DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 2

[Docket No. 2003P–0029]

RIN 0910–AF18

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulation on the use of ozone-depleting substances (ODSs) in self-pressurized containers to remove the essential-use designations for albuterol used in oral pressurized metered-dose inhalers (MDIs). Under the Clean Air Act, FDA, in consultation with the Environmental Protection Agency (EPA), is required to determine whether an FDA-regulated product that releases an ODS is an essential use of the ODS. Two albuterol MDIs that do not use an ODS have been marketed for more than 3 years. FDA has determined that the two non-ODS MDIs will be satisfactory alternatives to albuterol MDIs containing ODSs and is removing the essential-use designation for albuterol MDIs as of December 31, 2008. Albuterol MDIs containing an ODS cannot be marketed after this date.

DATES: This rule is effective December 31, 2008.

ADDRESSES: Received comments, a transcript of, and material submitted for, the Pulmonary-Allergy Advisory Committee meeting held on June 10, 2004, the environmental assessment, and the finding of no significant impact may be seen in the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, between 9 a.m. and 4 p.m., Monday through Friday.

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

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I. Introduction and Highlights of the Rule

We published a proposed rule in the **Federal Register** of June 16, 2004 (69 FR 33602) (the 2004 proposed rule), proposing to remove the essential-use designation for albuterol MDIs. Albuterol MDIs containing chlorofluorocarbons (CFCs) or other ODSs cannot be marketed without an essential-use designation. We have determined that the following four criteria for removing an essential use have been met or will be met by the effective date of the final rule:

- More than one non-ODS product with the same active moiety is marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the ODS product containing that active moiety;
- Supplies and production capacity for the non-ODS products will exist at levels sufficient to meet patient need;
- Adequate U.S. postmarketing use data is available for the non-ODS products; and
- Patients who medically required the ODS product will be adequately served by the non-ODS products containing that active moiety and other available products.

We have also determined that the appropriate effective date for the removal of the essential-use designation for albuterol MDIs is December 31, 2008.

We will discuss our determinations on the criteria and the effective date in section V of this document ''Comments on the 2004 Proposed Rule.''

II. Background

A. Albuterol

Albuterol is a relatively selective beta$_2$–adrenergic agonist used in the treatment of bronchospasm associated with asthma and chronic obstructive pulmonary disease (COPD). Albuterol has the molecular formula $C_{13}H_{21}NO_3$. Albuterol is the name established for the drug by the U.S. Pharmacopeia and the U.S. Adopted Names Council. FDA uses the name albuterol, and it is the name commonly used in the United States. In most of the rest of the world, the drug is called salbutamol, which is the International Nonproprietary Name for the drug (the name recommended by the World Health Organization). Albuterol is widely used in its sulfate salt form, which has the molecular formula $(C_{13}H_{21}NO_3)_2H_2SO_4$. We will use ''albuterol'' to refer to both albuterol base and albuterol sulfate, unless otherwise indicated.

Albuterol is available in many dosage forms for the treatment of asthma and COPD. Syrups and tablets may be taken by mouth to be absorbed into the blood through the digestive tract. Albuterol drug products are marketed in various forms for inhalational use. Albuterol is available in inhalation solutions for use

in nebulizers, and was previously marketed in the United States in a compact dry-powder inhaler. Most important for purposes of this document, albuterol is marketed in MDIs, which are small, pressurized aerosol devices that deliver a measured dose of an aerosolized drug into a patient's mouth for inhalation into the lungs.

Albuterol MDIs were first approved for use in the United States in 1981, when the new drug applications (NDAs) for VENTOLIN (NDA 18–473) and PROVENTIL (NDA 17–559) albuterol MDIs were approved by FDA. The first generic albuterol MDI was approved in 1995. Albuterol MDIs have historically used the CFCs trichlorofluoromethane (CFC–11) and dichlorodifluoromethane (CFC–12) as propellants.

Albuterol MDIs are among the most widely used drug products for the treatment of asthma and COPD. Because of albuterol's relatively rapid onset of action, albuterol MDIs are frequently used as ''rescue'' inhalers for treatment of bronchospasm during acute episodes. Albuterol MDIs can be considered lifesaving for some patients at certain times; they are very important for controlling symptoms in many more patients who suffer from asthma or COPD. We recognize and take very seriously our obligation to examine with particular care any action that could affect the availability of these important drugs.

B. CFCs

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, where they release 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.

C. 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). The 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 warning statements on their labeling (42 FR 22018, April 29, 1977; 42 FR 42780, August 24, 1977).

The 1978 rule prohibited the use of CFCs as propellants in self-pressurized containers in any food, drug, medical device, or cosmetic. As originally published, the rule listed five essential uses that were exempt from the ban. The third listed essential use was for ''[m]etered-dose adrenergic bronchodilator human drugs for oral inhalation.'' This language describes albuterol MDIs, so the list of essential uses did not have to be amended in 1981 when VENTOLIN and PROVENTIL albuterol MDIs were approved by FDA.

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

2. The Montreal Protocol

On January 1, 1989, the United States became a party to the Montreal Protocol on Substances that Deplete the Ozone Layer (Montreal Protocol) (September 16, 1987, 26 I.L.M. 1541 (1987)), available at *http://www.unep.org/ozone/pdfs/Montreal-Protocol2000.pdf*.[1] The United States played a leading role in the negotiations of the Montreal Protocol, believing that internationally coordinated control of ozone-depleting substances would best protect both the U.S. and global public health and the environment from potential adverse effects of depletion of stratospheric ozone. Currently, there are 188 parties to this treaty.[2] When it joined the treaty, the United States committed to reducing production and consumption of certain CFCs to 50 percent of 1986 levels by 1998 (Article 2(4) of the Montreal Protocol). It also agreed to accept an ''adjustment'' procedure, whereby, 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 phaseout 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 Parties that are developed countries by January 1, 1996 (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,

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

[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.

although, to date, all such decisions have been made by consensus.

To produce or import CFCs for an essential use under the Montreal Protocol, a Party must request and obtain approval for an exemption at a meeting of the Parties. One of the most important essential uses of CFCs under the Montreal Protocol is their use in MDIs for the treatment of asthma and COPD. The decision on whether the use of CFCs in MDIs is ''essential'' for purposes of the Montreal Protocol turns on whether: ''(1) It is necessary for the health, safety, or is critical for the functioning of society (encompassing cultural and intellectual aspects) and (2) there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health'' (Decision IV/25). Each request and any subsequent exemption is for only 1 year's duration (Decision V/18). Since 1994 the United States and some other Parties to the Montreal Protocol have annually requested, and been granted, essential-use exemptions for the production or importation of CFCs for their use in MDIs for the treatment of asthma and COPD (see, among others, Decisions VI/9 and VII/28). The exemptions have been consistent with the criteria established by the Parties, which make the grant of an exemption contingent on a finding that the use for which the exemption is being requested is essential for health, safety, or the functioning of society, and that there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of health or the environment (Decision IV/25).

Phasing out the use of CFCs in MDIs for the treatment of asthma and COPD has been an issue of particular interest to the Parties to the Montreal Protocol. Several decisions of the Parties have dealt with the transition to CFC-free MDIs, including the following decisions:

- Decision VIII/10 stated that the Parties that are developed countries would take various actions to promote industry's participation in a smooth and efficient transition away from CFC-based MDIs (San Jose, Costa Rica, 1996).
- Decision IX/19 required 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 sold or distributed within that country and the approval and marketing status of non-CFC MDIs and dry-powder inhalers. 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 no essential uses of CFCs will be authorized for Parties that are developed countries at the 17th meeting of the Parties (in autumn 2005), or thereafter, 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. The action plan must be submitted before the 25th meeting of the Open-Ended Working Group[4] in the summer of 2005 (Nairobi, Kenya, 2003).

In addition to fulfilling our obligations under the Clean Air Act and other provisions of the Montreal Protocol, this rule is intended to provide, for purposes of Decision XV/5, the specific date after which the United States will not request essential-use allocations of CFCs for albuterol MDIs.

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 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 phaseout of the production of CFCs by 2000 (42 U.S.C. 7671c),[5] while section 610 of the Clean Air Act (42 U.S.C. 7671i) required EPA to issue regulations banning the sale or distribution in interstate commerce of nonessential products containing CFCs. Sections 604 and 610 provide exceptions for ''medical devices.'' Section 601(8) (42 U.S.C. 7671(8)) of the Clean Air Act defines ''medical device'' as

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

4. EPA's Implementing Regulations

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

The prohibition on production and import of CFCs contains an exception for essential uses and, more specifically, for essential MDIs. The definition of essential MDI at 40 CFR 82.3 requires that the MDI be intended for the treatment of asthma or COPD, be essential under the Montreal Protocol, and if the MDI is for sale in the United States, be approved by FDA and listed as essential in FDA's regulations at § 2.125.

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

[4] The Open-Ended Working Group (OEWG) was established in 1989 at the first meeting of the Parties to the Montreal Protocol held in Helsinki. The OEWG, among other duties, considers proposals for amendments and adjustments to the Montreal Protocol and prepares consolidated reports based on the reports of various scientific, technical, and economic panels. These proposals and reports may subsequently be acted on by a meeting of the Parties to the Montreal Protocol.

[5] In conformance with Decision IV/2, EPA issued regulations accelerating the complete phaseout of CFCs, with exceptions for essential uses, to January 1, 1996 (58 FR 65018, December 10, 1993).

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).

Among other changes, the 2002 final rule, in revised § 2.125(g)(3), set standards that FDA would use for determining whether the use of an ODS in a medical product is no longer essential. The 2002 final rule provided that to remove an essential-use designation, FDA must find that:

- At least one non-ODS product with the same active moiety is marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the ODS product containing that active moiety;
- Supplies and production capacity for the non-ODS product(s) exist or will exist at levels sufficient to meet patient need;
- Adequate U.S. postmarketing use data is available for the non-ODS product(s); and
- Patients who medically required the ODS product are adequately served by the non-ODS product(s) containing that active moiety and other available products.

To remove the essential-use designation of an active moiety marketed in an ODS product represented by one NDA, there must be at least one acceptable alternative, while for an active moiety marketed in ODS products and represented by two or more NDAs, there must be at least two acceptable alternatives.

Because there are multiple NDAs for albuterol MDIs containing an ODS, the rule requires that there must be at least two acceptable alternatives available for us to remove the essential-use designation for albuterol. We have determined that there are two acceptable alternatives for albuterol MDIs containing an ODS.

FDA approved the NDA for PROVENTIL HFA, albuterol sulfate MDI, on August 15, 1996 (NDA 20–503), and the product was introduced into the U.S. market later that year. PROVENTIL HFA is manufactured by 3M Co. (3M) and marketed by Schering-Plough Corp. (Schering). VENTOLIN HFA, albuterol sulfate MDI, was approved on April 19, 2001 (NDA 20–983), and it was introduced into the U.S. market in February 2002. VENTOLIN HFA is manufactured and marketed by GlaxoSmithKline (GSK). Both of these products use the hydrofluoroalkane HFA–134a as a replacement for ODSs. HFA–134a does not affect stratospheric ozone. We will use the phrase ''albuterol HFA MDIs'' to refer to both of these products in this document. IVAX Corp. (IVAX) has recently begun marketing an albuterol HFA MDI, but the short period of time that the IVAX MDI has been on the market prevents us from considering the drug an alternative to albuterol CFC MDIs for purposes of this rulemaking (see our response to comment 14 of this document). Albuterol HFA MDIs are the subject of patents, listed in our publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), which will, presumably, block the marketing of generic albuterol HFA MDIs until they expire. See our response to comment 36 of this document for a discussion of the patent issues that were raised in this rulemaking.

There is a separate essential-use designation for metered-dose ipratropium bromide and albuterol sulfate, in combination, administered by oral inhalation for human use, § 2.125(e)(2)(viii). This essential use was added to the list of essential uses (§ 2.125(e)), even though albuterol and ipratropium bromide were already separately included in the list of essential uses. (See 60 FR 53725, October 17, 1995, and 61 FR 15699, April 9, 1996.) The only drug product marketed under the essential-use designation for metered-dose ipratropium bromide and albuterol sulfate, in combination, is Boehringer Ingelheim Phamaceuticals' product COMBIVENT. Because COMBIVENT has two active ingredients, it is not subject to Decision XV/5, which concerns MDIs with albuterol as the sole active ingredient. This rule will not affect the essential-use status of COMBIVENT.

III. Comments on the 2004 Proposed Rule

On June 10, 2004, we held a meeting of the Pulmonary-Allergy Drug Advisory Committee (the PADAC meeting) to discuss the issues involved in removing the essential-use designation for albuterol MDIs (see the **Federal Registers** of May 11, 2004 (69 FR 26169), and June 2, 2004 (69 FR 31126)). Presentations were made by 13 speakers representing patient advocacy groups, medical professional organizations, an industry organization, an environmental advocacy group, an economics consulting firm, GSK, Schering, Honeywell Chemicals (Honeywell), and IVAX. We address the comments made in written material submitted to the committee and oral comments made during the open public hearing and committee discussion portions of the meeting in addition to the written and electronic comments submitted to the docket in response to the 2004 proposed rule.[6]

We received over 75 written and electronic comments in response to the 2004 proposed rule. They were submitted by patients, health care providers, patient advocacy groups, professional groups, manufacturers, a law firm, an economics consulting firm, and industry organizations. Most of the parties who spoke at the PADAC meeting also submitted written comments.

A. General Comments

(Comment 1) We received several comments that expressed general approval for the 2004 proposed rule.

[6] Fran Du Melle, Executive Vice President of the American Lung Association, submitted a citizen petition on behalf of the U.S. Stakeholders Group on MDI Transition on January 29, 2003 (Docket No. 2003P–0029/CP1) (Stakeholders' petition). The Stakeholders' petition requested that we initiate rulemaking to remove the essential-use designation of albuterol MDIs. Several comments were submitted in response to the petition. All of the opinions and information in those comments, with one exception (see comment 39 of this document), were also contained in testimony at the PADAC meeting or in comments on the proposed rule. In nearly every case, parties submitting comments on the petition also testified at the PADAC meeting, submitted comments on the proposed rule, or both. Accordingly, with the exception of comment 39 of this document, we will not be directly responding in this document to the Stakeholders' petition or the comments on the petition.

We appreciate the effort that the people who submitted these comments, and all other comments, made in expressing their opinions on this important rulemaking.

(Comment 2) We received several comments that expressed a general opposition to the phaseout of albuterol CFC MDIs, without giving any reasons for the opposition.

We cannot address these general comments. Comments that gave specific reasons why the person submitting the comment opposes the elimination of the essential-use designation for albuterol CFC MDIs will be discussed in the appropriate sections of this document.

(Comment 3) A few comments seemed to be based on a perception that this rulemaking would remove all albuterol MDIs from the market.

The perception is inaccurate. This rulemaking is based on the fact that there will be at least two different albuterol MDIs that are acceptable alternatives under § 2.125(g) available after the rule goes into effect.

(Comment 4) Several comments were made advocating an expeditious phaseout of albuterol CFC MDIs. A few comments recommended we proceed slowly and cautiously.

We believe this final rule provides for the phaseout of albuterol CFC MDIs with a speed that is consistent with our duty to protect the public health and our legal obligations.

(Comment 5) One comment requested we publish this rule by December 31, 2004.

We did not publish this rule by December 31, 2004, because it involves complicated and sensitive issues that required extensive consultation and deliberation within FDA and the Department of Health and Human Services (HHS), and with EPA and other Federal agencies. We have issued this rule in the most expeditious manner, consistent with the complexities and sensitivity of the issues involved.

(Comment 6) One comment asked that we consider in this rulemaking the availability of CFC drug products that do not have a non-CFC substitute, the availability of generic albuterol MDIs, and the impact that higher priced drugs may have on the public health.

As we discuss in several places in the 2004 proposed rule and this document, issues of price and generic competition were major concerns to us. However, because this rulemaking deals exclusively with the essential-use designation for albuterol MDIs, we did not examine the availability of non-CFC substitutes for drug products other than albuterol CFC MDIs.

(Comment 7) One comment stated we did not adequately communicate to the medical community the details of our policy regarding CFC MDIs. The comment expressed concern that we did not give a timeframe for the phaseout of albuterol CFC MDIs.

We believe we have done a good job of keeping the public and the medical community informed on our policy regarding the elimination of essential-use designations for medical products. We first discussed our general policy on the issue in the 1997 ANPRM. We received nearly 10,000 comments in response to the 1997 ANPRM, which demonstrates that this document received wide publicity. We received additional comments in response to the 1999 proposed rule, which proposed changes in § 2.125 to provide a mechanism for eliminating essential uses. A citizen petition was submitted on behalf of the U.S. Stakeholders Group on MDI Transition (stakeholders group) on January 29, 2003 (Docket No. 2003P–0029/CP1), essentially requesting that we initiate this rulemaking. This stakeholders group consists of both patient advocacy and professional organizations. These groups were aware of our policies. FDA staff has spoken several times before professional medical organizations, patient advocacy groups, and the National Asthma Education and Prevention Program Coordinating Committee of the National Institutes of Health. FDA staff have also answered countless telephone calls and correspondence on the subject. We have provided press releases and opportunities for interviews to the general, trade, and professional media. We believe we have done what can be reasonably expected to inform the public and the medical profession. However, we were not able to provide a timeframe for eliminating the essential-use designation for albuterol MDIs. We specifically solicited comments on an appropriate effective date for the elimination of the essential-use designation for albuterol MDIs. The effective date could not be established until we had finished our evaluation of the comments submitted in response to the 2004 proposed rule, prepared a draft of this document, and consulted with EPA and other Federal agencies.

B. The Same Active Moiety with the Same Route of Administration, for the Same Indication, and With Approximately the Same Level of Convenience of Use

1. The Same Active Moiety with the Same Route of Administration, for the Same Indication

We did not receive any comments disagreeing with our tentative conclusions stated in the 2004 proposed rule, or addressing the conclusions in any substantive way, that albuterol HFA MDIs have the same active moiety with the same route of administration for the same indications as albuterol CFC MDIs. We therefore finalize our tentative conclusion that albuterol HFA MDIs have the same active moiety with the same route of administration for the same indications as albuterol CFC MDIs.

2. Approximately the Same Level of Convenience of Use

(Comment 8) One comment asserted that the VENTOLIN HFA MDIs were not an adequate alternative for albuterol CFC MDIs because the VENTOLIN HFA MDI requires more force to operate.

Although we do have some data on the force needed to operate the various albuterol MDIs, because that information comes from different sources using different measuring techniques and apparatus, we are not able to meaningfully compare the amounts of force needed to operate albuterol HFA MDIs compared to the force needed for albuterol CFC MDIs. However, of the approximately 20 comments we received that indicated that the person submitting the comment had some experience using albuterol HFA MDIs, only one complained that the albuterol HFA MDIs required excessive effort to operate. None of the thirteen comments from health care providers indicated that their patients had problems operating the albuterol HFA MDIs. The PROVENTIL HFA MDI is somewhat shorter and wider than the VENTOLIN HFA MDI. Patients who find it difficult to apply adequate pressure to the VENTOLIN HFA MDI may wish to try the shorter PROVENTIL HFA MDI or other albuterol HFA MDIs that may come onto the market.

(Comment 9) One comment said that the VENTOLIN HFA MDIs were not an adequate alternative for albuterol CFC MDIs because the VENTOLIN HFA MDI needs to be primed before use.

The approved labeling for both PROVENTIL HFA and VENTOLIN HFA recommend that patients prime the MDI before using it for the first time and in cases where the MDI has not been used for more than 2 weeks by releasing four

test sprays into the air, away from the face. The approved labeling for PROVENTIL CFC MDIs and Warwick brand albuterol CFC MDIs contain a similar instruction about priming, but recommend priming if the MDI has not been used for 4 days, as opposed to the more convenient 2 weeks for the albuterol HFA MDIs. The approved labeling for VENTOLIN CFC MDIs, and for the generic albuterol CFC MDIs which refer to the VENTOLIN CFC MDI, contain an essentially identical recommendation, but refer to the operation as ''test sprays'' rather than priming. These test sprays are recommended if these albuterol CFC MDIs have not been used for more than 4 weeks. Therefore, priming is recommended for all of the albuterol CFC MDI products affected by this rulemaking. The only difference between albuterol CFC MDIs and albuterol HFA MDIs that would inconvenience patients is the shorter period of non-use before priming is recommended for the albuterol HFA MDIs compared to VENTOLIN CFC MDIs and the generic albuterol CFC MDIs which refer to the VENTOLIN CFC MDI. We consider this difference to be at most a minor inconvenience, and not a ''significant [variation] in convenience that materially impede[s] patient compliance.'' (See the 2002 final rule (67 FR 48370 at 48377).) When we compare the albuterol HFA MDIs to PROVENTIL CFC MDIs and Warwick brand albuterol CFC MDIs, the albuterol HFA MDIs are actually more convenient, because of the longer period of non-use before priming is recommended.

(Comment 10) One comment stated that the VENTOLIN HFA MDIs were not an adequate alternative for albuterol CFC MDIs because the float test cannot be used to determine whether the VENTOLIN HFA MDI is empty.

The float test is a widely described, but inaccurate, method of ascertaining whether an MDI is empty by seeing if it floats. In addition to being an inaccurate method to ascertain whether an MDI still contains usable quantities of the drug, the float test can damage the MDI (See Refs. 1 and 2). The float test is not recommended in the approved labeling of any albuterol CFC MDI. The only accurate way to determine whether an MDI still contains usable quantities of the drug is to keep track of the number of actuations. This is true for both albuterol CFC and HFA MDIs. Therefore we cannot view the inability to perform the float test on the albuterol HFA MDIs as a ''significant [variation] in convenience that materially impede patient compliance.'' (See the 2002 final rule (67 FR 48370 at 48377).)

We find that albuterol HFA MDIs have approximately the same level of convenience of use as albuterol CFC MDIs.

C. Supplies and Production Capacity for the Non-ODS Products Will Exist at Levels Sufficient to Meet Patient Need

(Comment 11) At the PADAC meeting a representative of GSK stated GSK was currently producing approximately 300,000 albuterol HFA MDIs annually at their Zebulon, NC, plant. She further stated the current installed capacity at Zebulon is 15 million albuterol HFA MDIs annually, but that it would take GSK 6 to 12 months after a final decision on an effective date in this rulemaking to hire staff and reconfigure existing space to take full advantage of the installed capacity. She stated it would take GSK 12 to 18 months after a final decision on an effective date in this rulemaking to install additional manufacturing equipment and secure required component supplies to enable GSK to manufacture 30 to 33 million albuterol MDIs.

A representative of Schering stated at the PADAC meeting that 3M would be able to manufacture enough albuterol MDIs to meet Schering's ''share of the expected demand'' for approximately 50 million albuterol HFA MDIs (transcript of PADAC meeting at p. 130). Answering a question from a committee member, the Schering representative clarified that his statement regarding Schering's and 3M's share of the manufacturing capacity was consistent with the earlier statements made on behalf of GSK.

In a subsequent written comment (2003P–0029/C20), GSK revised its production estimates and stated they would begin increasing production before the publication of this rule, and that they currently anticipated having the capacity to produce 30 million albuterol HFA MDIs annually by December 31, 2005. GSK further said they will also begin building up their inventory at least 3 months before the effective date of this rule. GSK also said they would reevaluate their expansion plans if the effective date of this rule were substantially beyond December 31, 2005.

Schering also revised their projections on increasing production capacity in a written comment submitted after the PADAC meeting (2003P–0029/C31). Schering said they will have adequate production available to meet demand for albuterol HFA MDIs by December 2005. Schering also said they would reevaluate their expansion plans if the effective date of this rule were substantially beyond December 2005. 3M, which produces the albuterol HFA MDIs Schering markets, confirmed Schering's comment by stating that they will have the capacity to manufacture 30 million albuterol HFA MDIs annually by December 31, 2005.

These projections were major considerations we took into account in establishing the effective date for this rule. We discuss our rationale for setting a December 31, 2008, effective date in our response to comment 32 of this document.

(Comment 12) A comment from a manufacturer of HFA–134a stated there would be more than adequate supplies of HFA–134a for albuterol MDIs if the essential-use designation is removed.

We appreciate this confirmation that adequate supplies of HFA–134a will exist to meet the increased demand for the propellant.

(Comment 13) A few comments from patients expressed concerns that shortages of albuterol MDIs may result from the elimination of the essential-use status of albuterol MDIs. Comments from a trade organization and a chain drug store expressed concerns about whether production capacity for albuterol HFA MDIs would be in place as quickly as had been discussed in the 2004 proposed rule.

The issue of adequate supply and production capacity has been key to this rulemaking. We regard the statements by GSK, Schering, and 3M that they will have adequate production in place as the best evidence on the availability of production capacity. When we chose December 31, 2008, as the effective date of this rule, we did so with every reasonable expectation that adequate supplies and production capacity would be in place by December 31, 2008.

(Comment 14) A representative of IVAX stated at the PADAC meeting that IVAX had submitted an NDA for an albuterol HFA MDI in January 2003, and received an approvable letter[7] from FDA for the NDA on November 28, 2003. He also said IVAX had submitted a separate NDA for an albuterol HFA breath-actuated inhaler in August 2003. He said he expected the products to be on the market in the near future. He stated that IVAX would soon have the capacity to manufacture 50 to 60 million HFA MDIs a year at IVAX's Waterford,

[7] An ''approvable letter'' is a written communication to an applicant from FDA stating that we will approve the NDA if specific additional information or material is submitted or specific conditions are met. An approvable letter does not constitute approval of any part of an NDA and does not permit marketing of the drug that is the subject of the NDA (21 CFR 314.3).

Ireland, plant, although he did not specify what proportion of that capacity would be allocated to albuterol HFA products or to products for the U.S. market.

We did not consider this information in making our decision on the essential-use designation for albuterol MDIs. The IVAX albuterol HFA MDI was approved on October 29, 2004, and introduced into the market in December 2004. Because this product has been on the market for such a short time, the available U.S. postmarketing use data is inadequate for purposes of § 2.125(g)(3)(iii). IVAX's albuterol HFA breath-actuated inhaler has not been approved or marketed. Section 2.125(g)(4)(i) requires alternative products to be marketed. In addition, because the product has not been marketed, there can be no U.S. postmarketing use data available to allow us to evaluate whether the breath-actuated inhaler will be an acceptable alternative to albuterol CFC MDIs.

(Comment 15) One comment asserted the entire supply of albuterol HFA MDIs for the United States would be produced at one GSK facility and one 3M facility. The comment concluded that adequate supplies of albuterol HFA MDIs were insufficient because it was unclear whether one facility could supply the entire market if the other facility were forced to close.

We appreciate the concerns expressed in this comment; however, the factual premise for the comment is misstated. We believe that a switch to albuterol HFA MDIs will improve the security of the U.S. supply of albuterol MDIs. Immediately after the phaseout of albuterol CFC MDIs, we will have one GSK facility and two 3M/Schering facilities supplying the U.S. market for albuterol MDIs. This compares favorably to the current situation with albuterol MDIs, where one Schering facility and one IVAX facility supply 95 percent of the U.S. market for albuterol CFC MDIs (comment from NERA dated August 13, 2004 (2003P–0029/C25)), exhibit 4; and corrected comment from GSK, dated August 25, 2004 (2003P–0029/CR1). IVAX's recently approved albuterol HFA MDI, although not considered an alternative product for purposes of this rule (see our response to comment 14 of this document), gives additional assurance that there will be adequate supplies of albuterol HFA MDIs if there is an interruption of production at one of the GSK or 3M approved manufacturing sites. We also would like to point out that GSK and 3M have overseas production facilities that are not listed as authorized manufacturing facilities in the approved NDAs for PROVENTIL HFA and Ventolin HFA. These facilities may be able to export albuterol HFA MDIs to the United States in an emergency shortage situation.

In our rulemaking establishing the criteria for eliminating an essential-use designation, we considered requiring multiple production sites to ensure a secure supply of non-ODS drug products (see the 1997 ANPRM (69 FR 10242 at 10245), the 1999 proposed rule (64 FR 47719 at 47723), and the 2002 final rule (67 FR 48370 at 48377)). We chose not to require multiple production sites for the alternative products as a criterion for eliminating the essential-use designation. In any case, albuterol HFA MDIs can be manufactured at three or more sites, which will provide a high degree of security for continued supplies of albuterol HFA MDIs, compared to the supply of other drugs intended for treatment of serious or life-threatening diseases, many of which are only manufactured in one facility.

(Comment 16) One comment recommended we delay the effective date for this rule until albuterol MDIs from IVAX and Sepracor Inc. (Sepracor) are on the market to ensure adequate supplies and provide price competition. Another comment recommended we establish an earlier effective date if the albuterol MDIs from IVAX and Sepracor Inc., are approved.

The IVAX albuterol HFA MDI is already approved (see our response to comment 14 of this document). Sepracor's levalbuterol tartrate[8] MDI XOPENEX HFA was approved on March 11, 2005, but has not been marketed by the time this document was published. Because XOPENEX HFA has not been marketed, we cannot consider it an alternative to albuterol CFC MDIs (see our response to comment 14 of this document). While we believe that the presence of additional suppliers of non-ODS albuterol products would be desirable for the reasons given in the comment, we do not believe they are necessary for the purposes of this rulemaking. Based on statements from GSK, Schering, and 3M, we expect that adequate production capacity for alternative products evaluated under § 2.125(g) will exist by the effective date of this rule. As we discuss in our responses to comment 18 and in section V of this document, we also believe that anticipated prices for albuterol HFA MDIs will not prevent patients from being adequately served by the albuterol HFA MDIs, even without the downward price pressure of additional competition.

We find that supplies and production capacity for albuterol HFA MDIs will exist at levels sufficient to meet patient needs by December 31, 2008.

D. Adequate U.S. Postmarketing Use Data is Available for the Non-ODS Products

We did not receive any substantive comments about whether adequate U.S. postmarketing use data is available for the albuterol HFA MDIs. We therefore finalize our tentative conclusion that adequate U.S. postmarketing use data is available for PROVENTIL HFA and VENTOLIN HFA, the albuterol HFA MDIs that we considered as alternatives in this rulemaking.

E. Patients Are Adequately Served by the Non-ODS Products

(Comment 17) A representative of GSK speaking at the PADAC meeting described GSK's Bridges to Access program. Bridges to Access provides GSK drugs at very low cost to lower-income individuals and families. She also mentioned GSK's Orange Card Program and the Together Rx program in which GSK participates. Both of these programs allow eligible Medicare patients to purchase drugs at significantly reduced prices. She added that GSK intended to annually distribute 2 million VENTOLIN HFA MDIs to physicians as samples. She also said GSK expected that many physicians would primarily provide these samples to their lower-income patients.

A subsequent written comment from GSK provided additional information on the Bridges to Access, Orange Card, and Together Rx programs. The comment also describes a Ventolin HFA Savings Check program which will distribute at least 3 million $10 coupons for use in purchasing VENTOLIN HFA MDIs.

A representative of Schering speaking at the PADAC meeting said Schering's SP Cares program, which is similar to GSK's Bridges to Access program, distributes free drugs, including PROVENTIL HFA, to low-income uninsured patients.

A written comment asserted that the Bridges to Access program provided albuterol HFA MDIs to only approximately 1.4 percent of the uninsured patients who need albuterol MDIs, and that the program would have to be expanded to an extreme degree to

[8] Levalbuterol tartrate is the tartrate salt of levalbuterol, the single R-enantiomer of albuterol, which is the active ingredient in both CFC and HFA MDIs as a racemic mixture of the two stereoisomers (R and S) at a 1:1 ratio. We have not determined whether we will, in the future, consider products whose active ingredient is a stereoisomer to be alternatives to drug products whose active ingredient is the corresponding racemic mixture.

provide meaningful supplies of albuterol MDIs to all uninsured patients. This comment also asserted that GSK's commitment to annually provide 2 million free albuterol HFA MDIs would have a limited benefit to the uninsured population because large numbers of uninsured patients receive medical care in the emergency departments of hospitals rather than in a physician's office, and it is unlikely that the free albuterol HFA MDIs will be distributed to the emergency departments. This comment was submitted before GSK's comment describing the Ventolin HFA Savings Check program.

Another comment stated that any patient assistance program must be targeted to those most in need, particularly low-income children and minority populations, while yet another comment stressed the importance of patient assistance programs in the transition to albuterol HFA MDIs.

We took these comments into consideration in determining that patients would be adequately served by albuterol HFA MDIs. These patient assistance programs have the potential to alleviate difficulties that lower income patients may have in obtaining the higher-priced albuterol HFA MDIs.

We agree with the comment that stated that these programs must carefully target the populations most in need of financial assistance in procuring needed albuterol MDIs, and we strongly recommend that GSK and Schering take all reasonable steps to ensure that their programs serve patients with the greatest needs, regardless of whether those patients are treated in a physician's office, clinic, or hospital emergency department. This targeting is particularly important in distributing free albuterol HFA MDIs.

We believe that many of the concerns expressed by the comment critical of GSK's Bridges to Access are valid, but that the comment underestimates the positive effect that Bridges to Access and other patient assistance programs can have. The estimate in the comment did not factor in the 2 million free albuterol HFA MDIs GSK has committed to distribute to physicians as samples and whatever free albuterol HFA MDIs Schering may distribute. The comment also could not factor in the effect of GSK's Ventolin HFA Savings Check program. With successful targeting, these free albuterol HFA MDIs and $10 coupons should have a beneficial impact; with less successful targeting the impact could be very limited (see section VII.D.2 of this document). The comment also ignores the potential impact of Schering's SP Cares program, which is similar to GSK's Bridges to Access program. We recognize that the Bridges to Access and SP Cares programs will have to expand to reach all uninsured low and moderate income patients who will need albuterol HFA MDIs, but the degree of expansion required would be smaller than that described in the comment critical of the Bridges to Access program. We also believe that GSK and Schering understand the need to expand these programs, and that this understanding was implicit in their testimony at the PADAC meeting and written comments (see pp. 5–6 of GSK's corrected comment of August 25, 2004 (2003P–0029/CR1) and p. 4 of Schering's comment of August 13, 2004 (2003P–0029/C31)).

(Comment 18) A speaker at the PADAC meeting said because albuterol HFA inhalers retail for $20 more than generic albuterol CFC MDIs, an early phaseout of albuterol HFA MDIs could result in a total $5 billion in additional treatment costs until HFA inhalers come off patent. The speaker also said the economic burden would fall most heavily on those Americans least able to pay the price, with a disproportionate effect on minorities, inner-city children, elderly patients on fixed incomes, and the rural poor. The speaker asserted that eliminating the essential-use designation before lower-priced generic albuterol HFA MDIs are on the market would force many lower-income patients to discontinue use of albuterol MDIs. The speaker also referred to a recent study in *JAMA: The Journal of the American Medical Association* indicating that increasing copayments can reduce prescription drug use up to 32 percent. She further stated this would result in a cascading increase in total health care costs, as patients who discontinue their albuterol are admitted to emergency rooms and hospital wards.

A speaker representing an economics consulting firm under contract to GSK stated at the PADAC meeting that patients would be adequately served by albuterol HFA MDIs. He projected the average price per MDI would increase by $9.87 and the yearly average cost per patient would rise by $16.02. He also said adequate programs were in place to minimize the adverse impact on lower-income patients.

Several comments from patients, health care professionals, and other parties stated the elimination of lower-priced generic albuterol MDIs that would result from this rule would force many patients to discontinue the use of albuterol MDIs, with significant adverse impact on their health, increased hospitalizations, loss of time at work, and a worsening quality of life. Many of these comments recommended the essential-use status of albuterol MDIs not be removed until after generic albuterol HFA MDIs are approved and marketed.

Other comments agreed with our tentative conclusion stated in the 2004 proposed rule that patients will be adequately served by albuterol HFA MDIs.

While we do not agree with the statement from the speaker from the contract economic consulting firm that the average price per MDI would only increase by $9.87 and that the yearly average cost per patient would only rise by $16.02, we do agree with the conclusion of the speaker that the price of albuterol HFA MDIs will not prevent patients from being adequately served. As discussed in more detail in section V of this document, we estimate that the retail cash price per MDI would increase by $27 and the average yearly cost to uninsured patients would rise $95. While higher drug prices are undesirable, we do not believe that asthma and COPD patients will be forced to stop using albuterol MDIs because of price increases. We believe that the programs discussed in comment 17 of this document can, if properly utilized, provide a safety net for lower-income patients who otherwise could not afford this very important drug. Section V of this document contains a fuller discussion of the economic issues presented by this rulemaking. While we recognize that sales of albuterol MDIs may decline by approximately 1 or 2 percent as a result of this rulemaking, this decline in sales does not necessarily equate to patients having to forgo appropriate treatment of their asthma or COPD because of price increases. There are many ways patients may modify their behavior in order to minimize the impact of elimination of generic albuterol MDIs, including: increasing their use of other asthma and COPD drugs, including non-albuterol bronchodilators (and thereby decreasing their need for albuterol); buying fewer MDIs to keep in different locations because they have chosen to limit the number of MDIs they have beyond the one patients generally carry on their person. Patients with infrequent bouts of bronchospasm may also choose not to purchase albuterol HFA MDIs that the patients believe they might not use, even though the patients are financially able to do so.

(Comment 19) A speaker at the PADAC meeting said an FDA policy that removed lower priced generic drugs from the market was contrary to the intent of the Drug Price Competition and Patent Term Restoration Act of 1984

(Public Law 98–417) (Hatch-Waxman amendments). A written comment asserted the real intent of this rulemaking was to remove generic albuterol MDIs from the market.

We recognize that one of the consequences, although not one we desire, of this rulemaking will be the removal, for a period of time, of generic albuterol MDIs from the market. We agree with the speaker at the PADAC meeting that one of the general intentions of the Hatch-Waxman amendments is to encourage the entry of lower-priced generic drug products into the market. However, another key purpose of the Hatch-Waxman amendments is to encourage significant innovations in human drugs (*see generally* 130 Cong. Rec. H9113–14 and H9121–22 (Sept. 6, 1984) (statements of Rep. Waxman)). The development of HFA inhalers represents large investments of time and money by innovator firms. This investment resulted in innovative products that significantly serve the public health by protecting the stratospheric ozone. While the provisions of the Hatch-Waxman amendments do not directly apply to this rulemaking, the underlying general policy of encouraging innovation and protecting investment in research and development does apply as much as the policy of encouraging the availability of lower-priced generic drugs. Most importantly, there is no specific provision in the Hatch-Waxman amendments that prohibits us from removing generic albuterol MDIs from the market. There is, however, specific language in the Clean Air Act (42 U.S.C. 7671) that requires us to evaluate whether a use of an ozone-depleting substance in a drug product is, or remains, an essential use. We are obligated to follow the specific mandate Congress gave us in the Clean Air Act, rather than one of two general policies underlying another piece of legislation.

(Comment 20) One comment suggested we approve generic albuterol HFA MDIs immediately, to lower expenses incurred by asthma patients.

Albuterol HFA MDIs are the subject of patents that may affect the availability of generic albuterol HFA MDIs until they expire. FDA's ability to approve generics is constrained by the patent and exclusivity protections afforded by the Hatch-Waxman amendments. FDA may not approve generic albuterol HFA MDIs before permitted by law.

(Comment 21) One comment expressed concern that the removal of the essential-use designation for albuterol MDIs would lead to higher costs to the Federal Government as a result of the Medicare prescription drug benefits that will go into effect on January 1, 2006 (see Title I of the Medicare Prescription Drug Improvement and Modernization Act of 2003 (Public Law 108–173, December 8, 2003)). The comment recommended that the essential-use designation for albuterol not be removed until generic albuterol HFA MDIs come on the market, to minimize spending by the Federal Government.

Although cost to the Federal Government is not a criterion under § 2.125(g), the availability of prescription drug benefits under Medicare does affect whether patients are adequately served by the non-ODS products. In fact, the prescription drug benefits will reduce the impact of higher prices for albuterol MDIs on Medicare-eligible patients, who would not otherwise have prescription drug insurance benefits. This will help ensure that patients are adequately served by albuterol HFA MDIs.

(Comment 22) A few comments suggested that prices for albuterol HFA MDIs would increase after the rulemaking. A GSK spokesperson at the PADAC meeting stated that GSK had committed to a price freeze on VENTOLIN HFA until December 31, 2007. The commitment was repeated in GSK's subsequent written comments.

We believe that GSK's price freeze will be effective in keeping prices at the current level through much of the transition period before the effective date of this rule. Although Schering has not made a similar commitment, it seems unlikely that they will raise their prices knowing that one of their two competitors is committed to a price freeze. The presence of both GSK and Schering in the market should provide downward pressure on prices for albuterol HFA MDIs that will continue after the effective date of this rule (see pp. 13–20 of the National Economic Associates' comment of August 13, 2004 (2003P–0029/C25), and section V.D.1 of this document). Even if this pressure does not result in price decreases, it may prevent price increases. A representative of IVAX indicated at the PADAC meeting that IVAX's albuterol HFA MDI would be priced lower than PROVENTIL HFA and VENTOLIN HFA. IVAX's entry into the albuterol HFA MDI market and the potential market entry of additional albuterol HFA MDIs will provide additional downward pressure on prices even before the entry of generic albuterol HFA MDIs.

(Comment 23) One comment objected to the elimination of the essential-use designation for albuterol MDIs, saying the price of albuterol HFA MDIs is more than $100 per MDI compared to generic albuterol CFC MDIs, which cost less than $10 per MDI.

The issue of the impact of higher prices for albuterol HFA MDIs is one that we have given a great deal of thought, but the difference is not nearly as great as this comment states. The weighted average (across all payer types) of retail prescription price for generic albuterol CFC MDIs during the first half of 2004 was about $13.50 per MDI and the weighted average retail prescription price for albuterol HFA MDIs was about $39.50 per MDI (see section V.C.6 of this document). As we discuss in our response to comment 18 and section V of this document, we do not believe that this price difference prevents patients from using albuterol HFA MDIs.

(Comment 24) One comment recommended that we perform a cost-benefit analysis using Medical Expenditure Panel Survey (MEPS) data from the Agency for Healthcare Research and Quality (AHRQ).

The analysis of impacts described in section V of this document uses the MEPS data. While the analysis does look at both the costs and benefits of this rulemaking, we would not characterize the analysis as a full cost-benefit analysis because we are unable to fully quantify the public health costs and environmental benefits in dollar terms; however, we do quantify these costs and benefits to the extent we are able.

(Comment 25) One comment asserted that, while our analysis in the 2004 proposed rule of the economic impact of this rulemaking on patients was appropriate to the extent the analysis focused on whether higher prices would deter patients from using albuterol MDIs, those portions of the economic analysis that dealt with more general societal costs were inappropriate and contrary to the provisions of § 2.125.

We are required to examine the broader societal costs and benefits of any rulemaking. Executive Order 12866 directs us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. The Regulatory Flexibility Act (5 U.S.C. 601–612) requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 (Public Law 104–4) requires that agencies prepare a written statement that includes an assessment of anticipated costs and benefits before proposing any rule that includes any Federal mandate that may result in significant expenditure by State, local,

and tribal governments, or the private sector.

(Comment 26) A few comments stated albuterol HFA MDIs were unacceptable alternatives because they did not propel the drug with adequate force into the lungs. Other comments stated that they had to use an albuterol HFA MDI several times to get the same effect they had received from significantly fewer uses of an albuterol CFC MDI. Several comments from patients stated that their experience indicated albuterol HFA MDIs were less effective than albuterol CFC MDIs, while other comments from patients stated that they had found albuterol HFA MDIs to be more effective than albuterol CFC MDIs. One physician commented that she believed HFA MDIs were better drug delivery systems than CFC MDIs.

The wording of certain comments leads us to believe that at least some of people submitting these comments may be confusing dry powder inhalers (DPIs) or aqueous (AQ) pumps with HFA MDIs. There are currently no albuterol DPIs or AQ pumps being marketed. We did not consider any DPI or AQ pump as a potential alternative to albuterol CFC MDIs. Other comments may reflect the common misperception that MDIs propel drugs into the lungs. MDIs do not in fact propel any significant amount of drug into the lungs. MDIs propel the drug into the mouth and the drug is then inhaled into the lungs. Albuterol CFC MDIs and albuterol HFA MDIs work in same way; both contain the active ingredient as a very fine powder which is delivered in a suspension into the patient's mouth. MDIs that forcefully deliver the drug suspension may actually be less effective at delivering the drug into the lungs. In these instances, a significant portion of the drug may be sprayed onto the surfaces in the back of the mouth, from which they will be swallowed rather than inhaled into the lungs. An explanation that we believe likely for some of these perceived differences is the possibility that the albuterol HFA MDIs that were being used had clogged mouthpieces. Cleaning the mouthpieces as described in the labeling for PROVENTIL HFA and VENTOLIN HFA should alleviate these problems.

Whatever the perceived differences between albuterol CFC MDIs and albuterol HFA MDIs may be, clinical studies have shown the albuterol HFA MDIs are as effective as the albuterol CFC MDIs in treating asthma and COPD.

(Comment 27) One comment stated we should not remove the essential-use designation for albuterol MDIs because members of the person submitting the comment's family are allergic to the lactose contained in alternative products.

Neither VENTOLIN HFA nor PROVENTIL HFA contains lactose. While other inhaled drug products for the treatment of asthma and COPD do contain small amounts of lactose, our determination on the essential-use designation for albuterol MDIs is based exclusively on the suitability of VENTOLIN HFA and PROVENTIL HFA as alternatives.

(Comment 28) One person said in his comment he had an adverse reaction that included tachycardia (elevated heart rate) after taking PROVENTIL HFA. He attributed the adverse event to ethanol, which is an inactive ingredient in PROVENTIL HFA and to which he is sensitive.

Reports of an allergic reaction attributed to the very small amounts of ethanol contained in PROVENTIL HFA are extremely rare.[9] VENTOLIN HFA, which does not contain ethanol, should be considered for asthma and COPD patients who may be sensitive to ethanol. Unlike the albuterol CFC MDIs, VENTOLIN HFA and PROVENTIL HFA do not contain identical active ingredients, and patients having difficulties with one product should discuss with their physicians switching to the other.

(Comment 29) One person said in his comment he had an asthma attack after his first use of a QVAR (beclomethasone dipropionate) HFA MDI. He attributed the adverse event to the HFA propellant in the QVAR MDI and concluded that HFA MDIs would not serve patients who were sensitive to HFA.

Another person said in her comment her use of an albuterol HFA MDI caused irritation and triggered an asthma attack.

A third comment suggested HFA MDIs could be less likely to cause paradoxical bronchospasm because of tighter specifications for the various compounds in the MDIs.

Bronchospasm may occur after using any inhaled asthma drug, including both albuterol CFC and HFA MDIs. The approved labeling for both albuterol CFC and HFA MDIs, as well as QVAR and most other approved inhaled drugs, describe paradoxical bronchospasm as an adverse event that can be expected in a small number of patients. Paradoxical bronchospasm seems to be associated with the first use of an MDI or vial of an inhaled drug. The warnings about paradoxical bronchospasm represent a general concern with inhaled drugs, and do not represent a special concern for albuterol CFC and HFA MDIs or QVAR. Paradoxical bronchospasm is very rare; a study conducted in the United Kingdom of 10,472 patients regularly using VENTOLIN EVOHALER (an albuterol HFA MDI marketed in the United Kingdom that is substantially similar to VENTOLIN HFA) over five 3-month observation periods, did not show any incidents of paradoxical bronchospasm (Ref. 3). We have not seen any evidence from the clinical studies of various HFA MDIs that this type of adverse event is more or less common with HFA MDIs than with CFC MDIs. Absent other data, we cannot assume that the adverse events described in the comments were caused by the HFA propellant in the MDIs.

(Comment 30) A few comments stated albuterol HFA MDIs left a powdery residue at the back of the throat. One person said in her comment that after using an albuterol HFA MDI she felt the need to rinse her mouth out. One comment said this tendency to leave a powdery residue could lead to thrush and other infections.

A very small number of patients have reported an unpleasant powdery residue in the oral cavity after use of an albuterol HFA MDI. Any MDI can leave a residue in the oral cavity. Use of a spacer can minimize the amount of residue left in the mouth. Patients who experience this problem may wish to speak to their physicians about using a spacer with the MDI. We do not consider problems with a powdery residue to be either prevalent enough or serious enough to prevent patients from being adequately served by albuterol HFA MDIs.

Thrush, also known as candidiasis, is occasionally seen with the use of inhaled corticosteroids. Although thrush may be seen in patients who are taking both inhaled corticosteroids and inhaled albuterol, there is no evidence to suggest that use of albuterol or HFA contributes to the development of thrush. Accordingly, we do not believe thrush to be a problem with use of albuterol HFA MDIs.

(Comment 31) One comment stated albuterol HFA MDIs are not an adequate substitute because they cannot be used with spacers.

Commercially available spacers can be used with both albuterol HFA MDIs. Patients who are having difficulties with any MDI may wish to speak to their

[9] We are only aware of one report in our MedWatch system of an allergic reaction attributed to the very small amounts of ethanol contained in PROVENTIL HFA. VENTOLIN HFA, which does not contain ethanol, should be considered for asthma and COPD patients who may be sensitive to ethanol. MedWatch is the FDA safety information and adverse event reporting program, which allows health care professionals and consumers to report serious problems that they suspect are associated with the drugs and medical devices they prescribe, dispense, or use.

physicians about using a spacer in conjunction with the MDI.

We find that patients who medically require albuterol CFC MDIs are adequately served by albuterol HFA MDIs.

F. Effective Date

(Comment 32) Several speakers at the PADAC meeting and comments, including comments from Schering, 3M, and GSK, recommended an effective date of December 31, 2005.

Schering, 3M, and GSK have all stated that adequate production capacity and supplies would be in place by December 31, 2005. However, the December 31, 2005, date is merely a projected date, and neither Schering, 3M, nor GSK provided the basis for their projections. No timelines, construction and installation schedules, or training goals were provided to us. We have no descriptions of what new machinery must be procured, nor any idea when that machinery can be up and running. While we believe that the projections were made in good faith, unanticipated delays and shortages could push the date on which adequate production capacity and supplies are in place significantly beyond December 31, 2005. Due to the lack of underlying information, we are unable to evaluate the likelihood or length of any possible delays.

If this rule were to go into effect before adequate production capacity and supplies were in place, there would not be a smooth transition from albuterol CFC MDIs to albuterol HFA MDIs. We could be forced to publish a document postponing the effective date. We could see resumption of production at albuterol CFC MDI lines that had been closed and increased production to restock supplies of albuterol CFC MDIs that had been allowed to dwindle in anticipation of the effective date of this rule. If needed CFCs, MDI components, or production facilities were unavailable, shortages of albuterol MDIs could exist.

Furthermore, if we were forced to push the effective date of this rule back because of the failure of manufacturers to have adequate production capacity and supplies in place, it would be very harmful to any transition education program. Patients and health care providers would be provided with different dates by which the transition from albuterol CFC MDIs to albuterol HFA MDIs would be completed. This could lead to confusion, lack of trust, and the belief that people would not have to think about the transition because it would probably be postponed again.

When we consider how serious and life threatening asthma and COPD are, and how important albuterol MDIs are in treating asthma and COPD, it becomes apparent that a conservative estimate of when sufficient supplies and production capacity will exist and a later effective date will better ensure that shortages do not happen and a smoother transition will be made. For these reasons we believe that a December 31, 2005, effective date does not provide an adequate safety margin to ensure that adequate production capacity and supplies will be in place. Accordingly, we have determined that December 31, 2008, is a more appropriate effective date for this rule.

We arrived at a December 31, 2008, effective date with the expectation that an orderly transition to albuterol HFA MDIs would be completed by that date. Although significant production and supplies may be in place prior to this date, in light of the serious consequences of inadequate supplies and the need to ensure that vulnerable patients have adequate access, the date of December 31, 2008, ensures that the criteria in § 2.125(g) will be met and that the transition to albuterol HFA MDIs can be accomplished smoothly. This transition period between the publication of the final rule and the effective date ensures that new facilities will be on line, that manufacturers will have successfully demonstrated their ability to produce necessary supplies of albuterol HFA MDIs, and patients and health care providers will be adequately educated about the transition to albuterol HFA MDIs. After the effective date, section 610 of the Clean Air Act would prohibit the sales of albuterol CFC MDIs in interstate commerce. As discussed in response to comment 42 of this document, the transition time under this rule should allow for retailers and their suppliers to deplete their stock.

(Comment 33) One comment suggested a 2007 effective date without giving reasons why this date would be more appropriate than others.

This comment did not provide any information or rationale for the date, and our rationale for the December 31, 2008, effective date is set out in our response to comment 32 of this document.

(Comment 34) A few comments asked that we set an effective date that will allow patients to try different albuterol HFA MDIs to see if they perform adequately for individual patients.

We believe the December 31, 2008, effective date provides ample opportunity for patients to work with their healthcare providers to determine the best substitute.

(Comment 35) Several comments urged us to set the effective date for this rule late enough to allow lower-priced generic albuterol HFA MDIs onto the market before the essential-use status of albuterol MDIs is removed.

As we discussed in our responses to comment 18 and in section V of this document, we do not believe that presence of generic albuterol HFA MDIs is necessary to ensure that patients are adequately served by albuterol HFA MDIs.

(Comment 36) In the 2004 proposed rule we asked for comments ''on when patents may cease to bar the marketing of generic albuterol HFA MDIs'' (69 FR 33602 at 33608). We did not receive any substantive comments on this issue. One comment, while agreeing with us that we do not have the institutional expertise to evaluate patents, criticized our statement that ''it seems at least possible that key patents could be successfully challenged well before 2015 or perhaps even 2010, allowing generic drugs to enter the market much earlier than anticipated'' (69 FR 33602 at 33608). The comment asserted it would be irresponsible to base any decision on the mere possibility that patents may be successfully challenged. The comment also stated competition would not be blocked because of the ability of firms to license HFA MDI technology from 3M. It also pointed to IVAX as a potential source of competition.

We did not receive any substantive comments on the validity of the patents listed in the Orange Book for albuterol HFA MDIs. Because we have determined that, as we discussed in our response to comment 18 and in section V of this document, the presence of generic albuterol HFA MDIs in the market is not necessary to ensure that patients are adequately served by albuterol HFA MDIs, it is not necessary for us to reach a conclusion on the validity of those patents. We do not believe that IVAX or entrants into the albuterol HFA MDI market that license HFA MDI technology from 3M will be priced as low as current generic albuterol CFC MDIs. We base this belief on the added expense that licenses will entail for manufacturers and the past history of drug pricing. However, we do believe that IVAX and other, potential, entrants can exert downward pressure on prices that could result in lower prices than we currently see for albuterol HFA MDIs.

(Comment 37) A representative of Honeywell, speaking at the PADAC meeting, said Honeywell planned to resume production of CFC propellants at a Louisiana plant, and gave

assurances that Honeywell Chemicals could supply CFC propellants for years to come, if needed. He also said FDA should not consider a shortage of CFC propellants in establishing a transition strategy. Honeywell later provided more details on the subject in a written comment.

Another speaker at the PADAC meeting said Honeywell's resumption of production at their Baton Rouge plant would violate U.S. law and the Montreal Protocol. He further said that according to statements made by Honeywell, current stockpiles of CFCs coupled with production of CFCs at Honeywell's Netherlands facility, which is scheduled to close at the end of 2005, should meet U.S. demand for CFCs for use in MDIs until 2008.

Another comment stated it was appropriate for us to take into account the disruptions in the supply of CFCs caused by Honeywell ending production of CFCs at their Netherlands facility and the equivocal legal status of Honeywell's resumption of production of CFCs at their Baton Rouge facility. It also said we should carefully scrutinize Honeywell's ability to manufacture pharmaceutical grade CFCs at the Baton Rouge facility.

Although we discussed Honeywell's continued production of CFCs in the 2004 proposed rule (69 FR 33602 at 33607–33608), this issue does not address any of the criteria under which we are making a determination on the essential-use status of albuterol MDIs. The criteria in § 2.125(g) direct us to examine the adequacy of supplies and capacity for the non-ODS substitutes, but not the supplies and capacity for the ODS product.

(Comment 38) Speakers at the PADAC meeting and written comments stated that the Parties to the Montreal Protocol were unlikely to continue to approve the United States' future nominations for allocations of CFCs for use in MDIs. One comment asked that we carefully consider the future supply of CFCs in setting an effective date for this rule. Another comment pointed out that a key raw material in the production of CFCs is carbon tetrachloride, an ODS that is being phased out under the provisions of the Montreal Protocol. The comment asserted that this could lead to a situation where it could be very difficult to obtain the needed raw materials for the manufacture of CFCs, even if the manufacture itself was allowed under the Montreal Protocol. Another comment urged us to not allow the fact that other Parties to the Montreal Protocol have initiated phaseouts of albuterol CFC MDIs pressure us into a premature action, pointing out that prices for albuterol HFA MDIs are lower in other countries.

We are obligated to follow the procedures and criteria in § 2.125 in this rulemaking, and the continued supply of CFCs under the Montreal Protocol or the phaseout strategies in other countries are not criteria listed in § 2.125(g) and these issues were not considered in this rulemaking.

(Comment 39) Prior to publication of the 2004 proposed rule, we received a comment from a manufacturer of MDI components submitted in response to the Stakeholders' petition. The manufacturer said it has the ongoing capacity to supply MDI components necessary for ongoing use of CFC MDIs, including albuterol CFC MDIs, and it will continue production as long as there is sufficient demand.

While we appreciate the information contained in this comment, the continued availability of MDI components necessary for continuing use of CFC MDIs is also not a criterion under § 2.125(g) upon which we may base our decision.

(Comment 40) One speaker at the PADAC meeting suggested that FDA monitor patient compliance and access to albuterol HFA MDIs and reserve the right to allow a certain number of albuterol CFC MDIs to be sold in case of a real emergency.

Under the Clean Air Act, a use of an ODS is either essential or it is not. We are currently unaware of any interpretation of the provisions of the Clean Air Act that would give us the flexibility to allow emergency sale or distribution of a CFC MDI once its use is determined to be non-essential.

(Comment 41) One comment recommended that we not set an effective date until we are certain that adequate production capacity will exist.

In choosing December 31, 2008, as the effective date of this rule, we did so with every reasonable expectation that adequate supplies and production capacity will exist by that time.

(Comment 42) A comment recommended that we not establish a date beyond which retail pharmacies are barred from selling albuterol CFC MDIs, even if we did establish a date beyond which albuterol CFC MDIs could not be manufactured.

The sale of remaining stocks of albuterol CFC MDIs was one of the factors we considered in establishing an effective date that is well after the date we expect the transition to HFA MDIs to be substantially completed by manufacturers of albuterol MDIs. This additional buffer period should give wholesalers and retailers adequate time to dispose of stocks of albuterol CFC MDIs. That being said, we do not have the authority to establish an effective dates for wholesalers and retailers that differs from an effective date for manufacturers. We can only make a determination on the date by which the criteria set out in § 2.125(g) will be met and the use of ODSs in albuterol MDIs is no longer essential. Once a product is no longer an essential use, the prohibitions in section 610 of the Clean Air Act automatically come into play. However, section 610 of the Clean Air Act only applies to sales in interstate commerce. If shipments of albuterol CFC MDIs by producers have stopped by December 31, 2007, or shortly thereafter, wholesalers and retailers should not find it difficult to distribute their stocks by December 31, 2008.

G. CFCs and the Environment

(Comment 43) A few comments asserted that CFCs used in MDIs do not have an adverse impact on the environment because the CFCs are inhaled rather than being released into the environment.

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 44) A few comments asserted that the amount of ODSs released from albuterol CFC MDIs is insignificant, and eliminating their use would not provide any environmental benefit.

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.

(Comment 45) A comment asserted that the Montreal Protocol is working well and that according to the Executive Summary of the ''World Meteorological Organization Global Ozone and Research Project—Report No. 47: Scientific Assessment of Ozone Depletion: 2002'' (Executive Summary) (available at *http://www.unep.org/ozone/Publications/6v_science%20assess%20panel.asp*), the continuing use of CFCs in albuterol MDIs would delay restoration of the Earth's ozone layer to its 1980 condition by an insignificant time past the currently projected date of 2050. The comment quoted the following passage from page xvii of the Executive Summary:

The updated, best-estimate scenario for future halocarbon mixing ratios suggests that the atmospheric burden of halogens will return to the 1980 pre-Antarctic-ozone-hole levels around the middle of the 21st century, provided continued adherence to the fully amended and adjusted Montreal Protocol. Only small improvements would arise from further reduced production allowances in the future.

The size of the delay in the date the ozone layer will be restored to its 1980 condition is not a criterion in determining which medical devices, diagnostic products, drugs, and drug delivery systems are essential under the Clean Air Act. These criteria are set out in § 2.125 and are discussed previously in this document. However, we note that the estimate described in the quoted paragraph assumes ''continued adherence to the fully amended and adjusted Montreal Protocol.'' As we discussed in section II.C.2 of this document, Decision IV/2 envisioned elimination of the production and importation of CFCs by January 1, 1996, by Parties that are developed countries. Although production and importation of CFCs for use in albuterol MDIs are permitted, year to year, as an essential use under the Montreal Protocol, we fail to see how a rule that permits sale and distribution of albuterol CFC MDIs into 2008 can be characterized as a reduction in production allowances. The Montreal Protocol is frequently called the most successful environmental treaty in history, yet its success is based primarily on voluntary compliance by all of the Parties to the treaty. If the United States were to continue sale and distribution of ODS products after adequate alternative products were available, this could lead other Parties to do the same, eventually threatening the integrity of the Montreal Protocol. In the words of the Executive Summary cited in the comment, ''Failure to comply with the Montreal Protocol would delay or could even prevent recovery of the ozone layer.'' (Executive Summary at xxv.) The continued existence of a strong Montreal Protocol is in the best interest of the public health of the United States, and our failure to take timely action on albuterol MDIs could potentially weaken the Montreal Protocol.

(Comment 46) One comment criticized our attempts in the 2004 proposed rule to quantify the environmental benefits of this rulemaking.

We agree with the comment that accurately quantifying the direct environmental benefits of this rule is very difficult and that quantifying the indirect environmental benefits may be impossible. However, as we discussed in our response to comment 25 of this document, we are under separate legal obligation to examine the broader societal costs and benefits of any rulemaking, including the environmental costs and benefits. Accordingly, the discussion of the environmental costs and benefits of this rule is separate from the determination as to whether the criteria in § 2.125 have been met.

(Comment 47) One comment stated the amount of CFCs released by MDIs is negligible compared to naturally occurring CFCs.

There are no naturally occurring CFCs.

(Comment 48) A few comments seemed to confuse CFCs with other greenhouse gases, such as carbon dioxide and nitrous oxide, when stating that MDIs were a minor source of CFCs compared to sources such as power plant and automobile emissions.

While CFCs are considered to be greenhouse gases, we are publishing this rule because the criteria in § 2.125 have been met, rather than any contribution CFCs may be making towards global warming.

(Comment 49) A few comments stated that MDIs were a minor source of CFCs compared to hair spray and deodorants.

CFCs were banned from deodorants, hair spray, and other cosmetics by the 1978 rule. Cosmetics containing CFCs have not been legally marketed in the United States since April 15, 1979, the effective date of the 1978 rule.

H. Comments on the Analysis of Impacts

(Comment 50) We received several comments about our estimates of the price increases that might result from the proposed rule.

One comment objected to FDA estimates of expected price increases based on the price gap between albuterol CFC MDIs and albuterol HFA MDIs from drugstore.com, because the Web site's market share is small and therefore does not accurately represent market prices. This comment recommended that we use retail cash albuterol MDI prices from IMS Health Inc. (IMS). Another comment took average wholesale prices of albuterol MDIs and inflated them according to average retail markups on albuterol for cash payers of 28.8 percent for branded MDIs and 363.3 percent for generic MDIs. From this, the comment calculated cash payers will pay on average $8.61 more per MDI.

Another comment contended that price increases are of limited importance, because insurers have an incentive to maintain lower copayments for albuterol. Lower copayments would minimize the costs to insurers for emergency department visits, hospitalizations, etc. that result from poorer compliance with albuterol therapy.

A few comments said individuals eligible for Medicare or Medicaid are unlikely to face higher costs for albuterol as a result of this rule.

We believe that cash albuterol MDI prices best reflect prices paid by the uninsured, and, consistent with the comment, have considered data on retail cash albuterol MDI prices from IMS, which are generally considered to be the best price data available. Although we did use prices from drugstore.com in the 2004 proposed rule,[10] this was done primarily because we did not have rights to use the IMS data when the 2004 proposed rule was being prepared. IMS retail price data reflect the impact on consumers better than other measures such as estimates derived from average wholesale cash prices inflated by average retail markups for cash payers.

After reviewing these comments, we continue to believe that the likely price increase will be approximately the current difference in price between generic albuterol CFC MDIs and albuterol HFA MDIs, although competition from IVAX's approved albuterol HFA MDI and other albuterol

[10] Although the prices derived from IMS data give us much greater assurance than the prices found on drugstore.com that the numbers we use accurately reflect market prices, in the case of albuterol MDIs the differences in prices are not very significant. The drugstore.com price for generic albuterol CFC MDIs is $13.99, while the weighted average retail price derived from IMS data is approximately $13.50. The drugstore.com prices for VENTOLIN HFA and PROVENTIL HFA are $39.61 and $38.99 respectively, while the weighted average retail price derived from IMS data for albuterol HFA MDIs is $39.50. The drugstore.com prices are those posted on February 10, 2005. See section V.C.6 of this document for more information on the prices derived from IMS data.

HFA MDIs that enter the market may lower prices somewhat.

We believe that price increases are an important determinant of access for individuals without insurance, who are likely to pay the full amount of price increases out of their own pockets. Copayments for albuterol MDIs for privately insured individuals may change when this rule goes into effect, but such changes will be determined by their insurers. While copayments are generally higher for branded drugs, they are not necessarily higher for branded drugs that lack a generic alternative. We are unable to predict how average copayments may change as a result of the rule.

We agree with the comments suggesting that individuals eligible for Medicare or Medicaid are unlikely to face higher out-of-pocket costs for albuterol as a result of this rule.

(Comment 51) Comments were submitted about our use of estimates of consumers' response to drug price increases taken from the Goldman article (Ref. 4). One comment noted that elasticity estimates in the Goldman article were based on a broad range of asthma drugs, many of which differ from albuterol MDIs in important ways. The comment contended that these differences prevent us from drawing meaningful conclusions about how demand for albuterol MDIs will respond to price increases.

A second comment noted that the proposed rule failed to make use of estimates in the Goldman article indicating a price elasticity of demand for asthma drugs as large as -.32.

We recognize the limitations of applying results from the Goldman article to the market for albuterol MDIs, and have sought to characterize fully the associated uncertainty. We believe, however, that focusing on a range of elasticity estimates from -.05 to -.15 is reasonable and appropriate given available information.

We used the Goldman article because it provides recent estimates of how consumer demand for asthma drugs responds to price increases. The article finds that among all users of asthma drugs, a doubling of copayments for asthma drugs reduced drug use by 32 percent. Among chronic asthma sufferers, use of asthma drugs decreased only 22 percent. To the extent that asthmatics are more willing to reduce their use of maintenance drugs, such as steroid inhalers, than to reduce their use of rescue drugs, such as albuterol MDIs, the true consumer response to albuterol MDI price increases may be less than the Goldman article suggests.

We acknowledge the potential shortcomings of applying estimates from the Goldman article to the market for albuterol MDIs but, lacking better information upon which to base our estimates, focus on the range of elasticity estimates from -.05 to -.15, the same range focused upon in the proposed rule.

(Comment 52) Several comments sought to place our analysis of impacts in proper historical context by suggesting that the reductions in use that we estimate are small compared with historical variations. One comment noted that introduction of generic albuterol MDIs to the market for albuterol MDIs in the mid-1990s, and the associated decline in prices, was not associated with any decrease in asthma morbidity.

A second comment noted that the introduction of cheaper generic albuterol MDIs did not result in an increase in consumption of albuterol MDIs, implying that removal of generic albuterol MDIs should not result in a decrease in consumption.

A third comment pointed out that the introduction of generic albuterol MDIs to the market coincided roughly with the entry of therapeutic alternatives such as salmeterol xinafoate, ipatropium bromide, fluticasone propionate, and COMBIVENT, which would have decreased demand for albuterol MDIs at the time lower priced generics became available.

A fourth comment noted that year-to-year fluctuations in demand for albuterol MDIs exceed 1 million units, implying that estimated decreases in albuterol demand are small relative to the market.

We believe it is difficult to draw conclusions about the future albuterol MDI market based on characteristics of the market from the 1990s. Our projected decrease in albuterol MDI sales assumes that, apart from price increases, other determinants of albuterol demand are held constant. In the mid–1990s, several factors that influence albuterol MDI demand changed including the prevalence and incidence of asthma and COPD and patterns of medical practice. However, the effects of these changes cannot easily be estimated with existing data. For example, changes in asthma prevalence before and after 1997 are complicated by changes in the design of the National Health Interview Survey in 1997. We believe the comment stating that introduction of new asthma drugs at this time decreased demand for albuterol MDIs is probably correct, but we lack the data needed to quantify any decrease in demand caused by introduction of new asthma drugs. Because important determinants of albuterol MDI demand are not held constant, the lack of a clear relationship between aggregate albuterol MDI sales and average prices in the 1990s does not undermine the projection that, all other factors remaining the same, use of albuterol MDIs will fall as prices rise.

We agree that a reduction in albuterol MDI use of several hundred thousand annually is a small percentage of the total number of albuterol MDIs used in the United States.

I. Other Comments

(Comment 53) Speakers at the PADAC meeting and written comments said albuterol MDIs were overused and the phaseout of albuterol CFC MDIs would be an appropriate time for physicians and patients to reevaluate the patients' use of asthma medication. The reevaluation would optimize drug regimens used by asthma patients by emphasizing use of maintenance drugs and deemphasizing the use of albuterol MDIs as a rescue medication. One comment suggested we incorporate strategies to encourage these interchanges into this final rule. Another written comment disagreed with these comments, and asserted that the elimination of the essential-use designation for albuterol MDIs should not be viewed as a teachable moment and it would be inappropriate to force patients to use other longer acting but more expensive drugs by effectively raising the price of albuterol MDIs.

While recognizing that many experts believe that albuterol MDIs are being overused, we do not have any reliable data that show that there is a significant pattern of overuse. In any case, the overuse or underuse of a drug product is not a factor that we consider under § 2.125(g). We do, however, welcome any opportunity for physicians and patients to reexamine the patients' drug use and to try to optimize the patients' treatment regimens. It is also important to remember that we do not regulate the practice of medicine and, depending on how the strategies are expressed, an effort on our part to incorporate into our regulation strategies to encourage these consultations might be construed as the regulation of the practice of medicine.

(Comment 54) A comment from an industry organization stated that educating patients and health care providers about the transition from albuterol CFC MDIs to albuterol HFA MDIs is very important, and offered to participate in cooperative education programs with FDA and other interested parties. GSK has outlined their education plans in their comments.

Other comments stated the importance of transition education.

We agree that educating patients and health care providers about the transition is very important. Anyone who wishes to discuss a cooperative educational effort with HHS and FDA should contact FDA or the Office of the Secretary of HHS.

(Comment 55) One comment recommended that, in setting an effective date, we take into consideration the time necessary to educate patients and health care providers about the transition to albuterol HFA MDIs, and one comment recommended more time for this education.

We believe that educating patients and health care providers about the transition to albuterol HFA MDIs is very important. From most patients' perspective, albuterol HFA MDIs are essentially identical[11] to the albuterol CFC MDIs they will be replacing. An explanation that an albuterol HFA MDI is being substituted for the albuterol CFC MDI the patient had been receiving and a explanation of the differences in using the new MDI should be adequate for the vast majority of patients. This explanation can be given by the patient's physician, pharmacist, or other health care provider. While we realize it will take some time to prepare and distribute educational material, we believe that adequate education can easily be provided before the final transition to albuterol HFA MDIs.

(Comment 56) One comment asserted that ''a premature phaseout would compromise the reward structure for innovation.'' The comment also asserted that firms that had made substantial investments in developing albuterol HFA MDIs would be adequately rewarded for the innovation even if this rule were made effective at a date that would allow generic albuterol HFA MDIs to enter the market before the removal of the essential-use designation for albuterol MDIs. The comment stated that GSK had profited handsomely from sales of its combination fluticasone and salmeterol DPI products in the United States and abroad.

We do not see, nor does the comment explain, how profits from the sale of combination fluticasone and salmeterol DPIs could be seen as a reward for GSK's albuterol HFA MDI research and development. Even if we assume that GSK's sales of other products somehow provide adequate incentives for its innovation, the comment does not assert how the research and development efforts of 3M, the manufacturer of the first albuterol HFA MDI marketed in the United States, have been rewarded.

The development of ozone-friendly products is important to achieving the goal of protection of the Earth's ozone layer. Accordingly, it is a factor we considered in our analyses of impacts (see 69 FR 33602 at 33614–33615 and section V of this document).

(Comment 57) One comment emphasized the importance of encouraging the development of ozone-friendly products and stated that, in consideration of the pharmaceutical firms developing ODS free alternatives, the U.S. Government had committed itself ''to ensure prompt removal of nonessential CFC MDIs as soon as new and reformulated products became available.''

As we said previously in this document, the development of ozone-friendly products is important to achieving the goal of protection of the Earth's ozone layer. However, we are unaware of the commitment described in this comment. The 2002 final rule and this rulemaking have been undertaken under our obligations under the Clean Air Act and the Montreal Protocol.

(Comment 58) A few comments expressed unfavorable opinions on salmeterol DPIs and combination fluticasone and salmeterol DPIs. Another comment complained about the high prices of levalbuterol hydrochloride (HCl) inhalation solution.

We have not considered salmeterol DPIs, combination fluticasone and salmeterol DPIs, or levalbuterol HCl inhalation solution to be alternatives to albuterol CFC MDIs. Comments about salmeterol DPIs, combination fluticasone and salmeterol DPIs, and levalbuterol HCl inhalation solution are not relevant to this rulemaking.

IV. Environmental Impact

We have carefully considered the potential environmental effects of this action. We have concluded that the action will not have a significant adverse impact on the human environment, and that an environmental impact statement is not required. Our 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.

V. Analysis of Impacts

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), the Unfunded Mandates Reform Act of 1995 (Public Law 104–4), and the Congressional Review Act. 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). We believe that this final rule is consistent with the regulatory philosophy and principles identified in the Executive order. This final rule is considered 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. We lack the data to certify that this final rule will not have a significant economic impact on a substantial number of small entities. Therefore, we have prepared a Regulatory Flexibility Analysis.

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 issuing ''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 $115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product. This rule, however, does not contain such a mandate.

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

Limitations in the available data prevent us from estimating quantitatively the anticipated costs and benefits to society, so we focus instead on proxy measures. The costs of this final rule include the benefits lost by consumers who would have bought albuterol MDIs at the current price but are unwilling or unable to buy them at

[11] While PROVENTIL HFA and VENTOLIN HFA can be substituted for albuterol CFC MDIs, they are not therapeutic equivalents to albuterol CFC MDIs, or to each other, as that term is defined in the Orange Book. There are minor differences between the formulations of VENTOLIN HFA and PROVENTIL HFA that might be significant for some small patient subpopulations (see our response to comment 28 of this document), but for the vast majority of patients these differences should not be significant.

a higher price. The price of albuterol MDIs will rise because this rule, by ending the essential-use designation for albuterol MDIs, will effectively remove less expensive generic versions of albuterol MDIs from the market. Consumers and third-party payers, including Federal and State Governments, will spend more for albuterol MDIs as a result of the price increase. But this increased spending is not part of social cost as conventionally defined, because it represents resources that are transferred from drug buyers (consumers and third-party payers) to drug sellers (drug manufacturers, wholesalers, pharmacies, etc.). The benefits of this rule include the value of improvements in the environment and public health that may result from reduced emissions of ODSs (for example, the reduced future incidence of skin cancers and cataracts). The benefits also include improved expected returns on investments in environmental technologies and greater international cooperation to comply with the Montreal Protocol. As we are unable to estimate the costs and benefits in dollar terms, we instead focus on the cumulative number of albuterol MDIs that might not be sold and the changes in CFC emissions as a result of the rule.

As a result of this rule, approximately 96 million to 430 million albuterol CFC MDIs will be removed from the market, depending on whether generic albuterol MDIs become available in 2010 or 2017. If generic albuterol HFA MDIs enter the market at the end of 2010 (when one of the earlier listed patents for albuterol HFA MDIs expires) then 96 million albuterol CFC MDIs would have been sold between the effective date of this rule (December 31, 2008) and the end of 2010, without the rule. If generic albuterol HFA MDIs enter the market at the end of 2017 (when the last listed patent for albuterol HFA MDIs expires)[12] 430 million albuterol CFC MDIs would otherwise have been sold between the effective date of this rule, and December 2017, without the rule. After generic albuterol HFA MDIs enter the albuterol MDI market and competition among albuterol HFA MDI producers determines the price, there would be no rationale related to patient access to albuterol MDIs for maintaining an essential-use designation for ODSs for albuterol.

Assuming generic albuterol HFA MDIs enter the market at the end of 2010, the removal of albuterol CFC MDIs will eliminate competition from low-cost generic drugs during the period between December 2008 and December 2010, thereby raising prices and increasing spending on albuterol MDIs by about $2.1 billion, assuming a 3-percent discount rate, or $1.7 billion, assuming a 7-percent discount rate (present value in 2005).

Assuming generic albuterol HFA MDIs enter the market at the end of 2017, the removal of albuterol CFC MDIs will eliminate competition from low-cost generic drugs during the period between December 2008 and December 2017, thereby raising prices and increasing spending on albuterol MDIs by about $8.3 billion, assuming a 3-percent discount rate, or $6.2 billion, assuming a 7-percent discount rate (present value in 2005).

Taking into account GSK's commitment to provide free samples and coupons, we estimate that higher prices due to the elimination of generic competition will reduce the number of albuterol MDIs sold by between 300,000 and 900,000 per year. This will induce U.S. consumers to use between 600,000 and 1.8 million fewer albuterol MDIs between the removal of albuterol CFC MDIs on December 31, 2008, and December 2010, or to use 2.7 million and 8.1 million fewer albuterol MDIs during the years between December 31, 2008, and December 2017. These estimates do not take into account the GSK and Schering patient assistance programs designed to provide free or low cost drugs to low-income patients. Should generic albuterol MDIs become available at the end of 2010, consumers will substitute 96 million albuterol HFA MDIs for albuterol CFC MDIs between 2008 and December 2010, reducing atmospheric CFC emissions by 2,400 tons in total. If generic albuterol MDIs become available at the end of 2017, substitution of albuterol HFA MDIs for the 430 million albuterol CFC MDIs that would have been consumed between 2008 and December 2017 will reduce atmospheric emissions of CFCs by about 10,800 tons in total. These quantitative estimates of the effects of this rule are summarized in tables 1 and 2 of this document.

TABLE 1.—SUMMARY OF QUANTIFIABLE EFFECTS OF THE FINAL RULE RELATIVE TO HFA PATENT EXPIRATION IN 2010

Number of Affected Albuterol MDIs (millions)	Increased Expenditures for Albuterol MDIs Present Value in 2005 (billions)		Possible Reduction in MDI Use (millions)	Reduced Aggregate Emissions Related to Phaseout (metric tons)
	3–percent discount rate	7–percent discount rate		
96 million	$2.1	$1.7	0.6 to 1.8	2,400

TABLE 2.—SUMMARY OF QUANTIFIABLE EFFECTS OF THE FINAL RULE RELATIVE TO HFA PATENT EXPIRATION IN 2017

Number of CFC Albuterol MDIs Removed From the Market	Increased Expenditures for Albuterol MDIs Present Value in 2005 (billions)		Possible Reduction in MDI Use (millions)	Reduced Aggregate Emissions Related to Phaseout (metric tons)
	3–percent discount rate	7–percent discount rate		
430 million	$8.3	$6.2	2.7 to 8.1	10,800

While the agency believes that the benefits of this regulation justify its costs, we cannot estimate quantitatively the public health effects of the phaseout. The decreased use of albuterol MDIs may adversely affect some patients, but we lack an ability to characterize such effects quantitatively. We also are unable to estimate quantitatively the reductions in skin cancers, cataracts, and environmental harm that may result from the reduction in CFC emissions by 10,800 metric tons during these years.

We state the need for the regulation and its objective in section V.B of this

[12] Since publication of the 2004 proposed rule, two patents that expire in 2017 have been listed in the Orange Book for VENTOLIN HFA.

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

B. Need for Regulation and the Objective of this Rule

This regulation is necessary because private markets are very unlikely to preserve levels of stratospheric ozone sufficient to protect the public health. Individual users of albuterol MDIs have no significant private incentive to switch to non-ozone depleting albuterol HFA MDIs. In fact, each user would bear all of the costs and virtually none of the benefits of such a switch, as the environmental and health benefits would tend to be distributed globally and occur decades in the future. Thus, the outcome of a private market would be continued use of the albuterol MDI available at the lowest price, even if the social value of reducing emissions were clearly much greater than the price premium for non-ozone depleting albuterol HFA MDIs.

The objective of this final rule is 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 albuterol MDIs because two acceptable ODS-free albuterol formulations have been successfully marketed in the United States for more than 2 years. Removing this essential-use designation will comply with obligations under the Montreal Protocol and the Clean Air Act, thereby reducing emissions that deplete stratospheric ozone, while preserving access to essential drugs by minimizing adverse effects on affected patient populations.

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 in the stratosphere. Excessive exposure to solar radiation is associated with adverse health effects such as skin cancer and cataracts, as well as other 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, environmental scientists from the United States and other countries advocated 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 III.B of this document. One hundred and eighty-six countries have now ratified the Montreal Protocol, and the overall usage of CFCs has been dramatically reduced. In 1986, global consumption of CFCs totaled about 1.1 million metric tons annually, and by 2000, total annual consumption had been reduced to fewer than 0.1 million metric tons (Ref. 5). This decline amounts to about a 90-percent decrease in consumption and is a key measure of the success of the Montreal Protocol. Within the United States, consumption of ODSs, and CFCs in particular, has fallen sharply—consumption of CFC–11 and CFC–12 is about 20 percent of 1990 consumption.[13]

A relevant aspect of the Montreal Protocol is that production of CFCs in any year by any country is banned after the phase-out date unless the Parties to the Montreal Protocol agree to designate the use as ''essential'' and approve a quantity of new production for that use. Each year, each Party nominates the amount of CFCs needed for each essential use and provides the reason why such use is essential. Agreement on both the essentiality and the amount of CFCs needed for each nominated use 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. 6). The benefits include reductions of hundreds of millions of nonfatal skin cancers, 6 million fewer fatalities due to skin cancer, and 27.5 million cataracts avoided between 1990 and 2165 if the Montreal Protocol were fully implemented. EPA estimates the value of these and related benefits to equal $4.3 trillion in present value when discounted at 2 percent over the period of 175 years. This amount is equivalent to about $6 trillion after adjusting for inflation between 1990 and 2004. This estimate includes all benefits of total global ODS emission reductions expected from the Montreal Protocol and is based on reductions from a baseline scenario in which ODS emissions would continue to grow for decades but for the Montreal Protocol.

4. Characteristics of COPD

Albuterol MDIs are used to treat COPD. While there is some overlap between asthma patients and COPD patients, COPD encompasses a group of diseases characterized by relatively fixed airway obstruction associated with breathing-related symptoms (for example, chronic coughing, expectoration, and wheezing). COPD is generally associated with cigarette smoking and is extremely rare in persons younger than 25.

According to the Centers for Disease Control (CDC), an estimated 10 million U.S. adults carried the diagnosis of COPD in 2000 (Ref. 7). Because the underlying surveys depend on patient-reported diagnoses and many affected individuals have not been formally diagnosed, the National Health Interview Survey (NHIS) suggests that as many as 24 million Americans may actually be affected by the disease. The proportion of the U.S. population with mild or moderate COPD has declined over the last quarter century, although the rate of COPD in females increased relative to males between 1980 and 2000. The most effective intervention in modifying the course of COPD is smoking cessation. Symptoms such as coughing, wheezing, and sputum production are treated with medication.

5. Characteristics of Asthma

Albuterol MDIs are also 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, viral infections, and others, may trigger an asthma attack.

[13] The ozone depleting potentials of CFC–11 and CFC–12 are equal. See *http://www.epa.gov/ozone/ods.html.*

According to the 2002 NHIS, approximately 20 million patients in the United States reported they had asthma (Ref. 8). The prevalence of asthma decreases with age, with the prevalence being 92 per 1,000 children ages 0–17 (6.1 million children) compared to 83 per 1,000 among adults ages 18–44 (7.4 million), 71 per 1,000 among adults ages 45–64 (4.6 million), and 59 per 1,000 among adults age 65 and over (1.9 million) (Ref. 8).

The NHIS reported that during 2002, about 12 million patients reported experiencing an asthma attack during the previous year (Ref. 8, table 10). According to the National Ambulatory Medical Care Survey, in 2001 there were 1.3 million outpatient asthma visits to physician offices and hospital clinics and 1.9 million emergency room visits (Ref. 8, table 16). According to the National Center for Health Statistics, there were 454,000 hospital admissions for asthma in 2001 (Ref. 8, table 12), and 4,269 mortalities (Ref. 8, table 1). The estimated direct medical cost of asthma (hospital services, physician care, and medications) was $9.4 billion (Ref. 8, table 17).

While the prevalence of asthma has been increasing in recent years, CDC reports that the incidence of asthma (or 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 have higher attack prevalence. The CDC notes that although numeric increases have occurred in the numbers and rates of physician office visits, hospital outpatient visits, and emergency room visits, these increases are accounted for by the increase in prevalence. This phenomenon might indicate early successes by asthma intervention programs that include access to medications.

6. Current U.S. Albuterol MDI Market

Albuterol is the preferred, and most commonly prescribed, short-acting relief medication for asthma and is also important in the treatment of COPD. For reasons of cost, convenience, and effectiveness, MDIs are the preferred, and most commonly prescribed, route of administration for albuterol.

We estimate that, in the first two quarters of 2004, U.S. consumers bought about 22.7 million generic albuterol MDIs through retail channels. This estimate is based on our analysis of IMS data (Ref. 10). Total consumption of albuterol MDIs has fluctuated around approximately 50 million MDIs annually over the last several years (Ref. 11). Based on retail sales, we estimate approximately 96 percent of albuterol MDIs sold were generic MDIs or branded MDIs relabeled and sold as generic (Ref. 10) (all containing CFCs), suggesting a total market for generic albuterol MDIs of approximately 48 million MDIs.

IMS provides data on average retail prices for marketers of albuterol MDIs for each of three payer types (cash customers, Medicaid recipients, and patients covered by other third-party payers), and the proportion of each marketer's sales to each payer type. As described in table 3 of this document, the weighted average (across all payer types) of retail prescription price for generic albuterol CFC MDIs during the first half of 2004 was about $13.50 per MDI, the weighted average retail prescription price for branded versions of albuterol CFC MDIs was about $38.90 per MDI, and the weighted average retail prescription price for albuterol HFA MDIs was about $39.50 per MDI.

TABLE 3.—SUMMARY OF CURRENT RETAIL PRICES FOR ALBUTEROL CFC AND HFA MDIS[1]

Payer Type	Generic Market Share (percent)	Albuterol CFC MDI Prices		Albuterol HFA MDI Prices	Price Premium: HFA MDI Price Relative to Generic Price		Estimated Units (millions)[2]
		Generics	Weighted Average Branded Products	Weighted Average	Dollars per MDI	Percent	
Cash	97.0	$19.13	$45.90	$46.32	$27.19	142	5.2
Medicaid[3]	97.3	$15.61	$37.10	$41.14	$25.53	164	8.7
Third-party	95.4	$12.03	$37.75	$38.60	$26.57	221	31.4
Total Market	96.0	$13.53	$38.87	$39.47	$25.94	192	45.3

[1] Source: (Ref. 10)
[2] These estimates reflect retail sales of generic albuterol MDIs, excluding sales at Internet and mail-order pharmacies.
[3] Medicaid prices do not reflect rebates given directly to States by drug companies.

We estimate albuterol CFC MDIs are responsible for roughly 1,200 metric tons of CFC emissions annually. Each albuterol CFC MDI contains about 21 grams of CFCs.[14] The estimated 48 million albuterol CFC MDIs sold annually therefore contain about 1,000 metric tons of CFCs. Adding an additional 20 percent to account for use in production, unusable batches, and other factors (as manufacturers typically do in the process of requesting essential-use allocations of CFCs for manufacturing) brings the total emissions to about 1,200 metric tons. To the extent that CFCs used in the production process are reclaimed and destroyed, this estimate overstates expected emissions reductions.

D. Benefits and Costs of the Final Rule

The benefits and costs of a government action are conventionally estimated relative to a baseline scenario that in this case is a description of the production, use, and access to albuterol MDIs in the absence of this rule. In this section we first describe such a baseline and then present our analysis of the benefits of the final rule. Next we turn to the costs of the rule and to an analysis of the effects on the Medicare and Medicaid programs.

1. Baseline Conditions

We developed baseline estimates of future conditions to estimate the economic effects of prohibiting marketing of albuterol CFC MDIs after December 31, 2008. It is standard practice to use, as a baseline, the state of the world absent the rulemaking in question, or where this implements a legislative requirement, the world absent the statute.

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

For the baseline in this analysis, we assume that access to CFC propellants, and therefore to albuterol CFC MDIs, continues indefinitely. This assumption focuses our analysis on the impact of removing less expensive generic albuterol CFC MDIs from the market, until the date that competition from generic albuterol HFA MDIs lowers prices. As stated previously in this document, we have identified listed patents on the HFA technology with expiration dates of 2009, 2010, 2014, 2015, and December 2017. In performing our analysis, we make two different sets of assumptions. First, we perform an evaluation based on the assumption that generic versions of albuterol HFA MDIS will come on the market after patents expire in 2010. Second, we perform an evaluation based on the assumption that generic albuterol HFA MDIs will come on the market after the last listed patent expires in 2017. Without this rule, U.S. commitments to the Montreal Protocol could limit future access to CFCs and, therefore, inexpensive generic albuterol CFC MDIs. This observation suggests an alternative baseline where Parties to the Montreal Protocol stop approving nominations for the use of CFCs in albuterol MDIs at a particular date. While the Parties could theoretically take such action for calendar year 2008, it would be speculative on our part to assume that they would take such action for that specific date or any other. As a result, we do not pursue a quantitative analysis with such alternative baselines.

Throughout our analysis, we assume that future prices for albuterol CFC and HFA MDIs do not change from current levels. This assumption overstates prices to the extent that competition from new entrants reduces future albuterol HFA MDI prices. We assume, however, that competition among the albuterol HFA MDI manufacturers will leave prices roughly stable and note that one manufacturer has pledged to freeze prices until at least the beginning of 2008.

Throughout this analysis, we assume that sufficient inventories of CFCs are available to meet demand up to December 31, 2008, and that albuterol HFA MDIs available on and after December 31, 2008, will be adequate to meet demand. In calculating the present value of increased expenditures, we discount expected future increases in expenditures by both 7 percent and 3 percent annually for each year after 2005.

2. Benefits of the Final Rule

The benefits of the final rule include environmental and public health improvements from protecting stratospheric ozone by reducing CFC emissions. Benefits also include expectations of increased returns on investments in environmentally friendly technology, reduced risk of unexpected disruption of supply of albuterol MDIs, and continued international cooperation to comply with the spirit of the Montreal Protocol, thereby potentially reducing future emissions of ODS throughout the world.

a. *Reduced CFC emissions.* Market withdrawal of albuterol CFC MDIs will reduce emissions by approximately 1,200 metric tons of CFCs per year. We have reviewed current CFC inventories and believe currently available quantities are likely to be sufficient to supply the albuterol CFC MDI market for approximately 12 months. Nominations for new CFC production are generally approved by the Parties to the Montreal Protocol 2 years in advance. The final rule bans marketing of albuterol CFCs after December 31, 2008. There is considerable uncertainty with respect to the amount of inventories that will be available in the future, but we anticipate that utilization of existing inventory will allow the United States to avoid requesting a 2008 exemption, or to significantly reduce the amount requested. Therefore, we estimate the final regulation will reduce CFC use by 1,200 metric tons per year after the end of 2008, a benefit that will continue beyond the evaluation period.

In an evaluation of its program to administer the Clean Air Act, EPA has estimated that the benefits of controlling ODSs under the Montreal Protocol are the equivalent of $6 trillion in current dollars. However, EPA's report provides no information on the total tons of reduced emissions or the incremental value per ton 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 ODS emissions from this regulation. Such benefits, in any event, were apparently included in EPA's earlier estimate of benefits.

As a share of total global emissions, the reduction associated with the elimination of albuterol CFC MDIs represents only a small fraction of 1 percent. Current allocations of CFCs for albuterol MDIs account for about 0.1 percent of the total 1986 global consumption of CFCs (Ref. 5). Furthermore, current U.S. CFC emissions from MDIs represent a much smaller, but unknown share of the total emissions reduction associated with EPA's estimate of $6 trillion in benefits because that estimate reflects future emissions growth that has not occurred.

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

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

Newly developed technologies to avoid ODS emissions have resulted in more environmentally ''friendly'' air conditioners, refrigerants, solvents, and propellants, but only after significant 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. 11).

These investments have resulted in several innovative products in addition to albuterol HFA MDIs. For example, breath-activated delivery systems, dose counters, dry powder inhalers, and mini-nebulizers have also been successfully marketed. This technology could also affect other drugs used for the treatment of asthma and COPD because of the likelihood that, eventually, CFCs will not be available for any drug use. To compare the effect of alternative phaseout dates on these returns to investment, we compare the ratio of the present value of increased revenues expected to accrue to innovative firms from a December 31, 2008, phaseout date and the present value of the future revenue stream of alternative phaseout dates, using both 7 percent and 3 percent annual discount rates. This ratio can provide a basis for relative assessments of the returns to investors for alternative phaseout dates. We present estimates of this ratio in a later discussion of alternatives.

Returns on investment are very sensitive to the current market prices in the United States. The pharmaceutical markets of other Parties to the Montreal Protocol operate with implicit or explicit price controls. These controls have depressed the potential returns to technological innovation. For example, in 2003, the ex-manufacturer prices (the prices of the drugs when they leave the production facilities) of the albuterol HFA MDIs most widely sold in France, Germany, and the United Kingdom ranged between roughly $3.30 and $6.40; in the United States these prices were in the neighborhood of $29 to $30.[15]

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

3. Costs of the Final Rule

The effects of the final rule include increased spending for needed albuterol medication. The social costs of the final rule include the lost benefits of albuterol use that may result from the price increase. We discuss the increased spending and then the social costs in turn.

In the absence of this regulation, we would expect 430 million generic albuterol MDIs to be sold during the entire period between December 31, 2008, and December 2017, when the last patent listed in the Orange Book for an albuterol HFA MDI will expire. Of these, 96 million would be sold before 2010, an earlier date when generics might arrive. These figures are based on the estimate that approximately 96 percent (Ref. 10) of the approximately 50 million albuterol MDIs sold per year (Ref. 11) are generic, suggesting that about 48 million generic albuterol MDIs are sold annually.

With this regulation, patients who would have used generic albuterol CFC MDIs are expected generally to switch to albuterol HFA MDIs. We estimated in section V.C.6 of this document a weighted average price difference at retail pharmacies (across all payer types) of about $26 between these products. If this difference can be applied to future transactions involving 48 million generic albuterol MDIs annually (less the 2 million free samples promised by GSK and decreased demand of 300,000 to 900,000 MDIs resulting from price increases—as calculated later in this analysis), then increased expenditures from consumers and private or public third-party payers would reach about $1.2 billion per year. This estimate is based, in part, on estimated increases in Medicaid prices that do not take into account rebates given directly to States by drug companies. To the extent that such rebates are larger for branded albuterol MDIs, which are more expensive, the increased expenditures are overestimated.

The present value of these increased expenditures in 2005 is about $6.2 billion using a 7 percent annual discount rate and $8.3 billion using a 3 percent annual discount rate. In estimating this increased spending, we focus on the period between December 31, 2008, and December 2017, when the last patent listed in the Orange Book will expire. We also ignore the fact that after a VENTOLIN HFA MDI is first used, it expires much more quickly than a PROVENTIL HFA MDI or albuterol CFC MDIs. Although this change in the usable life of some MDIs may affect the quantity consumed, we are unable to quantify the magnitude of such an effect.

These increased expenditures represent primarily transfers from consumers and third-party payers, including State and Federal Governments, to branded pharmaceutical manufacturers; they are, therefore, not net costs to society. Because these estimates are based on average retail prices, they include additional spending that will go to parties other than innovative manufacturers, such as distributors and retail pharmacies. We estimate that about 11 percent of this increase—about $130 million annually—may be paid by uninsured customers ($130 million) (Ref. 10). We derive these estimates assuming increased spending is the product of the number of albuterol MDIs sold for cash and the difference between the average price for generic albuterol MDIs and the simple mean of the prices for albuterol HFA MDIs. We estimate that 5 million generic albuterol MDIs are sold to uninsured patients annually and that retail cash prices for albuterol MDIs will rise by about $27 per MDI (details of these estimates follow later in this section of the document.) Taking in to account savings from coupons and free samples, uninsured albuterol users would therefore spend about $120 million more each year.[16]

According to MEPS, private nongroup and uninsured individuals used, on average, 3.3 albuterol prescriptions per year (Ref. 12). Based on IMS data, we estimate the average albuterol prescription is for 1.2 MDIs (Ref. 10). The average uninsured, or underinsured, albuterol user would therefore use about 4 MDIs/year. Based on these figures, we estimate that a population of uninsured albuterol users of about 1.25 million[17] would pay, on average, $95 more per year for albuterol.[18] This estimate does not take in to account the reduced use of albuterol MDIs among the uninsured that may result from higher prices or the extent to which quicker expiration of some HFA albuterol MDIs, relative to CFC MDIs, will increase albuterol MDI demand and expenditures. In the future, some fraction of these cash payers will likely be covered by Medicare (Ref. 10).

We expect price increases resulting from market withdrawal of less expensive generic albuterol MDIs will reduce albuterol use by several hundred thousand MDIs annually (as explained below), although there is substantial uncertainty about these estimates. The impact of this reduction on health outcomes is too uncertain to quantify given available data. Some patients, however, respond to price increases for medications for chronic conditions in ways that may adversely affect their health. A recent article found that:

***copayment increases led to increased use of emergency department visits and hospital days for the sentinel conditions of diabetes, asthma, and gastric acid disorder: predicted annual emergency department visits increased by 17 percent and hospital days by 10 percent when copayments doubled * * *.

However, the article proceeds to characterize these results as ''not definitive.'' (Ref. 4) This finding

[15] Analysis completed by FDA based on information provided by IMS Health, IMS MIDAS™, United States, Germany, France and the United Kingdom, 2003.

[16] (5 million MDIs - 300,000 free sample MDIs) x ($25/MDI) - (450,000 coupons) x ($10) = $117,500,000. Here, we assume coupons and free samples reach uninsured albuterol users in proportion to estimates of the uninsured fraction of the overall population (15 percent).

[17] (5 million MDIs) / 4 MDIs per uninsured user = 1.25 million uninsured users.

[18] ($117,500,000) / (1.25 million uninsured users) = $94.00 per uninsured user.

suggests that increased prices for albuterol may lead to some adverse public health effects among the populations that would face increased prices. This evidence is insufficient to permit us to quantify any adverse public health effects. We use expected reductions in albuterol MDI purchases as a surrogate measure of the impact.

Our approach to estimating the effects of the rule assumes that the primary effect of an elimination of albuterol CFC MDIs from the market would be an increase in the average price of albuterol MDIs. Given the price increase expected from the elimination of generics and existing estimates of market responses to price increases, we have projected how the quantity of albuterol MDIs consumed may decline as a result of this rule. As in the 2004 proposed rule, we assume that the reduction in the use of albuterol MDIs attributable to this rule can be calculated as the product of the sensitivity of use with respect to the price increase, the baseline use of albuterol MDIs among price—sensitive patients, and the price increase in percentage terms. We discuss these in turn.

We have no information about how consumers react to increases in the price of MDIs per se or to increases in the price of ''rescue'' types of MDIs, such as albuterol, in particular. Economists have researched the response of consumers to higher insurance copayments for drugs in general. The results appear to indicate price elasticities in the range of -.1 to -.2, meaning that a 10 percent increase in insurance copayments appears to lead to a reduction in the number of prescriptions of between 1 and 2 percent (Ref. 13). Some researchers have reported estimates of price elasticities as great as -.3 for asthma drugs (Ref. 4), but the authors report that there is wide variance based on the availability of over-the-counter substitutes. For example, for drugs with no over-the-counter substitute—a set that presumably includes albuterol—the reported price elasticity was -.15.[19] We have used price elasticities of between -.05 and -.15 to estimate the potential effect of price increases on demand. We recognize that elasticity estimates derived from insurance copayment studies may not be specifically applicable to the effects of average retail price increases on uninsured patients' demand for albuterol.

To derive an estimate of the number of albuterol MDIs not sold as a result of this rule, we need an estimate of the baseline use of albuterol MDI sales by price-sensitive consumers. From data on retail sales by payer type from the first half of 2004, we find about 5 million generic albuterol MDIs are sold to uninsured patients annually. This estimate includes sales to people over age 65 not covered by Medicaid who we expect will be covered by Medicare in the future, but it excludes mail order and Internet sales and sales through hospitals and nursing homes. Alternatively, if uninsured individuals under age 65 use albuterol MDIs in proportion to their share of the population (roughly 15 percent) (Ref. 14), then roughly 7 million of 46 million generic albuterol MDIs would be sold to the uninsured (46 million = 48 million generic albuterol MDIs - 2 million free samples).

Finally, to estimate the price increase from this rule, we first assess IMS data, which indicate that cash payers paid, on average, $19.10 for generic albuterol MDIs and $46.30 for albuterol HFA MDIs, a difference that would suggest a price increase of $27.20 per MDI, or 142 percent. However, alternative assumptions about the future market share of different albuterol HFA MDI manufacturers would result in a smaller price increase—130 percent. These estimated price differences faced by cash payers are only a proxy for price differences faced by uninsured patients, because some people with insurance may pay cash, and some uninsured patients may buy drugs from mail-order and Internet pharmacies.

We believe that estimates of the recent price premium for albuterol HFA MDIs may be a reasonable approximation of the price increase anticipated from this rule, at least to the extent that patent protection and the more costly criteria for FDA approval of albuterol HFA MDIs substantially curb competition. At least one listed patent is expected to expire in December 2017. While increased competition from new patented albuterol HFA MDIs may reduce future albuterol HFA MDI prices, such reduction may be small until generic albuterol MDIs are reintroduced into the market. Apart from any patents, marketing of new albuterol HFA MDIs before the patents expire requires FDA approval of a completed NDA. After the patents expire, FDA can approve generic albuterol HFA MDIs by the abbreviated new drug application (ANDA) process. The NDA process is more complicated, expensive, and time consuming than the ANDA process by which new generic drugs are brought to market. This NDA requirement constitutes a barrier to entry in the market that will tend to further limit competition until the patents expire as compared to markets where generic drugs can be marketed. Finally, as noted previously in this document, one manufacturer has also announced a voluntary price freeze on its albuterol HFA MDI until 2008.

We combine different measures of price elasticities (-.05 to -.15), the size of the uninsured generic albuterol MDI market (5 to 7 million MDIs), and estimated price increases (130 percent to 140 percent) to estimate the impact of price increases on use. For example, assuming a price elasticity of .15 and 6 million generic albuterol MDIs sold to the uninsured annually, a 130 percent price increase would reduce demand for albuterol MDIs from the uninsured by about 1.2 million MDIs annually (6 million x -.15 elasticity x 130 percent price increase = 1,200,000 MDIs). These preliminary estimates do not take into account offsetting increases in consumption from changes in promotional efforts already announced by GSK. We also note that the elasticity estimates are based on relatively small price changes and may not be applicable to large price changes such as these.

Manufacturers have announced programs to distribute free samples and coupons to mitigate any adverse effect of higher prices on utilization. For example, GSK has committed to provide 2 million albuterol HFA MDIs each year to physician offices in expectation that they would be distributed to patients in need (2003P–0029/CR1, p. 7). In addition, GSK has committed to annually providing 3 million coupons worth $10 each in rebates for VENTOLIN HFA to any patient. Both GSK and Schering currently operate outreach programs that assist patients to obtain needed medications, but we are unable to assess how many albuterol MDI users are currently helped by these programs or how many more would be helped in the future.

Free samples and coupons help mitigate adverse impacts on uninsured patients only to the extent that they are distributed to physicians and other health care professionals who then give them to uninsured individuals.[20] To assess how free samples and coupons might affect albuterol MDI use, we conducted a thorough review of the relevant peer-reviewed literature and

[19] Some patients may view PRIMATENE, an epinephrine MDI available over the counter, as a substitute for prescription albuterol MDIs. If this view is widespread, the decline in albuterol MDI use may be greater than that estimated here. However, insofar as PRIMATENE is effective in treating asthma, the adverse health effects would not be greater. We lack data to evaluate patients' willingness to substitute PRIMATENE for albuterol MDIs.

[20] We found no information addressing how pharmaceutical companies distribute free samples among physicians and clinics, but assume that GSK will not systematically channel free samples away from low-income areas.

found two pertinent articles. One found that, while 54 percent of the free samples were actually distributed to patients, only 9 percent of the patients who received free samples were uninsured (Ref. 15). These data suggest that 4.8 percent of the free samples were actually distributed to uninsured patients. Assuming this estimate is applicable to the albuterol HFA MDIs distributed by the GSK program, then about 96,000 albuterol HFA MDIs per year would reach the uninsured. The second article estimated that 71 percent of free samples were given to patients (Ref. 16). As an upper bound, assuming all samples are distributed to patients and that the uninsured receive them in proportion to their share of the population, approximately 300,000 MDIs (15 percent of 2 million) would reach the uninsured each year.

We expect coupons will do relatively little to improve access to albuterol among the uninsured. If 150,000 (5 percent (Ref. 15)) to 450,000 (15 percent) of the 3 million coupons reach uninsured patients each year and 100 percent of them are redeemed, this would increase albuterol MDI consumption by roughly 2,000 to 15,000 MDIs per year, based on the range of price elasticities considered.

Taking into account the offsetting effect of free samples and coupons, we focus on a range of 300,000 to 900,000 fewer albuterol MDIs sold each year as a result of increased prices stemming from removal of generic albuterol MDIs from the market. This assessment does not take into account Schering's and GSK's patient assistance programs designed to provide free or low cost drugs to low-income patients as we are unable to assess how many albuterol MDI users are currently helped by these programs or how many more would be helped in the future. Over the course of the evaluation period, this would equal between 2.7 million and 8.1 million fewer albuterol MDIs sold. We recognize that due to varying measures of the size of the generic albuterol MDI market for the uninsured, uncertainty about the magnitude of price increases, consumers' response, and the impact of free samples and coupons, and other factors, the true impact of the rule could fall outside this range.

4. Effects on Medicare and Medicaid

In order to apportion the possible spending increases described previously in this document to the Medicaid and Medicare programs, FDA and the Centers for Medicare & Medicaid Services (CMS) have analyzed utilization data related to Medicaid and Medicare, as well as Medicaid program spending data. As explained in this section of the document, these data suggest that, were this rule in effect in 2003, Medicaid spending (including spending by States) would have increased by approximately $100 million for that year. In addition (based on 2001 utilization and 2004 prices), it would have increased drug spending on Medicare beneficiaries by roughly $240 million, although this estimate includes copayments and coinsurance paid by individuals and may be too low because the estimate does not take into account increases in utilization associated with the increase in insurance coverage. These data yield the very rough estimate that the rule would increase Medicare and Medicaid spending by $340 million annually relative to a situation where access to generic albuterol CFC MDIs continued.

a. *Medicaid*. Medicaid spending on albuterol MDIs would have been higher by roughly $100 million in 2003—after taking into account rebates from drug companies—if albuterol CFC MDIs were not available. CMS estimates that 58 percent of this amount would be paid by the Federal Government and 42 percent by States.

Deriving this cost estimate required making some adjustments to available data. Our point of departure is the State Drug Utilization Data, available at *http://www.cms.hhs.gov/medicaid/drugs/drug5.asp* for 2003. These data on utilization and spending on drugs paid for by the Medicaid program suggest that State reimbursements under Medicaid would have been approximately $127 million higher in 2003 if no albuterol CFC MDIs were available (that is, if only albuterol HFA MDIs were available). This estimate assumes substitutes for all albuterol CFC MDIs were purchased at the weighted average price of albuterol HFA MDIs. However, it does not take into account the effect of the rebates from drug companies to States and the Federal Government. CMS estimates that Medicaid program rebates constitute roughly 20 percent of gross spending on prescription drugs under the Medicaid program, suggesting that Medicaid spending on albuterol MDIs after rebates would have been roughly $100 million higher in 2003 if albuterol CFC MDIs were not available. It is important to note that this is a rough estimate, as rebates for a specific drug may differ from the 20 percent estimate. Incomplete data for 2004 suggest that comparable estimates for 2004 are higher but we believe that these are not reliable because of the incompleteness of the data.

b. *Medicare*. Our analysis of the impacts of this rule on Medicare addresses: (1) The total utilization of albuterol MDIs, (2) the likely price increase, and (3) the aggregate spending increase.

CMS estimates that noninstitutionalized Medicare beneficiaries not eligible for Medicaid drug coverage filled about 8 million prescriptions for albuterol MDIs (including VENTOLIN and PROVENTIL) in 2001, based on the Medicare Current Beneficiary Survey (MCBS) and with an adjustment for under-reporting for aggregate analysis purposes. As noted in this section of the document, this estimate is based on Medicare beneficiaries' self-reported outpatient prescription drug utilization, including prescriptions filled at both retail and mail order pharmacies. In addition, the adjustment for underreporting is normally used for aggregate use or spending data in MCBS and may not necessarily reflect actual underreporting for albuterol.

This analysis used data from the 2001 MCBS, a continuous, multipurpose survey of a nationally representative sample of Medicare beneficiaries. The survey is focused on health care use, cost, and sources of payment. No ''paid claims'' data on use of albuterol MDIs exist because Medicare will pay for albuterol MDIs only after the implementation of the new Medicare outpatient prescription drug benefit in January 2006. MCBS is the largest nationally representative set of data available on prescription drug utilization and spending by Medicare beneficiaries. The MCBS data have been used by both CMS's Office of the Actuary and the Congressional Budget Office to prepare estimates related to the new Medicare prescription drug benefit. However, because the data are self-reported, there are considerable limitations, most notably underreporting. CMS has studied the underreporting in the survey and has developed methods to adjust the data. For purposes of the estimates done for the Medicare drug benefit, the data on drug spending are analyzed in the aggregate (that is, for large collections of drugs). Estimates of individual drug product utilization and spending, however, may be even more vulnerable to the limitations inherent in self-reported utilization data.

A reliable assessment of impacts must avoid double counting of people who are eligible for both Medicaid and Medicare. With the implementation of the new Medicare prescription drug benefit, payment for outpatient prescription drugs on behalf of

Medicare beneficiaries who are also eligible for prescription drug benefits under Medicaid will be moved from the Medicaid program to the Medicare program. For purposes of this analysis, this population of dually eligible beneficiaries (that is, Medicare beneficiaries also eligible for full-benefits under Medicaid) is excluded from the analysis of the MCBS data, since their albuterol MDI utilization is captured within the Medicaid data. Approximately half of total Medicaid prescription drug spending is for this dually eligible population. However, the proportion will vary based on the type of drug involved. It is worth noting that albuterol MDIs are used to treat asthma in both the aged and disabled in the Medicare/Medicaid dually eligible population, as well as to treat asthma in children, who make up a large share of Medicaid beneficiaries.

For purposes of this analysis, we assess only data for the time periods for which data are available and we do not make projections for future years. As was noted in the impact analysis for the proposed rule on the Medicare prescription drug benefit (69 FR 46632, August 3, 2004), there is considerable uncertainty in making estimates when there is no program experience from prior years. This uncertainty is exacerbated in the context of making estimates related to a particular drug. For example, in the context of preparing aggregate estimates for the Medicare drug benefit, CMS makes assumptions about how increased coverage induces greater utilization and, based on the National Health Expenditures, projects growth in per capita drug spending. But making such calculations for a specific individual drug would be difficult and not likely reliable. Furthermore, in the case of albuterol MDIs, the drug is subject to large annual fluctuations in demand per user and size of population using the drug due to the nature of the conditions being treated, such as asthma where acute episodes may vary by environmental factors (for example, allergies), prevalence of infectious diseases (for example, colds), and seasonal weather conditions (for example, temperature-related bronchial conditions). In addition, analyzing the effect on Medicare of a change related to one drug is further complicated, for example, by the need to consider the interactions with beneficiary cost-sharing in the context of the Medicare drug benefit design and the availability of additional low-income subsidies for certain populations. Also, the introduction of an albuterol HFA MDI from IVAX is expected to increase competition in the market to some extent, potentially dampening anticipated price increases in part. Our estimates, therefore, apply only to past years.

We believe that prices paid by private insurers offer a potentially reasonable approximation of prices negotiated in the context of a privately administered risk-based insurance program such as the new Medicare Part D drug plans. Using proprietary data from IMS Health, we determined that prices for patients with third-party insurance were on average about $30 more per prescription for albuterol HFA MDIs than for albuterol CFC MDIs, according to IMS's National Prescription Audit for the first half of 2004 (Ref. 10). This price estimate reflects transactions in U.S. retail pharmacies, excluding Internet and mail-order sales. It also reflects both payments by insurers and copayments or coinsurance payments by patients. We calculate the average price per prescription for the albuterol HFA MDIs and the albuterol CFC MDIs, respectively, as the weighted average of the price per prescription of different firms' products, where the weights are the firms' shares of the total albuterol MDIs sold. Price differences per prescription are larger than price differences per MDI, because some prescriptions are for more than one MDI.

Given this estimate of the price difference that would have existed without CFC albuterol MDIs, spending by, and on behalf of, Medicare beneficiaries without Medicaid drug coverage could have been roughly $240 million more in order to fill the 8 million prescriptions estimated to have been filled in 2001 (based on the MCBS data). This estimate is quite approximate because it relies on an estimate of albuterol MDI prescriptions from 2001 and estimates of prescription price differences from the first half of 2004. In addition, albuterol MDI use may grow as the Medicare drug benefit reduces the cost to individuals of using albuterol MDIs.

E. Alternative Phaseout Dates

In developing this rule, we considered removing the essential-use designation for ODSs in albuterol MDIs for different dates between 12 months after issuance of a final rule and December 31, 2009. As shown previously in this document, earlier removal would increase consumer expenditures while increasing environmental benefits. A later date would reduce the potential health effect from reduced access, but also reduce the environmental benefit and potentially put at risk international cooperation. We also considered and rejected small business exemptions as inconsistent with international commitments.

Table 4 of this document shows the effects of selecting December 31, 2005, as the effective date, and Table 5 of this document shows the effects if we had selected December 31, 2009 (assuming continued availability of CFCs).

TABLE 4.—EFFECTS OF PHASEOUT AS OF DECEMBER 31, 2005

Number of Affected of Albuterol MDIs (millions)	Increased Expenditures for Albuterol MDIs Present Value in 2005 (billions)		Possible Reduction in MDI Use (millions)	Reduced Aggregate CFC Emissions Related to Phaseout (metric tons)	Relative Return on Investment to New Technology (return for 12/31/08 phaseout = 1)	
	3-percent discount rate	7-percent discount rate			3-percent discount rate	7-percent discount rate
576	$11.6	$9.3	3.6 to 9.8	14,400	1.4	1.5

TABLE 5.—EFFECTS OF PHASEOUT AS OF DECEMBER 31, 2009

Number of Affected Albuterol MDIs (millions)	Increased Expenditures for Albuterol MDIs Present Value in 2005 (billions)		Possible Reduction in Albuterol MDI Use (millions)	Reduced Aggregate CFC Emissions Related to Phaseout (metric tons)	Relative Return on Investment to New Technology (return for 12/31/08 phaseout = 1)	
	3-percent discount rate	7-percent discount rate			3-percent discount rate	7-percent discount rate
384	$7.3	$5.3	2.4 to 7.2	8,400	.88	.85

F. Sensitivity Analyses

We have conducted a sensitivity analysis to address how key sources of uncertainty may affect our estimates. Our key focus is the effect of alternative dates when generic competition for albuterol HFA MDIs may begin.

In Table 6 of this document, we present estimates assuming that generic competition arrives in 2015.

TABLE 6.—EFFECTS OF PHASEOUT ON DECEMBER 31, 2008—ASSUMING GENERIC ENTRY IN 2015

Number of Affected Albuterol MDIs (millions)	Increased Expenditures for Albuterol Present Value in 2005 (billions)		Possible Reduction in MDI Use (millions)	Reduced Aggregate Emissions Related to Phaseout (metric tons)	Relative Return on Investment to New Technology (return for 12/31/08 phaseout with genetic entry in 017 = 1)	
	3-percent discount rate	7-percent discount rate			3-percent discount rate	7-percent discount rate
336	$6.7	$5.2	2.1 to 5.6	8,400	.81	.84

This analysis suggests that the eventual date that generic competition arrives will have a substantial effect on the total reduction in albuterol MDI use and the aggregate reductions in CFC emissions. Further analysis of the arrival of generic competition would require an evaluation of the legal merits of the different patents, but such an evaluation is beyond the expertise of FDA.

G. Small Business Impact

Current HHS guidance (Ref. 17) suggests that a 3 to 5 percent impact on total costs or revenues of small entities could constitute a significant regulatory impact. We lack the data to certify that this final rule will not have a significant economic impact on a substantial number of small entities. Therefore, this analysis, together with other relevant sections of this document, serves as FDA's Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

1. Affected Sector and Nature of Impacts

The affected industry sector includes manufacturers of pharmaceutical products (NAICS 32514). We obtained data on this industry from the 1997 Economic Census and estimated revenues per establishment. Although other economic measures, such as profitability, may provide preferable alternatives to revenues as a basis for estimating the significance of regulatory impacts, we do not believe it would change the results of this analysis.

The impact of this rule on generic manufacturers is the lost revenues currently generated by sales of generic albuterol CFC MDIs. While ''lost revenues'' are an imperfect measure, because production resources could be shifted to alternative markets, they provide a measure that suggests the magnitude of the impact.

The Small Business Administration (SBA) has defined as small any entity in this industry with fewer than 750 employees. According to Census data, 84 percent of the industry is considered small. The average annual revenue for a small entity is $26.6 million per entity. However, the agency does not have revenue information specific to the affected entities. According to retail sales in the first half of 2004, of the 22.7 million generic or relabeled annual prescriptions for albuterol, approximately 63 percent (14.3 million MDIs) were distributed by Schering, a large firm, under the Warrick label. Six different companies marketed the other 8.4 million albuterol MDIs, with three companies accounting for over 99 percent of these 8.4 million (Ref. 10). According to data collected by the Congressional Budget Office (Ref. 18), the value of shipments from manufacturers of generic drug products accounts for approximately 35 percent of the retail price of the product. If so, revenue from 1.7 million albuterol MDIs would approximate $8.0 million per year (1.7 million prescriptions X $13.50 per generic prescription X 35 percent). Because we lack company-specific revenue data, we are unable to estimate the impact of this rule on these small entities. To the extent that generic albuterol HFA MDIs might become available prior to the removal of the essential-use designation, any impact on small entities would be mitigated.

2. Outreach

The Montreal Protocol and Clean Air Act have been in place for more than a decade. Manufacturers of albuterol CFC MDIs have long known that CFCs would eventually lose their essential-use designations for this purpose. During the proposal stage of this rulemaking, we specifically solicited comments on the impact on small entities. No comments were received that explicitly addressed this issue.

H. Conclusion

This final rule could result in increased health care expenditures of about $1.2 billion for each year between the removal of the essential-use designation and reintroduction of generic competition at patent expiration. Taking into account GSK's commitment to provide free samples and coupons, we estimate that higher prices due to the elimination of generic competition will reduce the number of MDIs sold by between 300,000 and

900,000 per year. This estimate does not take into account Schering's and GSK's patient assistance programs designed to provide free or low cost drugs to low-income patients as we are unable to assess how many albuterol MDI users are currently helped by these programs or how many more would be helped in the future. In addition, each year without using CFCs in albuterol MDIs will reduce atmospheric emissions of ODSs by 1,200 metric tons and provide increased investment returns for environmentally friendly technology that may induce further gains. Removal of the essential-use designation is consistent with FDA's role in determining the essentiality of MDIs under section 601 of the Clean Air Act, and also meets U.S. obligations under international agreements. Finally, we lack the data to certify that this final rule will not have a significant economic impact on a substantial number of small entities.

VI. 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.

VII. Federalism

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

VIII. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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11. 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).

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17. U.S. Department of Health & Human Services, ''Guidance on Proper Consideration of Small Entities in Rulemakings of the U.S. Department of Health and Human Services,'' May 2003.

18. Congressional Budget Office, ''How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry,'' July 1998.

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 and the Clean Air Act and under authority delegated to the Commissioner of Food and Drugs, after consultation with the Administrator of the Environmental Protection Agency, 21 CFR part 2 is amended as follows:

PART 2—GENERAL ADMINISTRATIVE RULINGS AND DECISIONS

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

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

§ 2.125 [Amended]

■ 2. Section 2.125 is amended by removing and reserving paragraph (e)(2)(i).

Dated: March 29, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 05–6599 Filed 3–31–05; 8:45 am]

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