other law, are not applicable.[12] Finally, these amendments do not contain any collection of information requirements as defined by the Paperwork Reduction Act of 1995, as amended.[13]

III. Cost Benefit Analysis

The Commission is sensitive to the costs and benefits imposed by its rules. The rule amendments the Commission is adopting today re-delegate functions from the Associate Executive Director of OFIS to the Director of OCIE and the Secretary of the Commission to reflect the transfer of OFIS's responsibilities to OCIE and the Office of the Secretary. The re-delegation will update the Commission's rules to accurately reflect that OCIE and the Office of the Secretary are performing functions previously performed by OFIS. The Commission does not believe that the rule amendments will impose any costs on non-agency parties, or that if there are costs, they are negligible.

IV. Consideration of Burden on Competition

Section 23(a)(2) of the Securities Exchange Act of 1934 (''Exchange Act'') requires the Commission, in making rules pursuant to any provision of the Exchange Act, to consider among other matters the impact any such rule would have on competition. The Commission does not believe that the amendments that the Commission is adopting today will have any impact on competition.

V. Statutory Basis

The amendments to the Commission's delegations are being adopted pursuant to statutory authority granted to the Commission, including Section 4A of the Exchange Act.

VI. Text of Final Amendments

List of Subjects in 17 CFR Part 200

Administrative practices and procedures, Authority delegations (Government agencies).

■ For the reasons set out in the preamble, Title 17, Chapter II of the Code of Federal Regulations is amended as follows:

PART 200—ORGANIZATION; CONDUCT AND ETHICS; AND INFORMATION AND REQUESTS

Subpart A—Organization and Program Management

■ 1. The authority citation for part 200 subpart A continues to read in part as follows:

Authority: 15 U.S.C. 77o, 77s, 77sss, 78d, 78d–1, 78d–2, 78w, 78*ll*(d), 78mm, 80a–37, 80b–11, and 7202, unless otherwise noted.

* * * * *

■ 2. Amend § 200.30–7 by redesignating paragraph (c) as paragraph (d).

■ 3. Section 200.30–11(e) is redesignated as § 200.30–7(c).

■ 4. Amend § 200.30–18 by redesignating paragraph (j) as paragraph (m).

■ 5. Section 200.30–11 paragraphs (a), (b), and (c) are redesignated as § 200.30–18 paragraphs (j), (k), and (l).

■ 6. Remove and reserve § 200.30–11.

By the Commission.

Dated: November 13, 2008.

Florence E. Harmon,

Acting Secretary.

[FR Doc. E8–27403 Filed 11–18–08; 8:45 am]

BILLING CODE 8011–01–P

[12] 5 U.S.C. 601–12.

[13] 44 U.S.C. 3501–20.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 2

[Docket No. FDA–2007–N–0314] (formerly 2007N–0262)

RIN 0910–AF92

Use of Ozone-Depleting Substances; Removal of Essential-Use Designation (Epinephrine)

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 designation for epinephrine 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 epinephrine as a product that does not release ODSs, and therefore epinephrine would no longer be an essential use of ODSs as of December 31, 2011. Epinephrine MDIs containing an ODS cannot be marketed after this date.

DATES: This rule is effective December 31, 2011.

ADDRESSES: For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket number(s), found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Martha Nguyen or Michelle Bernstein, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6224, Silver Spring, MD 20993–0002, 301–796–3601.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Introduction and Highlights of the Rule

On September 20, 2007, FDA published a proposed rule in the **Federal Register** (72 FR 53711) (the proposed rule), proposing to remove the essential-use designation for epinephrine MDIs. Epinephrine MDIs containing chlorofluorocarbons (CFCs) or other ODSs cannot be marketed without an essential-use designation. There are three criteria that must all be met for epinephrine MDIs to retain their essential-use designation. For epinephrine MDIs to retain their essential-use designation, we must find that:

1. Substantial technical barriers exist to formulating the product without ODSs;
2. The product will provide an otherwise 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 otherwise unavailable important public health benefit.

In the proposed rule, we tentatively found that no substantial technical barriers exist to formulating an epinephrine MDI without ODSs and that the release of ODSs into the atmosphere from over-the-counter (OTC) epinephrine MDIs is cumulatively significant. After considering the information received at a December 5, 2007, public meeting and written comments submitted in response to the proposal, FDA has concluded that there are no substantial technical barriers to formulating epinephrine as a product that does not release ODSs, and therefore epinephrine no longer meets the criteria to be an essential use of ODSs. In addition, we had proposed an effective date for this rule of December 31, 2010. However, in response to the public input received in this rulemaking, we have determined that the appropriate effective date for the removal of the essential-use designation for epinephrine MDIs is December 31, 2011. We will discuss our determinations on the criteria and the effective date in section V 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 Earth's surface and extends up to about 50 km (31 miles) altitude. Within the stratosphere, there is a zone about 15 to 40 km (10 to 25 miles) above the Earth's surface in which ozone is relatively highly concentrated. This zone in the stratosphere is generally called the ozone layer. Once in the stratosphere, CFCs are gradually broken down by strong ultraviolet light, releasing chlorine atoms that then deplete stratospheric ozone. Depletion of stratospheric ozone by CFCs and other ODSs allows more ultraviolet-B (UV–B) radiation to reach the Earth's surface, where it increases skin cancers and cataracts, and damages some marine organisms, plants, and plastics.

B. Regulation of ODSs

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

1. The 1978 Rules

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

The 1978 rule prohibited the use of CFCs as propellants in self-pressurized containers in any food, drug, medical device, or cosmetic. As originally published, the rule listed five essential uses exempt from the ban. The third listed essential use was for ''[m]etered-dose adrenergic bronchodilator human drugs for oral inhalation.'' This use describes epinephrine MDIs.

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

2. The Montreal Protocol

On January 1, 1989, the United States became a Party to the Montreal Protocol on Substances that Deplete the Ozone Layer (Montreal Protocol) (September 16, 1987, 26 I.L.M. 1541 (1987)), available at *http://www.unep.org/ozone/pdfs/Montreal-Protocol2000.pdf*.[1] 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 192 Parties to this treaty.[2] When it

[1] 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**.

[2] 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

Continued

joined the treaty, the United States committed to reducing production and consumption of certain CFCs to 50 percent of 1986 levels by 1998 (Article 2(4) of the Montreal Protocol). It also agreed to accept an ''adjustment'' procedure, by which, following assessment of the existing control measures, the Parties could adjust the scope, amount, and timing of those control measures for substances already subject to the Montreal Protocol. As the evidence regarding the impact of ODSs on the ozone layer became stronger, the Parties used this adjustment procedure to accelerate the phase-out of ODSs. At the fourth Meeting of the Parties to the Montreal Protocol, held at Copenhagen in November 1992, the Parties adjusted Article 2 of the Montreal Protocol to eliminate the production and importation of CFCs by January 1, 1996, by Parties that are developed countries (Decision IV/2).[3] 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, the Parties may make such an essential-use decision by a two-thirds majority vote, 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 chronic obstructive pulmonary disease (COPD). The decision on whether the use of CFCs in MDIs is ''essential'' for purposes of the Montreal Protocol turns on whether ''(1) It is necessary for the 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 the Parties that are developed countries to present an initial national or regional transition strategy by January 31, 1999 (Montreal, Canada, 1997).
- Decision XII/2 elaborated on the content of national or regional transition strategies required under Decision IX/19 and indicated that any MDI for the treatment of asthma or COPD approved for marketing after 2000 would not be an ''essential use'' unless it met the criteria laid out by the Parties for essential uses (Ouagadougou, Burkina Faso, 2000).
- Decision XIV/5 requested that each Party report annually the quantities of CFC and non-CFC MDIs and dry-powder inhalers (DPIs) sold or distributed within its borders and the approval and marketing status of non-CFC MDIs and DPIs. Decision XIV/5 also noted ''with concern the slow transition to CFC-free metered-dose inhalers in some Parties'' (Rome, Italy, 2002).
- Decision XV/5 states that, at the 17th Meeting of the Parties (in December 2005) or thereafter, no essential uses of CFCs will be authorized for Parties that are developed countries, unless the Party requesting the essential-use allocation has submitted an action plan. 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[4] (Nairobi, Kenya, 2003).
- Decision XVII/5 states that Parties that are developed counties should provide a date to the Ozone Secretariat[5] 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 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),[6] 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

Montreal Protocol may be found on the United Nations Environment Programme's Web site at *http://ozone.unep.org/Meeting_Documents/mop*.

[3] 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.

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

[5] 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.

[6] 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).

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 (21 CFR 2.125).

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

5. FDA's 2002 Regulation

In the 1990s, we decided that § 2.125 required revision to better reflect our obligations under the Montreal Protocol, the 1990 amendments, and EPA's 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[7] 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.

[7] 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, albuterol, as opposed to the active ingredient, which, using the same example, would be albuterol sulfate. 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 PROVENTIL HFA (among others). In describing material from treatises, journals, and other non-FDA approved publications, we will generally follow the usage in the original publication.

III. Epinephrine

Epinephrine is a short-acting adrenergic bronchodilator used in the treatment of asthma. A new drug application (NDA) for OTC epinephrine MDIs was approved in 1956. Epinephrine was included in the 1978 rule under the provision designating ''[m]etered-dose adrenergic bronchodilator human drugs for oral inhalation'' as an essential use. Approved NDAs for OTC epinephrine MDIs are currently held by Wyeth Consumer Healthcare (Wyeth) and Armstrong Pharmaceuticals, Inc. (Armstrong) (a subsidiary of Amphastar Pharmaceuticals, Inc.). Wyeth markets its OTC epinephrine MDIs as PRIMATENE MIST, while Armstrong labels their product as ''house brands'' for certain retail pharmacies. Epinephrine MDIs are the only MDIs for treatment of asthma (or any other disease) that are approved for OTC use.[8] Customers do not need a prescription from a health care provider to purchase OTC epinephrine MDIs. Wyeth has estimated that 2 to 3 million people with asthma use OTC epinephrine MDIs.[9] Based on the 2005 National Health Interview Survey (NHIS), the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS) has estimated that 7.7 percent of the U.S. population currently has asthma (Ref. 1). Using an estimate of the U.S. population of 300 million,[10] we can estimate that approximately 23 million people in the United States currently have asthma.

Epinephrine is also an active ingredient in many other drug products. For example, it is used in a self-

[8] The OTC monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products permits OTC marketing of epinephrine in a hand-held rubber nebulizer for use in the treatment of asthma (21 CFR part 341). While this product did not use CFCs, all of the information available to us shows that such products are no longer marketed. The OTC monograph for Cold, Cough, Allergy, Bronchodilator, and Antiashthmatic Drug Products permits OTC marketing of oral dosage forms of ephedrine. Ephedrine is not available in an MDI. In addition, OTC ephedrine products have a slower onset of action than epinephrine MDIs, and therefore they cannot be considered a suitable alternative to OTC epinephrine MDIs.

[9] This information was presented at a joint committee meeting of the Nonprescription Drug Advisory Committee and Pulmonary-Allergy Drugs Advisory Committee (NDAC/PADAC) held on January 24, 2006 (meeting transcript p. 51, Wyeth slide 19). The transcript of the NDAC/PADAC meeting, slides used in presentations made at the joint meeting, and written material presented to the committees for the meeting may be found at *http://www.fda.gov/ohrms/dockets/ac/cder06.html*.

[10] The U.S. Census' estimate of the U.S. Population was 299,948,296 as of October 10, 2006, 1804 GMT, with an estimated net increase in the population of 1 person every 11 seconds. See *http://www.census.gov/population/www/popclockus.html*.

injectable dosage form for treatment of severe allergic reactions. EPIPEN is a specific example of epinephrine in this dosage form. This rulemaking does not affect the availability of these drug products. It only affects OTC epinephrine MDIs, which contain CFCs.

IV. 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 are reviewing the essential-use designation for epinephrine under that authority. The process for removing the essential-use designation for such a drug must include a consultation with a relevant advisory committee and an open public meeting, in addition to a proposed rule and a final rule. The criterion established for removing the essential use in such circumstances is that it no longer meets the criteria specified in revised § 2.125(f) for adding a new essential use (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 opposed to ''or''), failure to meet any single criterion results in a determination that the use is not essential.

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 than 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 January 24, 2006, we convened a joint meeting of the Nonprescription Drug Advisory Committee (NDAC) and the Pulmonary and Allergy Drugs Advisory Committee (PADAC) on the essential-use status of OTC MDIs containing epinephrine. (NDAC/PADAC meeting).[11] Presentations were made by representatives of Wyeth Consumer Healthcare (Wyeth), two patient advocacy and public policy groups, and physician organizations. With regard to the criteria for removing the epinephrine essential-use designation, a presenter from Wyeth expressed concern about reformulating an epinephrine product without ODSs; however, no specific technical barriers to reformulation efforts were presented. In addition, some information on the therapeutic benefits of epinephrine CFC MDIs was presented and discussed at length by Wyeth, but many on the panel questioned the information presented, and the consensus opinion was that epinephrine CFC MDIs present no significant therapeutic benefit and no advantage over albuterol MDIs.

Opinions concerning the public health benefits of having an OTC MDI were also expressed, such as the convenience of having an OTC MDI for asthma. Some participants believed that a significant number of people with asthma do not have adequate access to health care, and a significant number of these people with asthma use OTC epinephrine MDIs. They asserted that many of these people with asthma who use OTC epinephrine MDIs do so because of barriers to obtaining health care. One speaker from a patient advocacy organization expressed the point that the longer duration of effect of albuterol and levalbuterol (and other newer prescription drugs that do not release ODSs) means that, while these drugs are more expensive per MDI and per dose, they may be cheaper than OTC epinephrine MDIs when the price is calculated for the number of inhalations needed per day. No data were provided, however, to support this assertion.

Much of the discussion at the NDAC/PADAC meeting focused on the issue of whether the risks of self-treatment of asthma outweigh the public health benefits that OTC epinephrine MDIs may provide. Issues considered were whether asthma was being properly diagnosed and treated by purchasers of OTC epinephrine CFC MDIs. Seven of the joint committee members recommended that epinephrine be retained as an essential use, while eleven members recommended that the essential-use designation be removed. The proposed rule contains a more extensive discussion of the NDAC/PADAC meeting and the views that were expressed at the meeting.

On December 5, 2007, following publication of the proposed rule, we held the required open public meeting to discuss the issues involved in removing the essential-use designation for epinephrine MDIs (see the **Federal Register** of November 8, 2007 (72 FR 63141)). Presentations were made by a representative of Amphastar Pharmaceuticals and Armstrong (a wholly owned subsidiary of Amphastar, which manufactures and distributes epinephrine CFC MDIs) and by a patient advocacy organization. The Armstrong representative stated that Armstrong did not oppose the proposal to eliminate the essential-use status for epinephrine, but requested postponing the effective date until December 31, 2011, to allow sufficient time for development and approval of an HFA-propelled epinephrine MDI before the CFC-containing MDI is phased out. The representative further stated that Armstrong anticipates being able to successfully develop and receive approval for a non-ODS epinephrine product by the beginning of 2011 and begin marketing by the end of 2011. The representative stated that removing OTC epinephrine from the market and attempting to switch patients to prescription medications will, in Armstrong's view, have significant costs and health consequences, which can be avoided by extending the effective date to allow time for a non-ODS OTC epinephrine product to be developed before the current product is phased out.

The patient advocacy organization presented results of two surveys, one directed to patients and the other

[11] The transcript of the NCPAC/PADAC meeting, slides used in presentations made at the joint meeting, and written material presented to the committees for the meeting may be found at *http://www.fda.gov/ohrms/dockets/ac/cder06.html*.

directed to medical professionals, on the essential-use status of OTC epinephrine. This organization found that the results demonstrated that CFC-propelled OTC epinephrine does not present a public health benefit worthy of continued essential-use exemption. In summary, medical professionals surveyed did not recommend the use of OTC epinephrine because it is an antiquated therapy, does not keep patients out of the emergency room or hospital, and asthma should be treated by a medical professional. According to the patient advocacy organization, the results of the patient survey showed that many patients do not have an appreciation for the seriousness of their condition and that the OTC drug is not keeping patients out of the emergency room or hospital. They also showed that patients and parents of pediatric patients overwhelmingly do not think removal of OTC epinephrine will seriously affect them. Input from the open public meeting is considered and discussed in section V together with the written comments that were submitted in response to the proposed rule.

V. Comments on the 2007 Proposed Rule

We received 32 written and electronic comments in response to the proposed rule. They were submitted by consumers, health care providers, a patient advocacy group, professional groups, manufacturers, an international governmental organization, and industry organizations. The speakers who participated in the open public meeting on December 5, 2007, also submitted written comments. In the discussion that follows, we address all the comments submitted in response to this rulemaking, 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 essential-use designation for the CFC-containing epinephrine 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 otherwise 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 otherwise unavailable important public health benefit. As discussed in the proposed rule, the failure to meet any one of these criteria must result in our determination that the use is not essential.

A. Do Substantial Technical Barriers To Formulating Epinephrine Products Without ODSs Exist?

We proposed to find that there are no technical barriers to formulating epinephrine MDIs without ODSs (72 FR 53711 at 53718). As noted in the 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 looked at the results of reformulation efforts for similar products, as well as statements made about the manufacturer's particular efforts to reformulate their product or products.

We did not receive any comments disagreeing with this tentative conclusion or otherwise addressing the conclusion in any substantive way. Indeed, in the context of its request for an effective date of December 31, 2011, discussed elsewhere in this document, the manufacturer of OTC epinephrine MDIs submitted comments suggesting that it would be ready to commercially produce and legally distribute, and have the capacity to meet current market demand for, a non-CFC alternative epinephrine MDI by 2011.

As noted in the proposed rule, as of this time, 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.[12] HFA MDIs have been formulated with both suspensions and solutions. Albuterol and levalbuterol are close chemical analogs of epinephrine. Given the chemical similarity between them and the success with reformulating albuterol (as albuterol sulfate in PROAIR HFA, PROVENTIL HFA, and VENTOLIN HFA) and levalbuterol (as levalbuterol tartrate in XOPENEX HFA), there appears to be no technical reason why epinephrine cannot be successfully reformulated into an HFA MDI. Therefore, after consideration of the public comments on the issue, we finalize our tentative conclusion that there are no technical barriers to the development of a non-ODS epinephrine product.

B. Do OTC Epinephrine MDIs Provide an Otherwise Unavailable Important Public Health Benefit?

In the proposed rule, we solicited comments on the public health benefits of OTC epinephrine MDIs (72 FR 53711 at 53718). 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.'' A petitioner 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). 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.''

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 exist for everyone using the CFC MDI, we can determine that the CFC MDI does not provide an otherwise

[12] 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 products in the United States, but fenoterol HFA MDIs and formoterol HFA MDIs have been approved in several foreign countries.

unavailable important public health benefit. In determining whether everyone is adequately served by the therapeutic alternatives, in the case of epinephrine MDIs, we take into consideration the fact that they are marketed OTC, while the therapeutic alternatives for epinephrine MDIs are prescription drugs. Because we have reached a conclusion that there are no substantial technical barriers to formulating epinephrine into a non-ODS product, we do not believe it is necessary to reach a conclusion on the public health benefits of OTC epinephrine MDIs. However, we received several comments in response to the proposed rule addressing the public health benefits of OTC epinephrine MDIs, and we believe it is appropriate to address the public health benefits in light of these comments.

1. Does Epinephrine Provide a Greater Therapeutic Benefit Than Similar Adrenergic Bronchodilators?

(Comment 1) Several comments from epinephrine users stated that their experience indicates that epinephrine CFC MDIs are more effective than other asthma MDIs, including HFA MDIs, and that there are no alternatives.

(Response) Albuterol and epinephrine are both adrenergic bronchodilators. Epinephrine is a non-selective beta adrenergic bronchodilator. Other available bronchodilators, including albuterol, are selective beta-2 adrenergic bronchodilators. Bronchodilation occurs primarily through stimulation of the beta-2 adrenergic receptor. Albuterol MDIs are therapeutic alternatives to OTC epinephrine MDIs and are, by far, the most widely prescribed short-acting bronchodilators. We are not aware of any data that support the commenter's contention that albuterol inhalers are not an appropriate alternative for epinephrine inhalers.

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 as a replacement for ODSs, which does not affect stratospheric ozone. The consensus at the NDAC/PADAC meeting, held prior to publication of the proposed rule, was that OTC epinephrine MDIs presented no significant therapeutic advantage over albuterol MDIs (72 FR 53711 at 53719). In addition, we are not aware of any adequate and well-controlled studies which support the commenters' view that epinephrine CFC MDIs are more effective than other asthma MDIs, including HFA MDIs.

(Comment 2) One comment stated that the OTC epinephrine CFC MDI is the fastest acting [asthma] inhaler.

(Response) Prior to publishing the proposed rule, we were presented with clinical data indicating that OTC epinephrine MDIs may be slightly quicker to onset of action than albuterol MDIs, although they have a significantly shorter duration of action. This slightly quicker onset of action may explain why some people with asthma describe OTC epinephrine MDIs as working better than other prescription inhalers for asthma. In the proposed rule, we stated that there were no clinical data to support a conclusion that this perceived quicker relief provided by epinephrine leads to better outcomes or that epinephrine CFC MDIs are more effective than other asthma MDIs, including HFA MDIs. No new data were submitted in response to the proposed rule or at the public meeting that would support the conclusion that epinephrine leads to better outcomes than albuterol MDIs for asthma.

In fact, at the open public meeting held after publication of the proposed rule, one organization presented results of a survey of medical professionals who overwhelmingly recommended against use of OTC epinephrine by asthma patients because they believe it is an antiquated therapy and does not work as well as prescription inhalers (December 5, 2007, hearing transcript at 25–34, available at *http://www.fda.gov/cder/meeting/ozone-dec2007.htm*). In addition, the NAEPP EPR–3 recommends against epinephrine's use and recommends that short acting beta-2 adrenergic bronchodilators are the most effective medication for relieving acute bronchospasm.[13]

(Comment 3) One comment stated that no other bronchodilators attach to the same receptors in the lungs as epinephrine, apparently suggesting that epinephrine has a unique mechanism of action and may therefore provide a unique therapeutic benefit.

(Response) Epinephrine is a nonselective beta adrenergic bronchodilator. Other available bronchodilators, including albuterol, are selective beta-2 adrenergic bronchodilators. Both epinephrine and albuterol achieve bronchodilation primarily via the beta-2 adrenergic receptor; therefore, they both bind to the same receptor that causes bronchodilation. Accordingly, we disagree with the commenter's implication that the OTC epinephrine MDIs provide any unique therapeutic or other advantage over the available alternatives.

We have carefully considered these comments asserting that epinephrine MDIs are more effective and/or faster acting than other asthma MDIs or provide some unique therapeutic benefit. 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 epinephrine provides a greater therapeutic benefit than similar adrenergic bronchodilators.

2. Does the OTC Marketing Status of Epinephrine MDIs Provide an Important Public Health Benefit?

Our discussion on the public health benefit of OTC epinephrine CFC MDIs must take into consideration the fact that they are marketed OTC, while the therapeutic alternatives for epinephrine MDIs are prescription drugs.

(Comment 4) We received several comments that expressed concern that removing the essential-use designation for epinephrine would eliminate an OTC asthma treatment option that should be available for low-income, elderly, and uninsured individuals. Several comments asserted that most individuals cannot afford private health insurance, and that physician visits and prescription medications are cost-prohibitive. Another comment stated that prescription bronchodilators are very expensive when compared to epinephrine CFC MDIs, and removal of the essential-use designation would result in increased health care costs. Another comment questioned why we were removing a product that lowered health care costs. We also received three comments emphasizing the importance of access to an OTC rescue MDI available for emergencies. One comment further stated that ambulances and emergency room visits are more costly than epinephrine CFC MDIs.

(Response) In the proposed rule, we recognized that a small population of

[13] 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*.

people with asthma who face barriers to health care may derive some benefit from having OTC epinephrine MDIs available OTC. However, we noted that use of programs providing low-cost or free prescription drugs and the availability of physician samples may reduce the number of people with asthma who face barriers to health care and depend on OTC epinephrine MDIs and minimize the adverse impact that may result from the absence of OTC epinephrine MDIs. In addition, OTC epinephrine MDIs are not available through low-cost drug plans. Prescription drugs obtained through these programs can be substantially less expensive than OTC epinephrine MDIs for people who can and do avail themselves of these programs. Finally, there are ways patients may modify their behavior in order to minimize the impact of elimination of OTC epinephrine MDIs, including buying fewer MDIs to keep in different locations. Considering the availability of programs providing low-cost or free prescription drugs that would allow low-income, elderly, and uninsured individuals to purchase alternative MDIs, and the availability of physician samples, we believe that patients will be adequately served by alternative MDIs.

We understand that maintaining current valid prescriptions and supplies of prescribed drugs is a regular and sometimes onerous, but necessary, task for many patients with chronic diseases. It would certainly be more convenient for these patients if some sort of therapeutic alternative were available OTC. However, there are no OTC remedies for most serious diseases. Of note, patients with anaphylaxis to bee stings or peanuts can face sudden, life-threatening attacks if exposed to their relevant triggers. Yet epinephrine autoinjectors, such as EPIPEN, are not OTC products because of considerations that include the proper evaluation and treatment of such patients so that appropriate treatment plans can be made. In the proposed rule, we noted that no evidence had been presented to indicate how asthma differs from other serious diseases in a way that necessitated having an OTC treatment available. We did not receive any additional information, either in written comments or testimony at the public meeting, that contradicted the view expressed in the proposed rule that asthma is a serious disease, comparable to other serious diseases that require evaluation and treatment by a health care professional, that would enable us to reach the conclusion that an OTC treatment option for asthma is absolutely essential to the public health.

(Comment 5) One comment stated that epinephrine MDIs permit a user to visually determine how much medication is still in the MDI, presumably making it more convenient to use than other available substitute MDIs.

(Response) OTC epinephrine MDIs, in fact, do not have a dose counter but do permit the user to see the amount of product remaining in the canister. An available therapeutic alternative, Ventolin HFA Inhalation Aerosol (Glaxo Smith Kline), contains a dose counter to track the number of doses remaining. Accordingly, this type of feature is not unique to OTC epinephrine MDIs. Moreover, we do not believe that this type of patient convenience would provide a basis to conclude that a product provides an otherwise unavailable health benefit.

(Comment 6) We received comments from patient advocacy and health care provider associations stating that self-medication of any inhaled medication to treat respiratory conditions without any clinical input from health care professionals to instruct and train the user can, in fact, endanger the health of the patient. Some comments stated, in particular, that epinephrine CFC MDIs should be removed from the market because they are not recommended by the National Heart, Lung, and Blood Institute's asthma treatment guidelines (Guidelines for the Diagnosis and Management of Asthma) and their OTC availability makes it difficult for health care professionals to monitor asthmatics' conditions and provide appropriate care. A patient advocacy group, in a written comment and at the December 2007 public meeting, asserted that medical professionals generally recommend against use of OTC epinephrine because asthma is a potentially life-threatening condition that should not be self-diagnosed or treated and because OTC epinephrine does not work as well as other treatments and has more unwanted side effects.

(Response) In the proposed rule, we evaluated the risks of self-treatment of asthma against the public health benefits that OTC epinephrine MDIs may provide. We noted that OTC epinephrine MDIs are only indicated for mild intermittent asthma and acknowledged the importance of obtaining a physician's diagnosis of asthma before using an OTC epinephrine MDI, as specified in the approved OTC epinephrine labeling. In addition, we noted the importance of patient education on such issues as how asthma affects the lungs, the difference between medications, consideration of environmental control measures, and proper use of an MDI. We also noted the possible effects of undertreatment of asthma, such as more frequent symptoms and attacks, missed work and school, activity limitations, fewer hospitalizations, emergency department visits and outpatient visits, a decline in lung health and function, and possibly, death. Finally, we noted that purchasers of OTC epinephrine MDIs who are self-treating may not provide important information to a health care provider that would allow the health care provider to accurately assess and advise on the patient's use of asthma inhalers.

In addition to providing proper diagnosis and instructions in the use of bronchodilators, health care professionals often prescribe additional or alternative prescription medications, such as inhaled steroids, to certain asthma patients who can benefit from this therapy. As described in the proposed rule, the treatment guidelines recommend use of an inhaled corticosteroid for treatment in most classes of asthma severity: for mild persistent asthma, daily use of an inhaled corticosteroid (available only by prescription) is recommended; if the patient has moderate persistent asthma, higher doses of inhaled corticosteroids and/or inhaled corticosteroids with a long-acting adrenergic bronchodilators are recommended; and for severe persistent asthma, still higher doses of inhaled corticosteroids are recommended in conjunction with a long-acting bronchodilator (available only by prescription). Taken properly, these drugs can actually improve the patient's condition (i.e., do more than just treat symptoms). As noted in the proposed rule, proper prescribing and use of inhaled steroids significantly reduces asthma morbidity. Specifically, the proposed rule cited a study of urban pediatric patients in which increased use of corticosteroids in accordance with the treatment guidelines resulted in fewer hospitalizations, emergency department visits, and outpatient visits. However, only patients who are seen by a qualified health care provider can benefit from this additional therapy. Thus, patients who are self-treating with OTC remedies will be foregoing such additional beneficial treatment. While we do not dismiss the impact of increased costs of prescription drugs to the patient, as discussed above, we believe that the general improvement in respiratory health that will result through consultation with a healthcare provider in terms of proper diagnosis,

treatment, and patient training in the use of MDIs is an important consideration. Accordingly, we believe that there are clear public health benefits that might accrue if fewer asthma patients self-diagnose and self treat with OTC drugs, including epinephrine.

In the proposed rule, we specifically requested comments on the expected costs and public health effects if OTC epinephrine MDIs were removed from the market without a similar product being available OTC (72 FR 53711 at 53724). Other than the comments described above, we received no data or information in response to our request. Because we received no new data or information on this issue, and given the evidence of significant benefit to asthma patients who seek assessment and treatment by a professional, rather than self-treating, we therefore agree with the commenter that the public health benefits that would result from increased assessment and treatment of asthma patients by a health care professionals may be significant.

We recognize that epinephrine MDIs may provide some public health benefits; however, nothing in this rulemaking suggests that continued use of OTC epinephrine 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 OTC epinephrine MDIs 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 possibility that, in the absence of the OTC drug product, additional patients may seek assessment and treatment for their asthma conditions from health care professionals and reduce their asthma morbidity as a result.

Based on the record in this rulemaking, we therefore remain very doubtful that the OTC availability of epinephrine constitutes an otherwise unavailable public health benefit. Given that we have already found no technical barriers to reformulation of OTC epinephrine 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.

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

As explained in the proposed rule, 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 the product, 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). 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 1970's, we reached a tentative conclusion in the proposed rule that the release of ODSs into the atmosphere from OTC epinephrine 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 manufactured CFCs. 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 quantity of CFCs used in OTC epinephrine 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 OTC epinephrine MDIs is cumulatively significant. (72 FR 53711 at 53715 and 53724).

(Comment 7) Several comments asserted that CFCs used in epinephrine CFC MDIs do not have an adverse impact on the environment because the CFCs are inhaled rather than released into the environment.

(Response) Nearly all of the CFCs inhaled into the lungs from an MDI are almost immediately exhaled into the environment. 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 8) A few comments asserted that the amount of ODSs released from epinephrine CFC MDIs is insignificant, and eliminating their use would not provide a significant environmental benefit. One comment also stated that the impact of CFCs on the ozone layer is much less than previously believed.

(Response) The United States evaluated the environmental effect of eliminating the use of all CFCs in an environmental impact statement (EIS) in the 1970s (see 43 FR 11301, March 17, 1978) (the 1978 rule). As part of that evaluation, FDA concluded that the continued use of CFCs in medical products posed an unreasonable risk of long-term biological and climatic impacts (see Docket No. 96N–0057). In 1990, Congress enacted Title VI of the Clean Air Act, which codified the decision to fully phase out the use of CFCs over time. Congress did not assign us 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. Congress did instruct us to determine whether such products are essential. This rulemaking fulfills that obligation with respect to epinephrine CFC MDIs. Moreover, as we stated in the proposed rule, the release of CFCs from epinephrine MDIs is currently significant and as the phaseout continues throughout the world, the significance of the quantities of CFCs released by epinephrine MDIs will, actually, increase. (72 FR 53715).

We received no additional comments disagreeing with our tentative conclusion in the proposed rule that any release of CFCs from OTC epinephrine MDIs is cumulatively significant, or addressing this conclusion in any substantive way. We therefore finalize our conclusion that any release of an ODS into the atmosphere from OTC epinephrine MDIs is cumulatively significant. However, because we have not reached a conclusion on the public health benefits of OTC epinephrine MDIs, we cannot 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. This does not effect the ultimate finding in this rulemaking that, because there are no significant technical barriers to reformulation of the

product, OTC epinephrine MDIs are no longer an essential use of ODSs and should be removed from the list of essential uses in § 2.125(e).

D. Effective Date

We proposed an effective date for removal of the essential-use designation for OTC epinephrine MDIs of December 31, 2010, and we solicited comments on this proposed effective date. We received a number of comments on the effective date and on the related issue of insuring adequate time to transition patients who use OTC epinephrine MDIs to non-CFC alternatives. After considering the comments, we were persuaded that December 31, 2011, rather than December 31, 2010, as proposed, is a more appropriate effective date for this rule. The December 31, 2011 date provides additional time to disseminate information about the transition to OTC epinephrine MDI users 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 to ensure adequate supplies of albuterol HFA MDIs for all patients who need them, including current OTC epinephrine MDI users who transition to albuterol HFA MDIs. Finally, while the availability of a non-CFC OTC replacement product for the OTC epinephrine MDIs is not necessary for this rulemaking, we believe a December 31, 2011, effective date gives sufficient time for the development of a non-CFC formulation of epinephrine MDIs and processing of an application for new drug approval for a drug that was previously the subject of an approved application and is being submitted for approval with a new formulation. In our responses to the comments below, we further explain the basis for our decision to extend the effective date by one year from that proposed.

(Comment 9) One comment urged an effective date of December 31, 2008, because all essential uses that destroy the ozone layer, including epinephrine, should be totally banned.

(Response) We disagree with this comment that a 2008 effective date would be appropriate. FDA has been committed to a vigorous and consistent policy of limiting the production, use, and importation of CFCs. In this regard, we have already removed, or proposed to remove, the essential-use designation for a number of drugs, including albuterol MDIs. See 70 FR 17168 (Apr. 4, 2005), 71 FR 70870 (Dec. 7, 2006), as confirmed at 72 FR 20942 (Apr. 27, 2007), 72 FR 32030 (June 11, 2007). We agree with the commenter that CFC-containing medical products should eventually be completely phased out. However, in addition to considering the environmental impact of CFCs, it is important to balance public health issues related to eliminating a treatment option for certain individuals with serious health concerns. In determining an appropriate effective date, we must provide sufficient time to permit an orderly transition for patients who rely on these drugs. Accordingly, we decline to follow the recommendation of this commenter that we adopt an earlier effective date of December 31, 2008. We believe that the effective date (see the **DATES** section of this document) that we are establishing in this final rule appropriately balances our duty to protect the public health and our various legal obligations as described elsewhere in this rule.

(Comment 10) We received a number of comments in support of the proposed December 31, 2010, effective date. One comment from a manufacturer of epinephrine CFC MDIs expressed disappointment in FDA's proposal to remove the essential-use designation for epinephrine but agreed that the proposed effective date of December 31, 2010, is required to provide consumers with sufficient time to transition to other asthma treatments. One comment from a patient advocacy organization supported our proposed effective date of December 31, 2010, on the basis that epinephrine CFC MDIs do not provide a public health benefit, are not recommended by the National Guidelines for the Diagnosis and Management of Asthma, and do not meet the criteria for essential-use exemptions.

(Comment 11) Several comments urged us to adopt a later implementation date than that proposed. One comment asked that we set an effective date that allows reasonable time to develop a non-CFC replacement for epinephrine CFC MDIs. One comment asked FDA to encourage pharmaceutical companies to develop a non-CFC formulation for epinephrine CFC MDIs. Two comments urged that we work with manufacturers to develop an inhaler that does not contain CFCs. A manufacturer of OTC epinephrine MDIs submitted two comments that both stated that it is in the process of transitioning to a new propellant and projects that it will not be ready to commercially produce and legally distribute a non-CFC alternative until 2011. This manufacturer believes that it will be able to meet current market demand for epinephrine MDIs and transition to a non-CFC formulation by December 31, 2011, and therefore requested that FDA set an effective date of December 31, 2011.

One comment was concerned that there would be inadequate time to transition patients to CFC-free MDIs. The comment urged FDA to begin proactive planning immediately to transition patients to available CFC-free alternatives by collecting relevant data regarding production capacity and supply from manufacturers of CFC-free alternatives, actively exploring opportunities with the manufacturers of both CFC epinephrine drugs and of the CFC-free alternatives on possible means to promote timely and effective patient education, and by obtaining relevant information on patient assistance programs available from MDI manufacturers.

(Response) As stated above, we carefully evaluated the comments submitted in response to the 2007 proposed rule and have determined that an effective date of December 31, 2011, is appropriate for the removal of the essential-use designation for epinephrine. While we believe that the presence of a non-CFC replacement for the epinephrine product may be convenient for users and a December 31, 2011 effective date allows a reasonable time to permit the development of a non-CFC replacement, we do not believe it is necessary for the purposes of this rulemaking. Currently, there are adequate non-CFC alternatives available in the form of HFA albuterol MDIs which are marketed as prescription drugs. Both albuterol and epinephrine MDIs are in the same therapeutic class (adrenergic bronchodilators), and albuterol MDIs are therapeutic alternatives to epinephrine. The effective date we are establishing for the removal of the essential-use designation for epinephrine provides an additional year for manufacturers to scale up production of albuterol HFA MDIs and will help ensure that there will be adequate supplies of albuterol HFA MDIs for all patients who need them, including those now using epinephrine MDIs. In choosing December 31, 2011, rather than 2010, as the effective date of this rule, we are providing additional assurance that adequate supplies and production capacity of albuterol HFA MDIs will exist by that time.

In addition, in the event a non-CFC formulation of epinephrine MDI is not developed, the December 31, 2011, date will allow adequate time to transition patients using epinephrine MDIs to albuterol MDIs. 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 OTC epinephrine. The need to ensure that we have permitted sufficient time for patient education for transitioning from OTC epinephrine CFC MDIs to an appropriate non-CFC substitute was an important factor in our decision to extend the proposed effective date by 1 year in this final rule, to December 31, 2011. Because epinephrine CFC MDIs are sold OTC, many purchasers do not interact with a doctor, pharmacist, or other health care provider who would normally disseminate information about the transition. Therefore, additional avenues of communication will be needed to communicate information to users about the transition away from OTC epinephrine CFC MDIs. For example, some OTC epinephrine CFC MDI users may need information to help them select a physician, and some may need time to find and avail themselves of free or low-cost health care and prescription drug programs. We realize that it will take some time to prepare and distribute educational materials before the final transition begins. The additional year from the proposed date of December 31, 2010, will provide for a longer transition period and ensure there is adequate time to disseminate transition information to OTC epinephrine CFC MDI users and sufficient time for these users to transition to an appropriate non-CFC substitute. Although we are cognizant of the environmental benefits and associated public health benefits of removing the essential-use designation of OTC epinephrine MDIs, as we discussed in reference to comments supporting such removal, we are equally cognizant of the treatment needs of asthma patients and the need to provide an adequate period of time for transition. In determining the appropriate length of the phase-out, we have also taken into account our recent experience with the on-going phase-out of CFC-containing albuterol products. While we are confident that the albuterol phase-out remains on track, given the fact that patients here may have additional decisions to make, in that they may need to both find a health care provider and switch to a drug with a different active moiety, we believe the additional year from that proposed is necessary to permit an orderly transition with minimal disruptions to patients currently using OTC epinephrine MDIs.

We will actively monitor the transition to CFC-free alternatives. Anyone who wishes to discuss a cooperative educational effort with the Department of Health and Human Services (HHS) and FDA should contact FDA or the Office of the Secretary of HHS.

In sum, we believe the effective date (see the DATES section of this document), provides for the phase-out of OTC epinephrine CFC MDIs in a manner that is consistent with our duty to protect the public health while still meeting our obligations under the Clean Air Act and Montreal Protocol.

E. Additional Comments on Miscellaneous Issues

(Comment 12) One comment from an international governmental organization asked that the final rule consider Decision VIII/10(1), regarding actions to promote industry's participation in a smooth and efficient transition away from CFC-based MDIs, including a request for companies to demonstrate research and development of alternatives to CFC MDIs, and Decision XIX/13(3), reached at the 19th Meeting of the Parties to the Montreal Protocol, regarding requests to companies for a commitment to reformulate products.

(Response) In order to remove the essential-use designation for a particular moiety, we are obligated to follow the procedures and criteria in § 2.125 of FDA regulations. The Decisions cited by the comment are not criteria listed in § 2.125(f); however, we believe that our actions in this area, including this rulemaking, are consistent with the general principles expressed in the Decisions cited by the comment.

(Comment 13) One comment from a nurse anesthetist supported the removal of the essential use for epinephrine CFC MDIs, but was concerned that albuterol MDIs remain necessary in the operating room.

(Response) This rulemaking is limited to removing the essential-use designation for epinephrine MDIs, which are currently marketed OTC, as PRIMATENE MIST, and as private label generics. This rulemaking does not affect any albuterol MDIs, which were the subject of a separate rulemaking that was completed in 2005 (70 FR 17168).

(Comment 14) One comment supported the phase-out of epinephrine CFC MDIs but recommended making albuterol HFA MDIs available without a prescription.

(Response) We have noted several times throughout this document that, in general, asthma is a chronic inflammatory disease of the airways that should be managed under the care and supervision of a health care provider. Consistent with this, even current OTC labeling for epinephrine MDIs directs patients to use the product only after they have first consulted a physician and received an appropriate asthma diagnosis, which is somewhat unique labeling for an OTC drug and reflects the importance of using these products with appropriate professional supervision. If a sponsor of an albuterol HFA MDI were to submit an application to FDA to switch the marketing status of an albuterol MDI to OTC, as with all NDAs, FDA would review the supporting data submitted with the application and determine whether the switch to OTC marketing status was appropriate. United States and international committees have provided guidelines for the management of asthma (NAEPP EPR–3 (Ref.2) and Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), 2007 (Ref. 3)) which recognize the importance of health care providers in the management of asthma.

F. Conclusions

We have concluded the following:

The pharmaceutical industry has had success in formulating similar moieties without ODSs. In particular, HFA MDIs containing albuterol, a close chemical analog of epinephrine, have been approved by FDA. We have no evidence to suggest that formulating epinephrine in a product that does not release ODSs poses unique technical challenges. Therefore, we conclude that no substantial technical barriers exist to formulating an epinephrine inhaler without ODSs.

We have therefore concluded that oral pressurized MDIs containing epinephrine are no longer an essential use of ODSs and should be removed from the list of essential uses in § 2.125(e).

VI. 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 25.31a(a).

VII. 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 known producers of OTC epinephrine CFC MDIs are not small entities and because of the likelihood that the final rule will not impose compliance costs, 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 $130 million, using the most current (2007) 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.

This final rule will prohibit sales of OTC epinephrine CFC MDIs in interstate commerce after December 31, 2011. If a non-CFC alternative is not available OTC by that time, this would force users to either visit a physician and get a prescription for an alternative drug product such as albuterol or to self-medicate with less effective therapies. Because OTC epinephrine CFC MDIs are widely regarded by physicians and people with asthma as the most effective relief medication for asthma available OTC, if users of these MDIs choose to self-medicate, they will be more likely to require hospitalization or an emergency department visit. Alternatively, if they choose to see a physician to obtain a prescription for albuterol, the OTC epinephrine CFC MDI users, or their insurers, will have to pay more, not only for visits to the physician, but also for more expensive drugs. More physician visits, however, may lead current OTC epinephrine MDI users to increase their use of prescription control medication, such as inhaled corticosteroids, which should decrease their likelihood of both asthma attacks and hospital visits. We have no data suggesting whether current OTC epinephrine MDI users are more likely to self-medicate or to visit a physician and get an albuterol MDI prescription once OTC epinephrine MDIs are no longer available. We therefore focus on scenarios where, if OTC epinephrine MDIs are no longer available, all current OTC epinephrine MDI users either self-medicate with other products such as herbal supplements, caffeine, and OTC ephedrine, or visit a physician to obtain, and fill, prescriptions for albuterol MDIs. These extreme scenarios offer plausible bounds for estimating the costs and benefits resulting from this final rule and regulatory alternatives assuming that no OTC non-CFC formulation of epinephrine MDIs is available.

If an OTC non-CFC formulation of epinephrine MDIs were approved by FDA, the impacts of this final rule would largely depend on the difference in price of currently available CFC-based MDIs and the new non-CFC formulation. According to ACNielsen data (Ref. 10) for the 52 weeks ending September 9, 2006, adjusted for sales through Wal-Mart, the average price of OTC epinephrine MDIs is $13.29 and annual retail sales of OTC epinephrine MDIs are roughly $60 million in the United States. We assume that a newly approved non-CFC epinephrine MDI would be branded with no generic alternatives. If we assume that the average price of the new branded non-CFC alternatives to be roughly the same as the current price of branded epinephrine MDIs of about $14.50, we estimate a 9 percent increase in annual expenditures on OTC epinephrine, or an increase of roughly $5 million.

CFCs available for production of OTC epinephrine MDIs may be exhausted prior to the effective date of this final rule if the United States is unable to obtain an essential-use allocation for CFCs under the Montreal Protocol for use in OTC epinephrine MDIs through 2011. If so, this final rule may not have any significant impacts. To the extent that CFCs for production of OTC epinephrine MDIs remain available, we estimate this final rule will have the impacts summarized below. As the estimates do not include the positive public health effects of improved medical care for asthma and ignores the likelihood of an HFA-based substitute, they should be viewed as upper bounds on net costs. If FDA were to approve an OTC version of an HFA-based substitute, consumers would not need to choose between self-medication and visiting a physician and the estimated impacts, as illustrated in the example above, would be far smaller.

TABLE 1.—SUMMARY OF ANNUAL QUANTIFIABLE EFFECTS OF THE FINAL RULE, ASSUMING CFCS FOR PRODUCTION OF OTC EPINEPHRINE MDIS REMAIN AVAILABLE

	Increased Health Care Expenditure, in 2007 Dollars	Increased Emergency Department Visits for Asthma	Increased Hospitalizations for Asthma	Reduced CFC Emissions from Phase-Out (tonnes)
If current OTC epinephrine MDI users self-medicate	$350 million to $1.1 billion	0 to 440,000	40,000 to 120,000	70
If current OTC epinephrine MDI users visit their physician for prescription albuterol (excluding controller medication)	$180 million to $355 million			70

We are unable to estimate quantitatively the reductions in skin cancers, cataracts, and environmental harm that may result from the reduction in CFC emissions by roughly 70 tonnes during these years. Although we cannot

estimate quantitatively the public health effects of the phase-out, based on a qualitative assessment, the agency concludes that the benefits of this regulation justify its costs.

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

B. Need for Regulation and the Objective of This Rule

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

An objective of this final rule is to respond to the obligations under the Montreal Protocol 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 epinephrine because we have concluded that no substantial technical barriers exist to formulating epinephrine in a product that does not release ODSs. Removing this essential-use designation will reduce emissions that deplete stratospheric ozone.

C. Background

1. CFCs and Stratospheric Ozone

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

2. The Montreal Protocol

The international effort to craft a coordinated response to the global environmental problem of stratospheric ozone depletion culminated in the Montreal Protocol, an international agreement to regulate and reduce production of ODSs. The Montreal Protocol is described in section I.B.2 of this document. One hundred and ninety-three countries have now ratified the Montreal Protocol, and the overall usage of CFCs has been dramatically reduced. In 2007, global production of CFCs totaled about 11,000 tonnes, down from base year levels exceeding 1.1 million tonnes (Ref. 4). This decline amounts to more than a 99-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 in 2007 was less than 1 percent of 1986 production and importation (Ref. 4).

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

Each year, each Party nominates the amount of CFCs needed for each essential use and provides the reason such use is essential. Agreement on both the essentiality and the amount of CFCs needed for each nominated use has been 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. 5). The benefits include reductions of hundreds of millions of nonfatal skin cancers, 6 million fewer fatalities due to skin cancer, and 27.5 million cataracts avoided between 1990 and 2165 if the Montreal Protocol were fully implemented. EPA estimates the value of these and related benefits to equal $4.3 trillion in present value when discounted at 2 percent over the period of 175 years. This amount is equivalent to about $6 trillion after adjusting for inflation between 1990 and 2004. This estimate includes all benefits of total global ODS emission reductions expected from the Montreal Protocol and is based on reductions from a baseline scenario in which ODS emissions would continue to grow for decades but for the Montreal Protocol.

4. Characteristics of Asthma

OTC epinephrine MDIs are used to treat asthma, a chronic respiratory disease characterized by episodes or attacks of bronchospasm on top of chronic airway inflammation. These attacks can vary from mild to life-threatening and involve shortness of breath, wheezing, cough, or a combination of symptoms. Many factors, including allergens, exercise, and viral infections may trigger an asthma attack.

Early release data from the first 9 months of the 2006 NHIS indicate that 8.0 percent of people in the United States have asthma (Ref. 6, fig. 15.5). The prevalence of asthma decreases with age, with the prevalence being 9.5 percent for children ages 0 to 14, compared to 7.8 percent for persons ages 15 to 34, and 7.4 percent for adults ages 35 and over (Ref. 6, fig. 15.5).

The early release data from the first 6 months of the 2006 NHIS also indicate 4.2 percent of Americans had an asthma episode in the previous 12 months, with 5.5 percent of children under age 14, 3.6 percent of persons ages 15 to 34, and 4.0 percent of adults over age 35 reporting episodes (Ref. 6, fig. 15.2).

According to data from the National Ambulatory Medical Care Survey, in 2004 there were about 15 million outpatient asthma visits to physician

offices and hospital clinics and 1.8 million emergency department visits (Ref. 7, table 19). According to data from the National Center for Health Statistics: National Hospital Discharge Survey, there were 497,000 hospital admissions for asthma in 2004 (Ref. 7, table 16) and 4,099 mortalities in 2003 (Ref. 7, table 1). The estimated direct medical cost of asthma (hospital services, physician care, and medications) was $11.5 billion in 2004 (Ref. 7, table 20).

We estimate that OTC epinephrine MDI users make roughly 280,000 to 370,000 visits to emergency departments and require roughly 75,000 to 100,000 hospitalizations annually. We know of no data or study suggesting OTC epinephrine MDI users differ from other people with asthma in their risk of requiring emergency department visits or hospitalizations. In a published study of 601 people with asthma (Ref. 8), the authors did not find any evidence that epinephrine users are more likely to visit emergency departments or to require hospitalization than people with asthma who do not use epinephrine. On the other hand, we know of no data suggesting that OTC epinephrine MDI users are less likely to visit emergency departments or require hospitalization. As described in section V.B.2.b of the proposed rule, we estimate that 1.7 to 2.3 million people with asthma use OTC epinephrine MDIs. This estimate is based on data provided by Wyeth, although Wyeth reached a different conclusion based on the same numbers.[14] Assuming 1.7 to 2.3 million people with asthma are OTC epinephrine MDI users, and that they require emergency department visits and hospitalization in proportion to their share of the population, OTC epinephrine MDI users account for roughly 280,000 to 370,000 emergency department visits annually [15 percent of 1.8 million = 280,000; 20 percent of 1.8 million = 370,000] and 75,000 to 100,000 hospitalizations annually [15 percent of 497,000 = 75,000; 20 percent of 497,000 = 100,000].[15]

While the prevalence of asthma (the percent of the population diagnosed with asthma) has been increasing in recent years, CDC reports that the incidence of asthma (the rate of new diagnoses) has remained fairly constant since 1997 (Ref. 9). Non-Hispanic Blacks, children under 17 years old, and females have higher incidence rates than the general population and also are more likely to have had an attack of asthma in the previous 12 months. The CDC notes that although increases have occurred in the numbers and rates of physician office visits, hospital outpatient visits, and emergency department visits, these increases are accounted for by the increase in prevalence. The CDC also notes that asthma mortality and asthma hospitalization rates were declining and stated that these downward trends might indicate early successes by asthma intervention programs.

5. Current U.S. Market for OTC Epinephrine MDIs

We estimate that 1.7 million to 2.3 million consumers purchase roughly 4.5 million OTC epinephrine MDIs in the United States each year, at an average price of $13.29 per MDI.

Based on data from ACNielsen for the 52 weeks ending September 9, 2006 (Ref. 10), we estimate 3.5 million OTC epinephrine MDIs are sold in the United States annually, excluding sales through Wal-Mart Stores, Inc. (Wal-Mart).[16] Wyeth estimates roughly 25 percent of OTC medications such as PRIMATENE MIST, a branded OTC epinephrine MDI product, are sold through Wal-Mart annually (Wyeth slide 32), implying a total market of roughly 4.5 million OTC epinephrine MDIs sold annually. This is equivalent to 1.3 billion inhalations per year, or 146 million days of therapy (at 9 inhalations per day, the highest recommended long-term dose).

Based on ACNielsen data (Ref. 10) for the 52 weeks ending September 9, 2006, adjusted for sales through Wal-Mart, we estimate OTC epinephrine MDI sales amount to roughly $60 million in the United States annually and the average U.S. retail price of OTC epinephrine MDIs is $13.29, equivalent to roughly $0.41 per day of therapy.

According to American Lung Association reports derived from the National Center for Health Statistics' 2004 NHIS (Ref. 7, table 10), 11.6 million individuals reported having had an asthma attack in the last 12 months. According to Wyeth Pharmaceuticals (Wyeth slide 32), 15 to 20 percent of adults with asthma who have had an asthma attack in the previous 12 months use OTC epinephrine MDIs. As we discussed in section V.B.2.b of the proposed rule, we estimate that 1.7 to 2.3 million people with asthma use OTC epinephrine MDIs. Each of these users, on average, purchases roughly 1.9 to 2.6 OTC epinephrine MDIs each year [4.5 million MDIs ÷ 1.7 million users = 2.6 MDIs per user per year; 4.5 million MDIs ÷ 2.3 million users = 1.9 MDIs per user per year].

We estimate 600,000 to 1.3 million OTC epinephrine MDI users do not regularly use prescription asthma products. According to Wyeth Pharmaceuticals, somewhere between 43 percent (Wyeth slide 33) and two-thirds (Wyeth slide 32) of OTC epinephrine MDI users also use prescription drugs for treatment of their asthma. This implies that 600,000 to 1.3 million OTC epinephrine MDI users do not use prescription asthma medicine [1,752,653 x .33 = 578,375; 2,336,871 x .57 = 1,332,016].

D. Benefits and Costs of the Final Rule

We estimate the benefits and costs of government action relative to a baseline scenario that, in this case, is a description of the production, use, and access to OTC epinephrine MDIs in the absence of this final rule. Our approach is the same as used in the proposed rule (see 72 FR 53711), except that we are using a phase-out date of December 31, 2011, and not December 31, 2010. In this section we first describe such a baseline, and then present our analysis of the benefits of the rulemaking. We also present an analysis of the most plausible regulatory alternatives, given the Montreal Protocol. Next, we turn to the costs of the rulemaking 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 OTC epinephrine MDIs after December 31,

[14] At the NDAC/PADAC meeting, Wyeth presented estimates that 15 to 20 percent of adults with asthma use OTC epinephrine (Wyeth slide 32). Applying these percentages to the number of adults who have asthma, Wyeth estimated that 2 to 3 million people used OTC epinephrine MDIs at any given time. Wyeth appears to have made a mistake. If we look at the 1993 ACNielsen study (Wyeth slide 29) where the study population was adults, it appears that Wyeth compared the number of respondents who reported using an OTC asthma drug (557) to the number of respondents who reported having an asthma incident in the previous 12 months (2,713). If we divide 557 by 2,713 we get 0.205 or 20 percent. The number of adults who have asthma is substantially higher than the numbers who have had an asthma incident in the previous 12 months; for 2004 the numbers are 14.4 million and 7.7 million adults. Applying 15 to 20 percent to the number of adults with asthma would result in a significant inflation of the number of OTC epinephrine MDI users. Applying 15 to 20 percent to the number of adults who have had an asthma incident in the previous 12 months provides an estimate of 1.7 to 2.3 million people using OTC epinephrine MDIs. We believe that this estimate is more accurate than Wyeth's estimate of 2 to 3 million OTC epinephrine MDI users.

[15] The 15 to 20 percent figures were derived, in part, from comparing the number of purchasers of OTC epinephrine MDIs to the number of adults suffering an asthma incident in the previous 12 months.

[16] Retail sales data from drug stores and supermarkets provided by ACNielsen do not include retail sales data from Wal-Mart because Wal-Mart does not participate in ACNielsen surveys.

2011. This date is 1 year later than what was used in the proposed rule. It is standard practice to use, as a baseline, the state of the world without the rulemaking in question, or where the rulemaking implements a legislative requirement, the world without the statute. For this final rule, we make the baseline assumption that it is questionable whether the United States would be able to obtain an essential-use allocation for CFCs for the manufacture of OTC epinephrine MDIs under the Montreal Protocol for 2011.[17] To the extent that new CFCs for production of OTC epinephrine MDIs remain available past that date, we estimate this rulemaking will have quantifiable impacts as summarized in table 1 of this document. If CFCs for the production of OTC epinephrine MDIs are no longer available by the end of 2011, this rule will have no impact.

2. Benefits of the Final Rule

The benefits of this final rule include environmental and public health improvements from protecting stratospheric ozone by reducing CFC emissions by roughly 70 tonnes annually. Benefits also include expectations of increased returns on investments in environmentally friendly technology, reduced risk of unexpected disruption of supply of OTC epinephrine MDIs, 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 promulgate this rule may lead the Parties to the Montreal Protocol to consider restrictions on access to the CFCs required to manufacture these OTC epinephrine MDI products, which could create the risk of removal of these products without adequate time for a deliberate and planned transition from the market.

a. *Reduced CFC emissions.* Withdrawal of OTC epinephrine MDIs from the market will reduce CFC emissions by approximately 70 tonnes 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 will ban marketing of OTC epinephrine CFC MDIs after December 31, 2011. There is some uncertainty with respect to the amount of inventory that will be available in the future, but the United States' ability to obtain an essential-use allocation for CFCs for the manufacture of OTC epinephrine MDIs in 2011 is questionable.

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

The reduction of CFC emissions associated with removing OTC epinephrine CFC MDIs from the U.S. market represents only a fraction of 1 percent of total global CFC emissions. Current allocations of CFCs for OTC epinephrine MDIs account for less than 0.1 percent of the total 1986 global production of CFCs (Ref. 11). Furthermore, current U.S. CFC emissions from MDIs represent a much smaller, but unknown share of the total emissions reduction associated with EPA's estimate of $6 trillion in benefits, because that estimate reflects future emissions growth that has not occurred.

If a final rule removing the essential-use designation of OTC epinephrine MDIs takes effect before CFCs cease to be available, the final rule may 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 the reduced emissions that might be associated with this final rule or the regulatory alternatives.

b. *Returns on investment in environmentally-friendly technology.* Establishing a phase-out date prior to the expiration of patents on HFA MDI technology and other aerosolized drug technology that does not use ODSs rewards the developers of the ozone-safe technologies. In particular, such a phase-out date would validate expectations that the government will protect incentives to research and develop ozone-safe technologies.

Newly developed technologies to avoid ODS emissions have resulted in more environmentally ''friendly'' air conditioners, refrigerants, solvents, and propellants, but only after significant 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, DPIs, and mini-nebulizers have also been successfully marketed.

c. *International cooperation.* The advantages of selecting a date that maintains international cooperation are substantial because the Montreal Protocol, like most international environmental treaties, relies primarily on a system of national self-enforcement, although it also includes a mechanism to address noncompliance. In addition, compliance with the Montreal Protocol's 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 of 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, and we would be risking losing the goodwill that comes from fulfilling our treaty obligations.

3. Costs of the Final Rule and Alternatives

The costs of removing OTC epinephrine MDIs from the market include the costs of increased physician visits, increased use of more expensive reliever MDIs, and potential increases in the use of controller medications, visits to emergency departments, and hospitalizations. Because we cannot predict whether OTC epinephrine MDI users will self-medicate or go to a physician for a prescription reliever once OTC epinephrine MDIs are removed from the market, we quantify the costs for two extreme cases. In the first case, OTC epinephrine MDI users not already seeing a physician self-medicate, while those who already see a physician switch from OTC epinephrine MDIs to albuterol HFA MDIs. In the second case, all OTC epinephrine MDI users visit their physician and switch to albuterol HFA MDIs. We propose these two cases as

[17] Even if there is no essential-use allocation under the Montreal Protocol for the year 2011, production of epinephrine CFC MDIs would likely continue well into the year with manufacturers using preexisting stocks of CFCs.

reasonable bounds for the expected cost of removing OTC epinephrine MDIs from the market. Of course, if FDA were to approve an OTC non-CFC formulation of epinephrine MDIs, consumers would not need to choose between self-medication and visiting a physician and the estimated costs would be far lower. For illustrative purposes, we assume the current average price of all OTC epinephrine MDIs is $13.29 and a new formulation would cost the same as the current price of branded epinephrine MDIs, or about $14.50. As annual retail sales of OTC epinephrine MDIs are roughly $60 million, the 9 percent in increase in price would result of an increase in expenditures of about $5 million.

a. *Self-medication*. If all OTC epinephrine MDI users who do not already see a physician for asthma were to self-medicate once OTC epinephrine MDIs were no longer available, and those who do see a physician were to increase their albuterol use, we estimate this rulemaking would result in $350 million to $1.1 billion in increased spending annually measured in 2007 dollars. This spending includes $300 million to $1.1 billion resulting from increased hospitalizations and emergency department visits, and roughly $50 million to $80 million in increased spending on more expensive medicines. Under the assumption of self-medication, we estimate that removing OTC epinephrine MDIs from the market would result in 40,000 to 120,000 more hospitalizations for asthma annually, and up to 440,000 more asthma-related emergency department visits each year. These estimates, based on calculations throughout this section, do not capture the decreased quality of life of OTC epinephrine MDI users, lost productivity, or the cost of alternative therapies, such as herbal remedies, caffeine, and OTC ephedrine.

The authors of a published study found that people with asthma who self-medicate with herbal products and caffeine, the most common forms of self medication, are at increased risk of requiring an emergency department visit or hospitalization (Ref. 8). They found that those using herbal treatments are 2.5 times as likely to require hospitalization, and that those who use caffeine to treat asthma are 3.1 times as likely as other people with asthma to require both an emergency department visit and hospitalization.

We estimate that OTC epinephrine MDI users who do not use prescription medicine for their asthma make roughly 100,000 to 200,000 emergency department visits and require roughly 25,000 to 50,000 hospitalizations annually. We estimate OTC epinephrine MDI users make roughly 280,000 to 370,000 emergency department visits and require about 75,000 to 100,000 hospitalizations annually, as described in section VII.C.4 of this document. We estimate somewhere between 43 percent and two-thirds of OTC epinephrine MDI users do not use prescription medicine for their asthma, as discussed in section VII.C.5 of this document. Assuming that OTC epinephrine MDI users who do not use prescription medicine for asthma do not differ in their rates of hospitalization and emergency department visits from those who do use prescription medicine for asthma, we estimate that OTC epinephrine MDI users who do not use prescription medicine for asthma make 100,000 to 200,000 emergency department visits and require 25,000 to 55,000 hospitalizations annually [275,700 emergency department visits x 1/3 = 91,900 emergency department visits; 367,600 emergency department visits x (1-.43) = 209,532 emergency department visits; 74,550 hospitalizations x 1/3 = 24,850 hospitalizations; 99,400 hospitalizations x (1-.43) = 56,658 hospitalizations].

If current OTC epinephrine MDI users who do not use prescription medicine for asthma were to self-medicate with herbal treatments, and those self-medicating with herbal treatments face 2.5 times the risk of a hospitalization, this would imply a lower bound increase of roughly 40,000 hospitalizations, calculated by netting out the baseline to get the incremental effect (2.5 - 1) or [24,850 hospitalizations x (2.5 - 1) = 37,275]. As an upper bound, if all OTC epinephrine MDI users were to self-medicate with caffeine, emergency department visits would increase by roughly 440,000 [209,532 emergency department visits x (3.1 - 1) = 440,017] and hospitalizations would increase by roughly 120,000 [56,658 hospitalizations x (3.1 - 1) = 118,983]. We do not have data that would allow us to estimate increases in hospitalizations and emergency department visits for patients using other forms of self-medication, such as OTC ephedrine, and do not include these factors in our analysis.

We estimate the 2006 cost of an emergency department visit for asthma at roughly $300 and the cost of hospitalization for asthma at roughly $7,500. Based on data from the 2004 National Hospital Discharge Survey, the American Lung Association estimates the 497,000 hospitalizations for asthma cost roughly $3.6 billion in inpatient care and physician services, equivalent to roughly $7,300 per hospitalization (Ref. 7). The 1.8 million emergency department visits for asthma cost about $518 million, equivalent to roughly $280 per visit. Adjusting these figures for inflation according to the Consumer Price Index for medical care, we estimate that the average hospitalization for asthma would cost roughly $7,500 and the average emergency department visit for asthma would cost roughly $300 in 2006.

Based on these estimates, if current OTC epinephrine MDI users who do not currently use prescription medicine were to self-medicate, the result would be costs of roughly $300 million in 2007 dollars [37,275 hospitalizations x $7,565.84 x 1.052 inflation = $296,681,642] to $1.1 billion annually [(118,982 hospitalizations x $7,565.84 x 1.052 inflation) + (440,017 emergency department visits x $294.17 x 1.052 inflation) = $1,083,180,231].[18]

Assuming current OTC epinephrine MDI users who do use prescription medicine for asthma increase their use of albuterol HFA MDIs without requiring more frequent physician visits, we estimate that they will pay roughly $50 million to $80 million more for medicine each year. As discussed in section VII.C.5 of this document, somewhere between 43 percent and two-thirds of OTC epinephrine MDI users also use prescription medicine for their asthma. Assuming current OTC epinephrine MDI users who also use prescription medicines for their asthma use roughly the same number of OTC epinephrine MDIs per year as those who do not, we estimate dual users use roughly 2 million to 3 million OTC epinephrine MDIs annually [4,486,104 MDIs x 0.43 = 1,929,025; 4,486,104 MDIs x 2/3 = 2,990,736 MDIs]. As discussed in the following section, we estimate an albuterol HFA MDI will cost between $16 and $25 more than an OTC epinephrine MDI, and that one albuterol MDI is roughly equivalent to one OTC epinephrine MDI. The lower priced albuterol MDIs are currently being withdrawn from the market, and will not be available at the time of the effective date of this rule (see 70 FR 71685). The higher price for albuterol HFA MDIs implies that if OTC epinephrine MDI users who also use prescription medicine for their asthma were to increase their use of albuterol HFA MDIs when OTC epinephrine MDIs are no longer available, they and their insurers would spend roughly $50 million to $80 million more per year for

[18] To inflate our 2006 analysis to 2007 dollars we use the year-over-year change in the CPI–U for medical care, which was 5.2 percent.

medicine in 2007 dollars [2,990,736 MDIs x $16.08 per MDI x 1.052 inflation = $50,591,769; 2,990,736 MDIs x $25.15 per MDI x 1.052 inflation = $80,392,184].

In total, self-medication by OTC epinephrine-only MDI users and increased albuterol use by those already using prescription medicine would result in increased spending of $350 million to $1.1 billion annually in 2007 dollars [$296,681,642 + $50,591,769 = $347,273,411; $1,083,180,231 + $50,591,769 = $1,133,772,000].

b. *Increased physician visits and albuterol use*. If, as a result of the removal of OTC epinephrine MDIs from the market, all current OTC epinephrine MDI users were to seek out prescription albuterol HFA MDIs through increasing the frequency of physician visits, we estimate that this scenario would result in roughly $180 million to $355 million in increased health care spending in 2007 dollars, including $105 million to $235 million in economic costs through an increase in visits to physicians and $75 million to $120 million in increased spending on prescription albuterol.

We estimate that if current epinephrine users who do not use prescription medicine for their asthma make one additional physician visit per year to enable them to switch from OTC epinephrine MDIs to albuterol MDIs, the result would be roughly 600,000 to 1.3 million additional physician visits annually. This estimate stems directly from the estimate presented in section VII.C.5 of this document that there are roughly 600,000 to 1.3 million epinephrine users who do not use prescription medicine for their asthma. These estimates assume that OTC epinephrine MDI users who do use prescription medicine for their asthma, and therefore already make regular physician visits, are able to increase their albuterol use without increasing the frequency of those visits.

We estimate the 2006 cost of a physician visit for asthma to be roughly $170. Based on 2004 data from the National Ambulatory Medical Care Survey, the American Lung Association estimates that 1.5 million physician visits and non-emergency outpatient hospital visits for asthma cost roughly $2.4 billion, equivalent to roughly $160 per physician visit. Adjusting these figures for inflation according to the CPI for medical care, we estimate that a physician visit for asthma would cost roughly $170 per visit in 2006. An increase of 600,000 to 1.3 million physician visits each year would therefore cost roughly $105 million to $235 million annually in 2007 dollars [584,217.75 visits x $168.966 per visit x 1.052 inflation = $103,846,009; 1,332,016.47 visits x $168.966 per visit x 1.052 inflation = $236,768,901]. These estimates do not take into account the value of the time patients spend visiting their physicians.

If all current OTC epinephrine MDI users were to switch to prescription albuterol HFA MDIs, we estimate the result to be roughly $75 million to $120 million in increased spending on medicine measured in 2007 dollars. We estimate that it will take roughly one albuterol HFA MDI to replace each OTC epinephrine MDI removed from the market. OTC epinephrine MDIs contain roughly 270, 405, or 540 inhalations, depending on the size of the MDI. Based on ACNielsen data for the 52 weeks ending September 9, 2006 (Ref. 10), we estimate that the average OTC epinephrine MDI contained 293 inhalations, equivalent to 32.6 days of therapy, assuming OTC epinephrine MDI users use, but do not exceed, the long-term maximum recommended dose of 9 inhalations per day. The usual dosage of albuterol HFA MDIs is 8 to 12 inhalations per day, and albuterol HFA MDIs contain 200 inhalations, implying that each MDI contains 17 to 25 days of therapy per MDI. Allowing for the greater therapeutic effectiveness of albuterol compared to epinephrine, we estimate it will take roughly one albuterol HFA MDI to replace each OTC epinephrine MDI removed from the market.

Based on ACNielsen data from the 52 weeks ending September 9, 2006 (Ref. 10), we estimate the average retail price of an OTC epinephrine MDI to be $13.29. Based on average retail sales prices across all payer types for the first half of 2004, the average albuterol HFA MDI cost $39.42 (Ref. 13). This estimate does not reflect less expensive albuterol HFA MDIs introduced to the market since that time. Some market analysts also predict that albuterol HFA MDI prices will decline up to 20 percent as the market switches away from albuterol CFC MDIs and large payers use their market power to drive down prices (Ref. 14). Taking these factors into consideration, we estimate the average retail price of an albuterol HFA MDI is $30 or more, a price increase of roughly $16 to $25 per MDI. If current OTC epinephrine MDI users must purchase one albuterol MDI for each OTC epinephrine MDI they currently purchase, total expenditures by current OTC epinephrine MDI users and their insurers would increase roughly $75 million to $120 million in 2007 dollars [4,486,104 MDIs x $16.08 per MDI x 1.052 inflation = $75,885,219; 4,486,104 MDIs x $25.55per MDI x 1.052 inflation = $120,588,277].

If, instead of self-medicating, OTC epinephrine MDI users go to the physician and increase their use of albuterol HFA MDIs, we estimate increased spending of roughly $180 million to $355 million annually in 2007 dollars [$103,846,009 for physician visits + $75,885,219 for medicine (albuterol) = $179,731,228; $236,768,901 in physician visits + $120,588,277 in medicines = $357,357,178].

These estimated expenditures would decrease dramatically if generic albuterol HFA MDIs were to be introduced to the market. Patents listed in ''Approved Drug Products with Therapeutic Equivalence Evaluations'' (Orange Book) for albuterol HFA MDIs expire in 2010 and 2017, making those possible dates for generic entry. Of course, unforeseen introduction of alternative therapies could reduce these expected increases in expenditures.

These increased expenditures represent, to some extent, transfers from consumers and third-party payers, including the Federal Government and State governments, to pharmaceutical manufacturers, patent holders, and other residual claimants. However, to some extent, these increased expenditures represent purchases of products that are more costly to manufacture and bring to market, and, therefore, would be social costs. We are unable to estimate the fraction of those increased expenditures on drugs that constitute social costs.

c. *Controller medication*. We estimate that the cost to current OTC epinephrine MDI users of filling additional prescriptions for controller medications would, on average, exceed the potential direct cost savings from reducing hospitalizations and emergency department visits by more than $280 per current OTC epinephrine MDI user.

In a study of almost 50,000 asthma patients (Ref. 15), the authors found that patients with low adherence to controller medication have significantly higher risk (odds ratio of 1.72) of emergency department visits or of hospitalization relative to patients with moderate or high adherence. The study found that patients receiving high daily doses of controller medication had the lowest risk (odds ratio of .37) of emergency department visits or of hospitalization. As discussed in section VII.D.3.a of this document, we estimate OTC epinephrine MDI users who do not use prescription medicines make roughly 100,000 to 200,000 emergency department visits and require about 25,000 to 55,000 hospitalizations

annually. If they all were to visit their physicians, receive prescriptions for a controller medication, fill them, and use the medication, based on the results of the study of almost 50,000 asthma patients, we estimate 20 to 40 percent of these emergency department visits and hospitalizations could be avoided, equivalent to roughly 20,000 to 80,000 fewer emergency department visits [20 percent of 91,900 is 18,380; 40 percent of 209,532 is 83,813] and 5,000 to 10,000 fewer hospitalizations [20 percent of 24,850 is 4,970; 40 percent of 56,658 is 11,332]. Assuming the average cost for an emergency department visit for asthma is about $300 and the average cost of a hospitalization for asthma is roughly $7,500, as discussed in section VII.D.3.a of this document, this would reduce health care costs by roughly $40 million to $110 million annually in 2007 dollars [($294.17 per visit x 18,380 x 1.052 inflation) + ($7,565.84 per hospitalization x 4,970 x 1.052 inflation) = $43,380,000; ($294.14 per visit x 83,813 x 1.052 inflation) + ($7,565.84 per hospitalization x 11,332 x 1.052 inflation) = $111,341,155]. This cost is roughly $75 to $85 per current OTC epinephrine MDI user per year [$43,380,000/ 584,218 OTC epinephrine only MDI users = $74.25; $111,341,000 / 1,332,016 OTC epinephrine only MDI users = $83.59].

We looked at a range of CFC-free controller medications such as FLOVENT HFA, ASMANEX TWISTHALER, PULMICORT TURBOHALER, and QVAR, and found the wholesale price of the smallest dose of the least expensive medication to be roughly $1.00 per day of therapy,[19] equivalent to roughly $370 per patient year of therapy. On average, the cost of increasing the use of controller medication among current OTC epinephrine MDI users who do not currently use prescription medicine would exceed the benefits, in terms of decreased emergency department visits and hospitalizations, by over $280 per person per year. This number would be lower if a greater fraction of people with asthma at high risk of emergency department visits were to begin using controller medication on a regular basis, and higher if a greater fraction of low risk people with asthma were to begin using controller medication on a regular basis. These estimates do not take into account the impact of asthma attacks on individuals' quality of life and productivity.

[19] Analysis completed by FDA based on information provided by IMS Health, IMS National Sales Perspective (TM), 2005, extracted March 2006.

4. Effects on Medicaid and Medicare

As a result of the removal of OTC epinephrine CFC MDIs from the market, we estimate State and Federal Medicaid spending will increase $35 million to $275 million annually and that Federal Medicare spending, together with private spending by Medicare beneficiaries, will increase $20 million to $275 million annually, all measured in 2007 dollars. Some OTC epinephrine MDI users may be eligible for both Medicare and Medicaid. To the extent this population is large, these estimates overstate potential spending increases from this final rule by counting these individuals twice, once in Medicaid estimates and once in Medicare estimates. We are unable to estimate the size of the population of OTC epinephrine MDI users eligible for both programs.

a. *Medicaid*. We estimate that 20 to 25 percent of the costs of the removal of OTC epinephrine MDIs from the market will be borne by State and Federal Medicaid programs, equivalent to $70 million to $275 million annually in 2007 dollars if Medicaid-eligible OTC epinephrine MDI users who do not use prescription medicine for their asthma were to self-medicate upon implementation of this final rule, and equivalent to $35 million to $90 million annually if Medicaid-eligible OTC epinephrine MDI users were to visit their physicians to obtain and fill prescriptions to enable them to switch to albuterol. Assuming epinephrine users with insurance, including Medicaid, are more likely to visit a doctor, and less likely to self-medicate, the costs of this final rule are more likely to fall in the $35 million to $90 million range.

According to proprietary surveys conducted by or for Wyeth between 1993 and 1994 (Wyeth slide 31), 27 percent to 33 percent of OTC epinephrine MDI users had incomes of less than $20,000 at the time the surveys were conducted. A 2005 Internet survey conducted by Wyeth found that 20 percent of OTC epinephrine MDI users had incomes of less than $25,000. Eligibility for Medicaid varies by State but is generally tied to the Federal poverty guidelines (Ref. 16). The 2006 Federal poverty guidelines establish a poverty threshold of $20,000 in annual income for a family of four (Ref. 17). Accordingly, if we assume 20 percent to 25 percent of OTC epinephrine MDI users are eligible for Medicaid, if Medicaid-eligible OTC epinephrine MDI users who do not use prescription medicine were to self-medicate, and if those who do self-medicate were to switch to albuterol, Federal Medicaid spending measured in 2007 dollars would increase roughly $70 million to $275 million annually [20 percent of $350 million = $70 million; 25 percent of 1.1 billion = $275 million]. If all current epinephrine users eligible for Medicaid were to instead visit their physicians and use prescription albuterol, we estimate that Federal Medicaid spending would increase by $35 million to $90 million dollars annually [20 percent of $179,731,228 = $35,946,246; 25 percent of $357,357,178 = $89,339,294]. These estimates exclude costs that may result from increased prescribing of controller medications, and do not take into account the impact of asthma attacks on individuals' quality of life and productivity.

b. *Medicare*. We estimate 10 percent to 25 percent of the costs of the removal of OTC epinephrine MDIs from the market will be paid by Federal Medicare spending and by Medicare beneficiaries. If all Medicare-eligible OTC epinephrine MDI users were to self-medicate upon implementation of this final rule, Federal Medicare spending and spending by Medicare beneficiaries would increase roughly $35 million to $250 million dollars annually. Alternatively, if all Medicare-eligible OTC epinephrine MDI users were to visit their doctors to obtain and fill prescriptions for albuterol, Federal Medicare spending and spending by Medicare beneficiaries would increase roughly $20 to $85 million annually. Assuming epinephrine users with insurance, including Medicare, are more likely to visit a doctor, and less likely to self-medicate, the costs of this final rule are more likely to fall in the $20 million to $85 million range.

According to proprietary surveys conducted by or for Wyeth between 1993 and 2005 (Wyeth slide 31), 16 percent to 33 percent of OTC epinephrine MDI users are over the age of 55, implying the percentage of epinephrine users over the age of 65, and therefore eligible for Medicare, must be lower. Accordingly, if we assume 10 percent to 25 percent of OTC epinephrine MDI users are over the age of 65, Medicare spending and private spending by Medicare beneficiaries measured in 2007 dollars would increase $35 million to $275 million annually if all Medicare-eligible OTC epinephrine MDI users were to self-medicate [10 percent of $350 million = $35 million; 25 percent of $1.1 billion = $275 million], and by $20 million to $90 million annually if they were all to visit their physicians for prescription

albuterol [10 percent of $179,731,228 = $18 million; 25 percent of $357,357,178 = $89,339,294]. These estimates exclude costs that may result from increased prescribing of controller medications, and do not take into account the impact of asthma attacks on individuals' quality of life and productivity.

E. Alternative Phase-out Dates

The alternatives we considered included the following phase-out dates:

1. December 31, 2008;
2. December 31, 2009;
3. December 31, 2010 (the proposed rule);
4. December 31, 2011 (the final rule).

Spending per year does not differ among the regulatory alternatives. The only difference among the alternatives is how long the estimated costs shown in table 1 of this document would accrue. At some time in the near future, the unavailability of CFCs—not the final rule or an alternative—may lead to removal of OTC epinephrine from the marketplace. Our current belief is that bulk CFCs are likely to be unavailable in 2010 (see section VII.A), so the costs for the first alternative would be the present value of the annual costs for 2 years, 2008–2009, and the cost for the second alternative would be the present value of the costs for 1 year, 2009. The third alternative, which was presented in the proposed rule, would have no quantifiable costs or benefits. The fourth alternative, which is this final rule, would have no quantifiable costs or benefits even if bulk CFCs were available in 2011, 1 year after we believe they will disappear from the marketplace.

F. Sensitivity Analyses

The estimated costs summarized in table 1 incorporate a range of estimates about the price increases consumers and other payers will face, the size of the affected market, and the consequences of consumers' response to the removal of OTC epinephrine MDIs from the market. This represents the full range of uncertainty 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, taking into account the possibility that in response to the removal of OTC epinephrine MDIs from the market, OTC epinephrine MDI users who do not currently use prescription medicines will either self-medicate or visit a physician to get an albuterol prescription. The estimated increases in emergency department visits and hospitalizations depend upon a range of estimates of the percentage of people with asthma who use OTC epinephrine MDIs (15 to 20 percent) and the fraction of OTC epinephrine MDI users who do not use prescription medicines and are therefore more likely to self-medicate (somewhere between 33 and 57 percent), as well as the rate we estimate hospitalizations and emergency department visits will increase among this population (2.5 to 3.1 times).

Similarly, estimates of the impact of the removal of OTC epinephrine MDIs from the market on public and private spending depends on whether or not OTC epinephrine MDI users self-medicate, the above estimates on increased hospitalizations and emergency department visits, and the cost of those visits. A range of estimates of the percentage of adults with asthma who use OTC epinephrine MDIs (15 to 20 percent) and the fraction of OTC epinephrine MDI users who do not use prescription medicine for their asthma (somewhere between 33 and 57 percent), in addition to the overall size of the OTC epinephrine MDI market, determines the number of additional physician visits these users will require to switch from OTC epinephrine MDIs to albuterol MDIs. Estimated increases in spending on medicine depend on the size of the OTC epinephrine MDI market, and the price premium current OTC epinephrine MDI users can expect to pay for their medicine, roughly $16 to $25 per MDI.

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 ODS emissions are potentially enormous but difficult to attribute to any of the small steps, such as this rulemaking, that make such cooperation effective. As discussed above in detail, the benefits of the removal of OTC epinephrine MDIs from the market 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. The removal of OTC epinephrine MDIs from the market could potentially cost public and private consumers of OTC epinephrine MDIs hundreds of millions of dollars annually, and increase hospitalizations and emergency department visits for asthma significantly. If CFCs cease to be available for OTC epinephrine MDIs before the effective date of a final rule removing the essential-use designation of OTC epinephrine MDIs, however, this final rule will have no benefits or costs.

VIII. Regulatory Flexibility Analysis

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because known current producers are not small entities and the likelihood that the final rule will not impose compliance costs, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

TABLE 2.—SUMMARY ACCOUNTING TABLE

Category	Primary Estimate	Low Estimate	High Estimate	Units			Notes
				Year Dollars	Discount Rate	Period Covered	
Benefits							
Annualized Quantified					7%	Annual	Reduction of CFC emissions by 70 tonnes
					3%	Annual	

TABLE 2.—SUMMARY ACCOUNTING TABLE—Continued

Category	Primary Estimate	Low Estimate	High Estimate	Units			Notes
				Year Dollars	Discount Rate	Period Covered	
Qualitative							Increased investment in environmentally friendly technologies. International cooperation.
Costs							
Annualized Monetized $millions/year		$180 - $355 million	$350 million - $1.1 billion	2007	7%	Annual	Range of estimates capture underlying uncertainty. No central tendency.
		$180 - $355 million	$350 million - $1.1 billion	2007	3%	Annual	
Qualitative							Depending on consumer willingness to self-medicate, potential increase in annual emergency department visits for asthma of 0 to 440,000 and hospitalizations for asthma of 40,000 to 120,000.
Transfers							
Federal Annualized Monetized $millions/year		$55 million	$550 million	2007	7%	Annual	Medicare and Medicaid. Rough approximation.
		$55 million	$550 million	2007	3%	Annual	
From/To	From: U.S. Government			To: Healthcare providers and drug manufacturers			
Effects							
Small Business							None. Affected entities are not small.

IX. 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.

X. 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.

XI. References

The following references have been placed on display in the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but we are not responsible for subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. National Center for Health Statistics, ''Early Release of Selected Estimates Based on Data From the 2005 National Health Interview Survey,'' figure 15.4, available at *http://www.cdc.gov/nchs/data/nhis/earlyrelease/200606_15.pdf*.

2. 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*.

3. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), updated 2007, available at *http://www.ginasthma.org*.

4. United Nations Environmental Programme, Status of information provided by Parties in accordance with Article 7 of the Montreal Protocol on Substances that Deplete the Ozone Layer—Report by the Secretariat, 2008.

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

6. National Center for Health Statistics, ''Early Release of Selected Estimates Based on Data From the January-September 2006 National Health Interview Survey'' March, 28, 2007 (available at *http://www.cdc.gov/nchs/about/major/nhis/released200703.htm#15*).

7. American Lung Association, ''Trends in Asthma Morbidity and Mortality,'' Epidemiology & Statistics Unit, Research and Scientific Affairs, July 2006.

8. Blanc, P. D. et al., ''Use of Herbal Products, Coffee or Black Tea, and Over-the-

Counter Medications as Self-Treatments Among Adults with Asthma,'' *Journal of Allergy and Clinical Immunology*, 100:(6\1) 789, December 1997.

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

10. Analysis completed by FDA based on retail sales data from drug stores and supermarkets provided by ACNielsen for the 52 weeks ending September 9, 2006.

11. U.S. Environmental Protection Agency, final rule, ''Protection of Stratospheric Ozone: Allocation of Essential Use Allowances for Calendar Year 2006,'' 71 FR 58504, October 4, 2006.

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

13. Analysis completed by FDA based on prescription data provided by IMS Health, National Prescription Audit, 2004; IMS Health, IMS MIDAS (TM), Q1/2004–Q2/2004.

14. Gal, A., and N. R. Chari, ''TEVA, SEPR: SGP to Phase Out CFC Albuterol Production by Early 2007; TEVA and SEPR Likely to Benefit,'' report prepared for Sanford C. Bernstein & Co., LLC (New York), October 17, 2006.

15. Berger, W. E. et al., ''The Utility of the Health Plan Employer Data and Information Set (HEDIS) Asthma Measure to Predict Asthma-Related Outcomes,'' Annals of Allergy, Asthma and Immunology, 93:538, December 2004.

16. Centers for Medicare and Medicaid Services, *Medicaid at-a-Glance 2005: A Medicaid Information Source*, available at *http://www.cms.hhs.gov/MedicaidEligibility/downloads/MedGlance05.pdf*.

17. Department of Health and Human Services, notice, ''Annual Update of the HHS Poverty Guidelines,'' 71 FR 3848, January 24, 2006.

List of Subjects in 21 CFR Part 2

Administrative practice and procedure, Cosmetics, Devices, Drugs, Foods.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act, 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. In § 2.125, remove and reserve paragraph (e)(2)(v).

Dated: November 13, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E8–27436 Filed 11–17–08; 11:15 am]

BILLING CODE 4160–01–S

DEPARTMENT OF JUSTICE

28 CFR Part 0

[Docket No. USMS 102; AG Order No. 3017–2008]

RIN 1105–AB14

Revision to United States Marshals Service Fees for Services

AGENCY: United States Marshals Service, Department of Justice.

ACTION: Final rule.

SUMMARY: This rule revises the United States Marshals Service fees to reflect current costs to the United States Marshals Service for personal service and execution of process in federal court proceedings. A proposed rule with request for comment was published in the **Federal Register** on June 16, 2008, at 73 FR 33955. No comments were received within the 60-day comment period. Accordingly, the proposed rule is finalized without change.

DATES: Effective December 19, 2008.

FOR FURTHER INFORMATION CONTACT: Joe Lazar, Associate General Counsel, United States Marshals Service, Washington, DC 20530–1000, telephone number (202) 307–9054.

SUPPLEMENTARY INFORMATION:

Legal Authority for the U.S. Marshals Service to Charge Fees

The Attorney General must establish fees to be taxed and collected for certain services rendered by the U.S. Marshals Service in connection with federal court proceedings. 28 U.S.C. 1921(b). These services include, but are not limited to, serving writs, subpoenas, or summonses, preparing notices or bills of sale, keeping attached property, and certain necessary travel. 28 U.S.C. 1921(a). To the extent practicable, these fees shall reflect the actual and reasonable costs of the services provided. 28 U.S.C. 1921(b).

The Attorney General initially established the fee schedule in 1991 based on the actual costs, e.g., salaries, overhead, etc., of the services rendered and the hours expended at that time. 56 FR 2436 (Jan. 23, 1991). Due to an increase in the salaries and benefits of U.S. Marshals Service personnel over time, the initial fee schedule was amended in 2000. 65 FR 47859 (Aug. 4, 2000). The current fee schedule is inadequate and no longer reflects the actual and reasonable costs of personal service and execution of process.

Federal Cost Accounting and Fee Setting Standards and Guidelines Being Used

When developing fees for services, the U.S. Marshals Service adheres to the principles contained in Office of Management and Budget Circular No. A–25 Revised (''Circular No. A–25''). Circular No. A–25 states that, as a general policy, a ''user charge * * * will be assessed against each identifiable recipient for special benefits derived from Federal activities beyond those received by the general public.'' *Id.* § 6.

The U.S. Marshals Service follows the guidance contained in Circular No. A–25 to the extent that it is not inconsistent with any federal statute. Specific legislative authority to charge fees for services takes precedence over Circular No. A–25 when the statute ''prohibits the assessment of a user charge on a service or addresses an aspect of the user charge (e.g., who pays the charge; how much is the charge; where collections are deposited).'' *Id.* § 4(b). When a statute does not address issues of how to calculate fees or what costs to include in fee calculations, Circular No. A–25 instructs that its principles and guidance should be followed ''to the extent permitted by law.'' *Id.* According to Circular No. A–25, federal agencies should charge the full cost or the market price of providing services that provide a special benefit to identifiable recipients. *Id.* § 6. Circular No. A–25 defines full cost as including ''all direct and indirect costs to any part of the Federal Government of providing a good, resource, or service. These costs include, but are not limited to, an appropriate share of'':

- Direct and indirect personnel costs, including salaries and fringe benefits such as medical insurance and retirement;
- Physical overhead, consulting, and other indirect costs including material and supply costs, utilities, insurance, travel, and rents or imputed rents on land, buildings, and equipment;
- The management and supervisory costs; and
- The costs of enforcement, collection, research, establishment of standards, and regulation. *Id.* § 6(d).