autohaler. The December 31, 2013, date provides additional time to disseminate information about the transition to Combivent Inhalation Aerosol and Maxair Autohaler users who may have multiple health conditions that may make it more difficult to transition, and allows these individuals more time to transition to appropriate non-CFC alternatives. It also allows sufficient time for manufacturers to increase production of albuterol HFA MDIs and ipratropium bromide HFA MDIs to ensure adequate supplies for patients. Finally, we believe a December 31, 2013, effective date gives sufficient time for the development of a non-CFC formulation of a combination product containing albuterol and ipratropium or a non-CFC formulation of pirbuterol and processing of an application for new drug approval. In our responses to the comments below, we further explain the basis for our decision to extend the effective date from that proposed for Combivent Inhalation Aerosol and Maxair Autohalers.

(Comment 31) We received many comments requesting that the effective date be delayed until a CFC-free Combivent Inhalation Aerosol is available and to ensure patients will continue to have access to Maxair Autohaler during the reformulation and regulatory review phases. BI requests that FDA refrain from removing the essential-use designation for Combivent Inhalation Aerosol and initiate a future rulemaking addressing Combivent Inhalation Aerosol once a non-CFC Combivent product has been developed and approved by the agency for marketing. Another comment suggests that FDA condition the effective date (and therefore the length of the transition period) on the submission of an NDA and reconsider the appropriateness and length of the date once the NDA has been submitted for review. Graceway recommends that the agency revisit the essential-use status of pirbuterol after December 2012 to ensure essential products are available and requests an effective date of December 31, 2015.

(Response) As stated above, we carefully evaluated the comments submitted in response to the proposed rule and have determined that an effective date of December 31, 2013, is appropriate for the removal of the essential-use designation for Combivent Inhalation Aerosol and Maxair Autohaler. We acknowledge that the presence of a non-CFC replacement for Combivent Inhalation Aerosol and Maxair Autohaler may be convenient for users. However, we note that a December 31, 2013, effective date allows a reasonable time to permit the development of a non-CFC replacement. Currently, we believe there are adequate non-CFC alternatives for Combivent Inhalation Aerosol available in the form of separate albuterol HFA MDIs and ipratropium bromide HFA MDIs. With respect to Maxair Autohaler, we believe adequate non-CFC alternatives exist in the form of Albuterol in HFA MDIs or in a nebulizer.

The effective date we are establishing for the removal of the essential-use designations for Combivent Inhalation Aerosol and Maxair Autohaler provides over 3 additional years for manufacturers to scale up production of albuterol HFA MDIs and ipratropium bromide HFA MDIs and will help ensure that there will be adequate supplies of the MDIs for patients. The effective date also provides over 3 years for patients and their health care providers to consider the different formulations of albuterol HFA MDI and levalbuterol HFA MDI and select the most appropriate therapeutic alternative. We are also permitting additional time for patients to transition from using a combination product to using two separate MDIs, to choose and adapt to a traditional press-and-breathe MDI, or to switch to using a nebulized solution.

We believe that educating patients and health care providers about the transition to other asthma treatments is very important to an orderly and safe transition of patients currently using Combivent Inhalation Aerosol and Maxair Autohaler, particularly for elderly patients, those with co-morbid conditions who are taking multiple medications, or those patients with coordination problems. The need to ensure that we have permitted sufficient time for patient education for transitioning from a Combivent Inhalation Aerosol or a Maxair Autohaler to an appropriate non-CFC substitute was an important factor in our decision to extend the proposed effective date in this final rule, to December 31, 2013. We will actively monitor the transition to CFC-free alternatives. Anyone who wishes to discuss a cooperative educational effort with DHHS and FDA should contact FDA or the Office of the Secretary of DHHS.

With respect to a conditional effective date for Combivent Inhalation Aerosol, we believe it is important to specify a date certain when Combivent Inhalation Aerosol can no longer be marketed so patients and their health care providers may transition to therapeutic alternatives in a timely and orderly manner. We also note that the December 31, 2013, effective date allows a reasonable time to permit the development and approval of a non-CFC replacement for Combivent Inhalation Aerosol.

We decline to exclude Combivent Inhalation Aerosol from the rulemaking, as requested by BI. As discussed elsewhere in this document, the United States is committed to phasing out the remaining essential-use designations in the context of the Montreal Protocol. We believe finalizing this rule now and setting an effective date for Combivent Inhalation Aerosol that provides over a 3-year transition affects the eventual transition in a manner that is consistent with our duty to protect the public health.

F. Conclusions

We conclude there are no substantial technical barriers to formulating flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil as products that do not release ODSs. The evidence presented to the agency during this rulemaking does not meet the high threshold required by the first criterion on substantial technical barriers. We therefore conclude that oral pressurized MDIs containing flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil are no longer essential uses of ODSs and will be removed from the list of essential uses in § 2.125(e) as of the effective dates specified in this rule.

V. Environmental Impact

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday. Under FDA's regulations implementing the National Environmental Policy Act (21 CFR part 25), an action of this type would require an environmental assessment under 21 CFR 25.31(a).

VI. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the final rule under Executive Order 12866 and 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 final rule is an economically significant regulatory action under 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. Because only one CFC MDI manufacturer may possibly be considered a small entity, and one single small entity among an industry of hundreds does not constitute a "substantial number" under the Regulatory Flexibility Act, the agency certifies that the final rule will not 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 $133 million, using the most current (2008) Implicit Price Deflator for the Gross Domestic Product. This final rule may result in a 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 final 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 Inhaler System) and MDIs delivering albuterol and ipratropium in combination (Combivent Inhalation Aerosol) will face higher prices because available substitutes cost more. In contrast, users of triamcinolone MDIs (Azmacort Inhalation Aerosol), metaproterenol MDIs (Alupent Inhalation Aerosol), pirbuterol MDIs (Maxair Autohaler), cromolyn sodium MDIs (Intal Inhaler), and nedocromil sodium MDIs (Tilade Inhaler) 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. In the transition, these consumers may also be inconvenienced by the need to become accustomed to using an alternative product.

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 the introduction of generic albuterol HFA MDIs to the market will eliminate price and spending increases resulting from this final 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 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 Inhalation Aerosol 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 an earlier rulemaking (70 FR 17168, April 4, 2005). The spending increases described here may therefore be viewed as costs of the larger transition away from CFC products, rather than costs resulting from this rule in particular. We cannot conclusively attribute these estimated spending increases to either the prior rule or this final rule. While table 1 provides the annual quantifiable effects after all moieties have been removed from the market, table 2 provides the total impacts, factoring in the staggered phase-out and using two different possibilities for the date of HFA patent expiration.

TABLE 1.—SUMMARY OF ANNUAL QUANTIFIABLE EFFECTS OF THE FINAL RULE AFTER ALL SEVEN MOIETIES ARE REMOVED FROM THE MARKET

Patient Days of Therapy Affected	Increased MDI Expenditures, in 2009 dollars	Possible Reduction in Days of Therapy Used (millions)	Reduced CFC Emissions From Phase-Out (tonnes)
300 million	$90–$280 million	0.20–4.2	310–365

TABLE 2.—SUMMARY OF IMPACTS FROM PHASE-OUT TO DATE OF HFA PATENT EXPIRATION

Date of HFA Patent Expiration	Possible Change in Use of Asthma and COPD Therapy (million days of therapy)	Discount Rate	Increases in Expenditures on CFC-based MDIs, Present Value in 2010 (billions)
2012	NA	3%	-$0.09 – -$0.04
		7%	-$0.09 – -$0.04

TABLE 2.—SUMMARY OF IMPACTS FROM PHASE-OUT TO DATE OF HFA PATENT EXPIRATION—Continued

Date of HFA Patent Expiration	Possible Change in Use of Asthma and COPD Therapy (million days of therapy)	Discount Rate	Increases in Expenditures on CFC-based MDIs, Present Value in 2010 (billions)
2017	0.33–14	3%	$0.16–$0.91
		7%	$0.12–$0.73

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

B. Need for Regulation and the Objective of this Rule

The objective of this final rule is to respond to the treaty requiring the United States to 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 ending the essential-use designation for ODSs used in MDIs containing triamcinolone, metaproterenol, pirbuterol, cromolyn sodium, nedocromil sodium, flunisolide, and albuterol and ipratropium in combination, because we have concluded 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 II.B.2 of this document. One hundred and ninety-six countries are now Parties to 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. 6). 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. 6).

A relevant aspect of the Montreal Protocol is that production of CFCs in any year by any country is 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 by consensus 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. 7). 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 estimated 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 $7 trillion in 2008 prices after adjusting for inflation between 1990 and 2008. 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 final 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 States

carried the diagnosis of COPD in 2007 (Ref. 8). 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. 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 in addition to 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 2007 NHIS, approximately 23 million adult patients in the United States reported they had asthma (Ref. 9). The prevalence of asthma decreases then increases with age, with the prevalence being 100 per 1,000 children ages 5–17 (5.3 million children) compared to 72 per 1,000 among adults ages 18–44 (8.0 million), 72 per 1,000 among adults ages 45–64 (5.5 million), and 75 per 1,000 among adults age 65 and over (2.7 million) (Ref. 9).

The NHIS reported that during 2007, about 12 million patients reported experiencing an asthma attack in the course of the previous year (Ref. 9, table 10). According to the National Ambulatory Medical Care Survey, in 2006 there were 1.2 million outpatient asthma visits to physician offices and hospital clinics and 1.7 million emergency room visits (Ref. 9, table 19). According to the National Center for Health Statistics, there were 444,000 hospital admissions for asthma in 2006 (Ref. 9, table 16) and 3,563 deaths (Ref. 9, table 1). The estimated direct medical cost of asthma (hospital services, physician care, and medications) was $14.7 billion (Ref. 9, table 20).

While the prevalence of asthma has been increasing in recent years, the CDC reports that the incidence of asthma (or the rate of new diagnoses) has remained fairly constant since 1997 (Ref. 10). 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. This phenomenon might indicate early successes by asthma intervention programs that include access to medications.

6. Current U.S. Market for CFC MDIs

For the 12-month period ending June 2009, we estimate that sales of these seven CFC MDIs provided roughly 300 million days of therapy, sufficient to treat roughly 800,000 COPD and asthma patients for a full year. We use 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. 11).

We calculate the average price per day of therapy for a CFC MDI as the total revenue derived from sales of that product in the 12 months ending June 2009, 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 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. 11)

CFC MDI	Non-ODS Alternatives	Price Premium per Day of Therapy	
		Maximum	Minimum
Aerobid Aerobid-M	QVAR PULMICORT TURBUHALER FLOVENT HFA ASMANEX TWISTHALER	$1.06	$0.34
Azmacort	QVAR PULMICORT TURBUHALER FLOVENT HFA ASMANEX TWISTHALER	-$1.10	-$1.82
Alupent	PROAIR HFA PROVENTIL HFA VENTOLIN HFA XOPENEX HFA	$0.34	-$0.31
Maxair	PROAIR HFA PROVENTIL HFA VENTOLIN HFA XOPENEX HFA	-$0.21	-$0.86

TABLE 3.—SUMMARY OF CFC MDIS, NON-ODS ALTERNATIVES, AND EXPECTED PRICE CHANGES PER DAY OF THERAPY (REF. 11)—Continued

CFC MDI	Non-ODS Alternatives	Price Premium per Day of Therapy	
		Maximum	Minimum
Intal	QVAR PULMICORT TURBUHALER FLOVENT HFA ASMANEX TWISTHALER	-$1.34	-$2.06
Tilade	QVAR PULMICORT TURBUHALER FLOVENT HFA ASMANEX TWISTHALER	N/A	N/A
Combivent	ATROVENT HFA + one of the following: PROAIR HFA PROVENTIL HFA VENTOLIN HFA XOPENEX HFA	$1.30	$0.65

Source: IMS Health, IMS National Sales Perspective (TM), 2009, extracted September 2009.

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 TURBUHALER, FLOVENT HFA, or ASMANEX TWISTHALER. The most expensive of these alternatives would cost roughly $1.10 cents less per day of therapy, and the least expensive would cost roughly $1.80 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 recent changes in prices of CFC MDIs did not differ systematically from the changes in prices of the proposed alternatives. For our Maxair calculations, we have added the annual purchase of a $30 spacer to the cost of switching to an alternative 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 2009, would increase 9 percent; if all users switched to the most expensive alternative therapy, the average price per day of therapy would increase 28 percent. These price differences represent differences in average ex-manufacturer prices across all distribution channels and do not incorporate differences introduced by retail markups or off-invoice discounts (Ref. 11).

It is not possible to attribute these estimated price increases exclusively to this final rule. These estimated price increases are driven almost entirely by the large population of Combivent users switching to both Atrovent Inhalation Aerosol 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. After 2003, the price of a day of Combivent therapy rose 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. The range of spending changes for Combivent therapy alone is $150 million to $300 million; excluding the effects of Combivent therapy, the range of spending changes is -$25 million to -$65 million.

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. Our recent data shows a decline in the use of the seven moieties to be phased out, so our low estimate may overstate the reduction in CFCs attributable to this final rule. The CFC MDI manufacturers requested roughly 365 tonnes of CFCs for production of the seven CFC MDIs for 2007, which we use for our high estimate.

D. Benefits and Costs of the Final 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 final 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. MDIs containing metaproterenol and nedocromil will be removed from the market June 14, 2010. MDIs containing triamcinolone and cromolyn will be removed from the market December 31, 2010. MDIs containing flunisolide will be removed from the market June 30, 2011. Those containing albuterol and ipratropium in combination and pirbuterol will be removed from the market December 31, 2013.

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 final 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.

Throughout this baseline analysis, we assume that sufficient inventories of CFCs are available to meet demand for these seven CFC MDIs through the date they lose their essential-use designation and that there will be sufficient therapeutic alternatives to meet demand after they are removed from the market.

However, in the absence of this final rule, the parties to the Montreal Protocol would still have the ability to restrict access to CFCs required for the manufacture of products using these seven moieties. This final rule, in establishing a timetable for phasing out these seven moieties, demonstrates a commitment to phasing out CFCs, which reduces the need for the parties to act on their own. In a sense, this final rule does not phase out these moieties, but attempts to establish a phase-out timetable preferable to the one that the parties to the Montreal Protocol might impose. The existence of a timetable imposed by the parties to the Montreal Protocol different from this final rule implies the costs detailed in the next section of this analysis will accrue, although perhaps at a different time, regardless of whether this final rule is enacted. The cost-benefit analysis presented here would then apply to the withdrawal of the CFC-containing products from the market rather than to the specific effects of the final rule.

2. Benefits of the Final Rule

The benefits of the final 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 to comply with the spirit of the Montreal Protocol, thereby potentially reducing future emissions of ODSs throughout the world.

Failure to enact this final rule would leave the timetable for phasing out these seven moieties in the hands of the parties to the Montreal Protocol. As the parties to the Montreal Protocol would see these drugs with therapeutic alternatives and no regulation in place to commit to their phase-out, their likely response would be to deny the provision of CFCs for their continued production and to do so in a way that did not provide for an adequate transition period.

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 final rule would ban marketing of two of the seven CFC MDIs after June 14, 2010, two more after December 31, 2010, one after June 30, 2011, and the remaining two after December 31, 2013.

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 nominating additional CFC production for 2010 through 2013. Therefore, we estimate the regulation will reduce CFC use by 310 to 365 tonnes per year after the end of 2013, a benefit that will continue indefinitely.

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 $7 trillion in 2008 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 apparently included in EPA's earlier estimate of benefits of the Clean Air Act.

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. 6). 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 $7 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 final 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 encourages other potential developers of ozone-safe technologies. Furthermore, a phase-out date would preserve expectations that the government protects incentives to research and develop ozone-safe and other new technologies.

Newly developed technologies to avoid ODS emissions have resulted in more environmentally "friendly" air conditioners, refrigerants, solvents, and propellants, but only after significant 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. 12).

These investments have resulted in several innovative products in addition to HFA MDIs. For example, breath-activated delivery systems, dose counters, dry-powder inhalers, 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 had adopted a later phase-out date, other Parties could attempt to delay their own control measures.

3. Costs of the Final Rule

The final rule would increase spending for needed medicines used to treat asthma and COPD. The social costs of the final rule include the health 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. 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 300 million days of therapy with 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, private, third-party, and public expenditures on inhaled medicines would increase by roughly $90 million to $280 million per year. These expenditure increases will be driven almost exclusively by Combivent users changing to both Atrovent and one of four available albuterol HFA products. With most, perhaps all, of this increase coming from estimated increased spending on albuterol HFA products, what happens to the prices of albuterol products will largely determine the change in overall spending. To the extent that expenditures rise, these higher costs 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 previous rulemaking (70 FR 17168, April 4, 2005) removed albuterol CFC MDIs, including generic albuterol CFC MDIs, from the market on December 31, 2008. If these cheaper generic albuterol MDIs had been able to remain on the market, the expected cost of switching from Combivent to both Atrovent and an albuterol HFA MDI would be essentially eliminated. Because expenditure increases resulting from this final 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. There are multiple patents listed in "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) for albuterol HFA MDIs, expiring from late 2009 to beyond 2020, creating a wide range of possible dates for generic entry. In the proposed rule, we assumed potential entry in 2010 and 2017. As moieties will not start to be removed from the market until June 14, 2010, generic entry in 2010 would eliminate almost all of the estimated costs of the transition. For this final rule, we use 2012 and 2017 for assumed entry of generic substitutes for current branded albuterol MDI products. One recent study predicted the introduction of a generic albuterol HFA MDI in 2012 (Ref. 13). For the year 2010, we include only the impact of Alupent and Tilade and for the years 2011 through 2013, we include in the analysis the impact of all moieties except Combivent and Maxair. Removing those five moieties from the market results in a change in annual private, third-party, and public expenditures of roughly -$20 million to -$50 million. Of course, unforeseen introduction of alternative therapies could reduce any 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 estimate that the average price increases resulting from market withdrawal of less expensive CFC MDIs could reduce use of inhaled therapy by a range of 0.20 to 4.2 million days annually, equivalent to roughly 0.5 to 12 thousand patient years of therapy. The impact of this reduction on health outcomes is too uncertain to quantify given available data. Some patients, however, respond to price increases for medications for chronic conditions in ways that may adversely affect their health.

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. 14). 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.

Another article found that, "a single inhaler containing both ipratropium and albuterol can increase compliance and decrease respiratory morbidity and charges over and above the effects achieved with separate inhalers for these 2 agents" (Ref. 5). The article found that access to single inhaler therapy was associated with a 17 percent reduction in monthly costs. This finding suggests that some current users of Combivent may suffer adverse health consequences because of compliance issues associated with using multiple inhalers. This preliminary evidence is insufficient to permit us to quantify 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 final 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 overall quantity of MDI and DPI therapy consumed may decline as a result of the increase in price. 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, estimated 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 anti-asthmatic drugs) to -0.22 (for anti-asthmatic 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. 14), 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. 14, p. 2348). Drugs included as anti-asthmatics in this study include anti-cholinergics, 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. To do so, we distinguish between the insured and the insured the uninsured. Based on IMS data, we estimate that asthma and COPD patients receive roughly 300 million days of therapy each year in the form of these seven CFC MDIs (Ref. 11). If users of these products are uninsured in proportion to the share of uninsured in the overall U.S. population (15.4 percent) (Ref. 15), then uninsured asthma and COPD patients receive roughly 46 million days of therapy [(300 million)x(15.4 percent)] in the form of these seven CFC MDIs, equivalent to roughly 126 thousand patient years.

Increases in the price of therapy, however, will mostly affect Combivent users with COPD. For Combivent users, we use the two major sources of decreased use, price increases for the uninsured and increased copayments for the insured, to calculate a very rough estimate of reduced patient days. According to the 2007 NHIS, 1.8 million individuals over the age of 65 have bronchitis and 1.7 million have emphysema. Data from the 2007 NHIS also suggest that approximately 31 percent of adults with emphysema also have chronic bronchitis (Ref. 8, Figure 2). Assuming this ratio holds for those over 65, there are about 3.1 million individuals over the age of 65 with COPD (3.6 million with either diagnosis—500,000 with both). This number of patients represents approximately 30 percent of the 10 million adults with COPD. Assuming all of those over 65 with COPD and about 85 percent of those under 65 have some form of drug insurance means that about 9.1 million of those with COPD are covered by drug insurance and 1.1 million are not. The uninsured estimate represents 10 percent of the population with COPD, so there would be approximately 23.7 million days of uninsured therapy for Combivent annually.

The midpoint of the high and low price increase estimates for Combivent is 27 percent. Assuming uninsured consumers face a 27 percent price increase and have an elasticity of 0.15, there would be among the uninsured an annual reduction in therapy of approximately 960,000 days after Combivent is removed from the market.

We do not know the characteristics of the prescription drug insurance held by those with COPD, but recognize that many of the 9.1 million insured face per-product copayments. These copayments will likely be a smaller fraction of income for the insured than are the price increases for the uninsured, so we assume the demand to be less elastic. Assuming 214 million annual days of insured therapy and an elasticity of 0.075, a 100 percent increase in the size of copayments would imply a 7.5 percent reduction in quantity demanded, or 16.0 million annual days of therapy foregone. Thus, a very rough estimate of a change in quantity of Combivent demanded in response to a price increase would be 17 million days of therapy (960,000 + 16.0 million). The appearance of a reformulated non CFC product combining albuterol and ipratroprium would avert the 16 million lost days of therapy potentially associated with the co-payment effect.

Finally, for an overall average estimate of the effects of the average price increases, we estimate that users of these seven CFC MDIs face an average price increase of between 9 and 28 percent per day of therapy after all seven moieties have been removed from the market, 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 for the twelve months ending June 2009. Excluding Combivent, users of the other six CFC MDIs would face prices somewhere between 15 and 41 percent lower. Excluding Combivent and Maxair, the users of the other five CFC MDIs would face prices between 17 and 39 percent lower.

We combine different measures of price elasticities (-0.15 to -0.33), the size of the uninsured CFC MDI market (15 to 46 million days of therapy), and estimated price increases (9 percent to 28 percent) to estimate the impact of average price increases on use. For example, assuming a price elasticity of -0.15 and 15 million days of therapy sold to the uninsured annually, a 9 percent price increase would reduce demand for inhaled therapy by the uninsured by roughly 200,000 days of therapy annually. By contrast, assuming a price elasticity of -0.33 and 46 million days of therapy sold to the uninsured annually, a 28 percent price increase would reduce uninsured demand by roughly 4 million days of therapy [(46 million days) x (-0.33 elasticity) x (28 percent price increase) = 4 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.

We recognize that as a result of this rulemaking, patients will lose access to products they prefer to use. This regulatory action will constrain consumption decisions, forcing patients to switch to substitute products they would not otherwise choose to consume, resulting in consumer welfare loss. We lack information to reliably estimate the social cost associated with the loss of preferred products, but we recognize such a cost exists.

4. Effects on Medicare and Medicaid

According to the 2006 Medical Expenditure Panel Survey (MEPS), Medicaid pays for 13.8 of the expenses attributable to COPD and asthma. Medicare pays for 30.6 percent of these expenses. Assuming these MEPS payment estimates for Medicaid and Medicare apply to the incremental expenses from switching to HFA MDIs, this final rule will increase annual Federal Medicaid spending between $12 and $39 million. We estimate that total spending by Medicare and Medicare beneficiaries will increase between $27 million to $87 million annually. The estimated annual impacts would apply after 2013, after all seven moieties have been phased out, and continue until the HFA technology loses patent protection. Where the impact would occur within these broad ranges would depend on the alternative therapies chosen.

For the year 2010, the change in Medicaid and Medicare spending would be associated with the costs of switching from Tilade and Alpuent. Medicaid spending would change somewhere between a decline of $50,000 and an increase of $60,000. The change in Medicare spending would be between a decline of $110,000 and an increase of $130,000. For the years 2011 through 2013, we include the impacts associated with all seven moieties except Maxair and Combivent. In those years, annual Medicaid spending would fall by an estimated $2.9 to $6.7 million. Medicare spending would decline between $6.3 and $15 million annually.

The present discounted value of the impact of the regulation on Medicaid expenses, assuming HFA patent expiration at the end of 2017 is from $20 million to $100 million at a 7 percent discount rate and from $20 million to $130 million at 3 percent. For Medicare, the present disounted value is from $40 million to $220 million at a 7 percent discount rate and from $50 million to $280 million at 3 percent. Assuming the HFA technology loses patent protection

at the end of 2012, the change in Medicaid expenditures is a present discounted -$12 million to -$5 million at 7 percent and -$13 million to -$5 million at 3 percent. For Medicare, the change in expenditures is -$30 million to -$10 million at a 7 percent discount rate and -$30 million to -$10 million at a 3 percent rate.

We are unable to estimate the extent to which Medicare cost 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 Medicare Part D plan they choose. Moreover, as we expect the characteristics of Medicare Part D and the types of plans chosen by beneficiaries to continue to evolve in coming years, past payment statistics may not reflect future conditions. These are rough estimates.

E. Alternative Phase-Out Dates

We consider the impacts of the alternative phase-out date of December 31, 2010, for the five moieties not already phased out at the end of 2010. The expense information in table 4 shows such an earlier phase-out would increase expenditures and further decrease the use of asthma and COPD therapy. Moreover, an earlier phase-out data 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. A phase-out date set too far in the future, however, would be incompatible with the timetable set by the Montreal Protocol. This leaves a narrow window for consideration.

TABLE 4.—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 2009 (billions)
2012	0.40–8.5	3%	$0.17–$0.54
		7%	$0.16–$0.51
2017	1.4–30	3%	$0.55–$1.77
		7%	$0.48–$1.53

F. Sensitivity Analyses

The estimated impacts of this final rule summarized in table 5 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 final 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 15 million to 46 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 9 to 28 percent per day of therapy, depending on whether they switch to the most expensive or least expensive of 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 final 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 300 million days of therapy in the form of CFC MDIs annually, and that prices will increase 9 to 28 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 15 to 41 percent decrease, depending on whether they switch to the most expensive or least expensive of available alternatives. If we also exclude Maxair, expected price effects range from a 17 to 39 percent decrease.

G. Conclusion

Limits in available data prevent us from quantifying the costs and benefits of the final 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 final rule, that make such cooperation effective. As discussed above in detail, the benefits of the final 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 final 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.

TABLE 5.—SUMMARY ACCOUNTING TABLE

Category	Primary Estimate	Low Estimate	High Estimate	Units			Notes
				Year Dollars	Discount Rate	Period Covered	
Benefits							

TABLE 5.—SUMMARY ACCOUNTING TABLE—Continued

Category	Primary Estimate	Low Estimate	High Estimate	Units			Notes
				Year Dollars	Discount Rate	Period Covered	
Annualized Quantified					7%	Annual	Reduction of CFC emissions by 310–365 tonnes.
					3%	Annual	
Qualitative							Compliance with Montreal Protocol. Increased investment in environmentally friendly technologies. International cooperation.
Costs							
Annualized Monetized $millions/year		-$12 million–-$4.9 million	$16 million–$98 million	2010	7%	Annual	Consumers lose access to therapies that, but for this action, would have been their preferred products. Uses 10-year annualization. Range of estimates captures underlying uncertainty. Low estimate assumes 2012 HFA patent expiration. High estimate assumes 2017 HFA patent expiration. No central tendency. These costs are transfers from payers to drug companies and are largely attributable to the withdrawal of generic albuterol which occurred under another rulemaking.
		-$11 million–-$4.5 million	$19 million–$100 million	2010	3%	Annual	
Qualitative							Consumers may respond to higher prices by forgoing medication, which could result in adverse health outcomes.
Transfers							

TABLE 5.—SUMMARY ACCOUNTING TABLE—Continued

Category	Primary Estimate	Low Estimate	High Estimate	Units			Notes
				Year Dollars	Discount Rate	Period Covered	
Federal Annualized Monetized $millions/year		-$5.2 million–-$2.2 million	$6.9 million–$43 million	2010	7%	Annual	Medicare plus Medicaid, 10-year annualization. Low estimate assumes 2012 HFA patent expiration. High estimate assumes HFA patent expires end of 2017. Rough approximation.
		-$4.7 million–-$2.0 million	$8.3 million–$46 million	2010	3%	Annual	
From/To	From: U.S. Government			To: Drug manufacturers			
Effects							
Small Business							A single drug manufacturer may meet threshold for small business. Affected entities are otherwise not small.

VII. 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. For purposes of determining whether a substantial number of small entities are affected by this rule, the industry includes all manufacturers of pharmaceutical products in the United States. According to the U.S. Department of Commerce, the industry of "pharmaceutical preparation manufacturers" includes 901 establishments controlled by 723 companies (Ref. 3). Of these establishments, 822 have fewer than 500 employees.

This rule significantly affects firms that manufacture the seven CFC MDIs. Because there is, at most, a single small CFC MDI manufacturer that would be significantly affected by the rule, in an industry with hundreds of small entities, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Additional discussion of our analysis can be found in section IV, Comments on the 2007 Proposed Rule, which responds to Comment 16 submitted by Graceway.

VIII. The Paperwork Reduction Act of 1995

This final 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.

IX. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has 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. Accordingly, the agency has 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.

X. 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.

1. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR–3), NIH Publication No. 07–4051, Bethesda, MD, U.S. Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program, 2007, available at *http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm*.

2. Hess, Dean R., "Aerosol Delivery Devices in the Treatment of Asthma," *Respiratory Care*, 53, 2008: 699–723.

3. United States, Department of Commerce, Census Bureau; Economics and Statistics Administration, *Pharmaceutical Preparation Manufacturing*: 2002, Washington, D.C., U.S. Census Bureau, 2004.

4. Envrios March, *Study on the Use of HFCs for Metered Dose Inhalers In the European Union*: Final report following submission to the ECCP (European Commission Climate Change Policy Group), Republic of Geneva: International Pharmaceutical Aerosol Consortium, December 2000.

5. Chrischilles, Elizabeth, Daniel Gilden, Joanna Kubisiak, Linda Rubenstein, and Hemal Shah, "Delivery of Ipratropium and Albuterol Combination Therapy for Chronic Obstructive Pulmonary Disease: Effectiveness of a Two-in-one Inhaler Versus Separate Inhalers," *The American Journal of Managed Care*, 8 (2002): 902–11.

6. United Nations Environmental Programme, Production and Consumption of Ozone-Depleting Substances: 1986–2004, 2005.

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

8. American Lung Association, "Trends in COPD (Chronic Bronchitis and Emphysema): Morbidity and Mortality," Epidemiology & Statistics Unit, Research and Scientific Affairs, February 2010.

9. American Lung Association, "Trends in Asthma Morbidity and Mortality,"

Epidemiology & Statistics Unit, Research and Scientific Affairs, January 2009.

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

11. Analysis completed by FDA based on information provided by IMS Health, IMS National Sales Perspective (TM), 2009, extracted September 2009. These data can be purchased from IMS Health. Please send all inquiries to: IMS Health, Attn: Brian Palumbo, Account Manager, 660 West Germantown Pike, Plymouth Meeting, PA 19462.

12. Rozek, R. P., and E. R. Bishko, "Economic 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).

13. Hendeles, L. G, L. Colice, and R. J. Meyer, "Withdrawal of Albuterol Inhalers Containing Chlorofluorocarbon Propellants," *New England Journal of Medicine*, 356:1344–1351, March 29, 2007.

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

15. DeNavas-Walt, C., B. D. Proctor, and J. C. Smith, U.S. Census Bureau, Current Population Reports, P60–236(RV), Income, Poverty, and Health Insurance Coverage in the United States: 2008, Table 7, p. 21, 2009.

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, 21 CFR part 2 is 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. Effective June 14, 2010, in § 2.125, remove and reserve paragraphs (e)(2)(iii) and (e)(4)(vii).

§ 2.125 [Amended]

■ 3. Effective December 31, 2010, in § 2.125, remove and reserve paragraphs (e)(1)(v) and (e)(4)(iv).

§ 2.125 [Amended]

■ 4. Effective June 30, 2011, in § 2.125, remove and reserve paragraph (e)(1)(iii).

§ 2.125 [Amended]

■ 5. Effective December 31, 2013, in § 2.125, remove and reserve paragraphs (e)(2)(iv) and (e)(4)(viii).

Dated: April 8, 2010.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2010–8467 Filed 4–13–10; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF THE TREASURY

31 CFR Part 103

RIN 1506–AA93

Financial Crimes Enforcement Network; Amendment to the Bank Secrecy Act Regulations; Defining Mutual Funds as Financial Institutions.

AGENCY: Financial Crimes Enforcement Network ("FinCEN"), Treasury.

ACTION: Final rule.

SUMMARY: FinCEN is issuing this final rule to include mutual funds within the general definition of "financial institution" in regulations implementing the Bank Secrecy Act ("BSA"). The final rule subjects mutual funds to rules under the BSA on the filing of Currency Transaction Reports ("CTRs") and on the creation, retention, and transmittal of records or information for transmittals of funds. Additionally, the final rule amends the definition of mutual fund in the rule requiring mutual funds to establish anti-money laundering ("AML") programs. The amendment harmonizes the definition of mutual fund in the AML program rule with the definitions found in the other BSA rules to which mutual funds are subject. Finally, the final rule amends the rule that delegates authority to examine institutions for compliance with the BSA. The amendment makes it clear that FinCEN has not delegated to the Internal Revenue Service the authority to examine mutual funds for compliance with the BSA, but rather to the U.S. Securities and Exchange Commission ("SEC") as the federal functional regulator of mutual funds.

DATES: Effective Date: This rule is effective May 14, 2010.

Compliance Date: Mutual funds must comply with 31 CFR 103.33 by January 10, 2011. The compliance date for all other aspects of this rulemaking is the same as the effective date.

FOR FURTHER INFORMATION CONTACT: The FinCEN regulatory helpline at (800) 949–2732 and select Option 6.

SUPPLEMENTARY INFORMATION:

I. Background

A. Statutory Provisions.

The Bank Secrecy Act, Public Law 91–508, codified as amended at 12 U.S.C. 1829b, 12 U.S.C. 1951–1959, and 31 U.S.C. 5311–5314; 5316–5332, authorizes the Secretary of the Treasury ("Secretary") to issue regulations requiring financial institutions to keep records and file reports that are determined to have a high degree of usefulness in criminal, tax, and regulatory investigations or proceedings, or in the conduct of intelligence or counter-intelligence activities, including analysis, to protect against international terrorism, and to implement anti-money laundering programs and compliance procedures.[1] Regulations implementing the BSA appear at 31 CFR part 103. The authority of the Secretary to administer the BSA has been delegated to the Director of FinCEN.

The definition of "financial institution" in the BSA includes investment companies.[2] The Investment Company Act of 1940, codified at 15 U.S.C. 80a–1 *et seq.* (the "Investment Company Act"), defines "investment company"[3] and subjects investment companies to regulation by the SEC.

B. Overview of Current Regulatory Provisions.

Regulations implementing the BSA currently apply only to investment companies that are "open-end companies," as the term is defined in the Investment Company Act. More commonly known as mutual funds, open-end companies are the predominant type of investment company. Open-end companies are management companies that offer or have outstanding securities that are redeemable at net asset value.[4]

Although FinCEN has issued individual rules that apply to mutual funds,[5] FinCEN has not included

[1] Language expanding the scope of the BSA was added by the Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001 ("USA PATRIOT Act"), Public Law 107–56.

[2] 31 U.S.C. 5312(a)(2)(I).

[3] *See* 15 U.S.C. 80a–3.

[4] 15 U.S.C. 80a–4; 15 U.S.C. 80a–5(a)(1); 15 U.S.C. 80a–2(a)(32). Face-amount certificate companies and unit investment trusts are excluded from the definition of "management company." 15 U.S.C. 80a–4(3).

[5] *Anti-Money Laundering Programs for Mutual Funds,* 67 FR 21117 (April 29, 2002); *Customer Identification Programs for Mutual Funds,* 68 FR 25131 (May 9, 2003); *Amendment to the Bank Secrecy Act Regulations—Requirement That Mutual Funds Report Suspicious Activity,* 71 FR 26213 (May 4, 2006); *Anti-Money Laundering Programs; Special Due Diligence Programs for Certain Foreign Accounts,* 71 FR 496 (Jan. 4, 2006); *Anti-Money*

Continued