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: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend 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 are currently marketed. FDA has tentatively determined that the two non-ODS MDIs will be satisfactory alternatives to albuterol MDIs containing ODSs and are proposing to remove the essential-use designation for albuterol MDIs. If the essential-use designation is removed, albuterol MDIs containing an ODS could not be marketed after a suitable transition period.

DATES: Submit written or electronic comments by August 16, 2004.

ADDRESSES: You may submit comments, identified by [Docket No. 2003P–0029], by any of the following methods:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.
- E-mail: *fdadockets@oc.fda.gov*. Include [Docket No. 2003P–0029] in the subject line of your e-mail message.
- FAX: 301–827–6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]: Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the agency name and Docket No. 2003P–0029 for this rulemaking. All comments received will be posted without change to *http://www.fda.gov/dockets/ecomments*, including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/dockets/ecomments* and/or the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Albuterol
II. CFCs
III. Regulation of ODSs
A. The 1978 Rules
B. The Montreal Protocol
C. The 1990 Amendments to the Clean Air Act
D. EPA's Implementing Regulations
E. FDA's 2002 Regulation
F. The Stakeholder's Petition
IV. Application of the Criteria to Remove the Essential-Use Designation for Albuterol CFC MDIs
A. Non-ODS Products Have 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
2. The Same Route of Administration
3. The Same Indications
4. Approximately the Same Level of Convenience of Use
B. Supplies and Production Capacity for the Non-ODS Products Will Exist at Levels Sufficient to Meet Patient Need
C. Adequate U.S. Postmarketing Use Data Are Available for the Non-ODS Products
D. Patients Are Adequately Served by the Non-ODS Products
V. Potential Effective Dates
VI. Decision XV/5
VII. Environmental Impact
VIII. Analysis of Impacts
A. Introduction
B. Objective of the Proposed Rule
C. Current Conditions
1. CFCs and Stratospheric Ozone
2. Effects of the Montreal Protocol
3. Asthma
4. COPD
5. Current U.S. MDI Market
D. Benefits of Earlier Phaseout Dates
1. Controlled Transition to Non-CFC MDIs
2. Value of Reduced ODS Emission
3. International Cooperation
4. Encouraging Innovation
E. Costs of Earlier Phaseout Dates
F. Insurance and Third Party Payers
G. Small Business Impact
1. Affected Sector and Nature of Impacts
2. Alternatives
3. Outreach
H. Conclusion
IX. References
X. The Paperwork Reduction Act of 1995
XI. Federalism
XII. Request for Comments

I. 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 aerosol 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 chlorofluorocarbons (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 may affect the availability of these important drugs.

II. 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.

III. 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 import of ODSs, including CFCs.

A. 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 III.E of this document.

B. The Montreal Protocol

On January 1, 1989, the United States became a party to the 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* (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document has published in the **Federal Register**). The United Sates 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 186 parties to this treaty.[1] 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 utilized this adjustment procedure to change the treaty's obligations and 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 in parties that are developed countries by January 1, 1996 (Decision IV/2).[2] The adjustment also indicated that it would apply ''save to the extent that the Parties decide to permit the level of production or consumption that is necessary to satisfy uses agreed by them to be essential'' (Article 2A(4)). Under the treaty's rules of procedure, the parties may make such an essential use decision by a two-thirds majority vote, although, to date, all such decisions have been made by consensus.

To produce or import CFCs for an essential use under the Montreal Protocol, a party must request and obtain approval for an exemption at a meeting of the Parties. One of the most important essential uses of CFCs under the Montreal Protocol is their use in

[1] 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 proposing. 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*. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

[2] 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.

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 required the parties that are developed to 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, 1997).

• Decision XII/2 elaborated on the required 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, 1999).

• 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 the party 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, 2002).

• Decision XV/5 required parties that are developed countries to submit a plan of action that includes a specific date by which time the party will stop seeking essential-use exemptions for CFCs for albuterol MDIs (Nairobi, 2003). Decision XV/5 is discussed in more detail in section VI of this document.

On the basis of these decisions, many Parties have made substantial progress in phasing out CFCs from MDIs.

C. 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)[3], 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 the U.S. EPA].

[3] 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).

D. 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 transfer 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 transfer 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 or other pressurized dispensers. The aerosol product ban contains an exception for medical devices listed in § 2.125(e). The term ''medical device'' is used with the same meaning it was given in the 1990 amendments and includes drugs as well as medical devices.

E. 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 to remove 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 (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 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 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 rule) (corrected in 67 FR 49396, July 30, 2002, and 67 FR 58678, September 17, 2002).

Among other changes, the 2002 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 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 tentatively concluded 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. 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. 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 HFA MDIs to refer to both of these products as we discuss in section IV of this document how these products meet the criteria for being alternatives to albuterol CFC MDIs.

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 (discussed in section VI of this document), which concerns MDIs with albuterol as the sole active ingredient. This rulemaking will not affect the essential use status of Combivent.

F. The Stakeholders Petition

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)(the Stakeholders' petition). The petition requested that we initiate rulemaking to remove the essential-use designation of albuterol MDIs. In addition to manyother issues discussed in the petition, the petitioners expressed concerns about the possibility that the parties to the Montreal Protocol could refuse to allocate CFCs for use in albuterol CFC MDIs adversely affecting a smooth transition that ensured adequate supplies of both albuterol CFC MDIs and albuterol HFA MDIs (Stakeholder's petition at 3-4). Another concern expressed in the petition was the possibility that supplies of pharmaceutical grade CFCs could be interrupted by actions of other countries. These issues are discussed in section IV.D of this document.

Many comments were submitted to the docket for this petition. Commenters included GlaxoSmithKline (GSK), Honeywell Chemicals (Honeywell), National Economic Research Associates, Inc., patient advocacy groups, a drug industry association, and a law firm. Comments on the Stakeholder's petition may be seen in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday.

While we found the citizen petition and comments on the petition informative and relied on some of the information provided by the petition and comments in preparing this document, this proposed rule is not being issued in response to the petition. Section 2.125(g) requires that a petition present ''compelling evidence'' demonstrating that the criteria for removing an essential use are met. We concluded that the petition, though informative, did not provide the level of evidence needed for us to initiate rulemaking. This proposed rule is being issued on our own initiative in accordance with the Clean Air Act and the Montreal Protocol.

IV. Application of the Criteria to Remove the Essential-Use Designation for Albuterol CFC MDIs

A. Non-ODS Products Have the Same Active Moiety With the Same Route of Administration, for the Same Indication, and With Approximately the Same Level of Convenience of Use

Section 2.125(g)(4)(i) provides that alternatives must ''contain the same active moiety * * * with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the ODS products.'' We will examine how each component of this criterion applies to the albuterol HFA MDIs.

1. The Same Active Moiety

Active moiety is defined in § 314.108(a) (21 CFR 314.108(a)) as

> the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

The active ingredient in the albuterol CFC MDIs is the albuterol base, albuterol, while the active ingredient in albuterol HFA MDIs is the sulfate salt of albuterol, albuterol sulfate. The active moiety of both is albuterol; therefore, both the albuterol CFC MDIs and albuterol HFA MDIs have the same active moiety.

2. The Same Route of Administration

Both the albuterol CFC MDIs and albuterol HFA MDIs are MDIs used for oral inhalation. They both have the same route of administration.

3. The Same Indications

We have provided, for comparison, the labeled indications for albuterol CFC MDIs and albuterol HFA MDIs in table 1 of this document.

TABLE 1.—INDICATIONS FOR ALBUTEROL MDIS

Products	Indications
PROVENTIL (ODS)[1]	PROVENTIL Inhalation Aerosol is indicated in patients 12 years of age and older, for the prevention and relief of bronchospasm in patients with reversible obstructive airway disease, and for the prevention of exercise-induced bronchospasm.
PROVENTIL HFA	PROVENTIL HFA Inhalation Aerosol is indicated in adults and children 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.
VENTOLIN (ODS)[2]	VENTOLIN Inhalation Aerosol is indicated for the prevention and relief of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.
VENTOLIN HFA	VENTOLIN HFA is indicated for the treatment or prevention of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

[1] The labeled indications for Warrick brand albuterol metered-dose inhalers (MDIs) are identical to those of PROVENTIL ozone-depleting substance (ODS). Warrick MDIs contain ODSs.

[2] The labeled indications for generic albuterol MDIs manufactured by Armstrong Pharmaceuticals and PLIVA are identical to those of VENTOLIN (ODS). Generic albuterol MDIs contain ODSs.

The labeled indications for albuterol HFA MDIs are essentially identical to those for VENTOLIN(ODS) MDIs and somewhat broader than the indications for PROVENTIL (ODS) MDIs (''adults and children 4 years of age and older'' for albuterol HFA MDIs as opposed to ''patients 12 years of age and older'' for PROVENTIL (ODS)).

We have also looked at significant uses of albuterol CFC MDIs that may not be included in the labeled uses. We are unaware of any off-label use of albuterol CFC MDIs for which albuterol HFA MDIs would not be a satisfactory alternative.

4. Approximately the Same Level of Convenience of Use

In the preamble to the 2002 rule, we stated that in evaluating whether an alternative has approximately the same level of convenience of use compared to the ODS product containing the same active moiety, FDA will consider whether:

- The product has approximately the same or better portability,
- The product requires approximately the same amount of or less preparation before use, and
- The product does not require significantly greater physical effort or dexterity (67 FR 48370 at 48377).

Albuterol HFA MDIs are approximately the same small size and light weight as the albuterol CFC MDIs and are, therefore, equally portable.

The only noteworthy difference in amount of preparation between the albuterol CFC MDIs and albuterol HFA MDIs is that patients using albuterol HFA MDIs may need to more closely follow the labeling instructions on cleaning the mouthpiece, even though cleaning instructions are included in the patient labeling for both albuterol CFC MDIs and albuterol HFA MDIs. We do not consider 30 seconds spent cleaning the mouthpiece once a week to prevent clogging (see approved labeling for PROVENTIL HFA and VENTOLIN HFA) to be a significant difference in amount of preparation.

The method of operation of the albuterol CFC MDIs and albuterol HFA MDIs is the same, and although the albuterol CFC MDIs and albuterol HFA MDIs use different valves, the MDIs do not differ significantly in the amount of strength needed to operate them. We have tentatively concluded that albuterol HFA MDIs have approximately the same level of convenience as albuterol CFC MDIs.

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

In many ways, this is the most difficult criterion to apply. Industry is understandably reluctant to allocate the resources necessary to establish new manufacturing facilities to ensure adequate supplies and production of albuterol HFA MDIs without assurance that albuterol CFC MDIs will be phased out. At the same time, we cannot eliminate the essential use of ODSs for albuterol MDIs until we are assured of adequate supplies and production of alternative products. We have carefully considered GSK's comment on the Stakeholders' petition (Docket No. 2003P–0029/C2) (GSK comment). In their comment, GSK projected that they could have capacity to produce adequate supplies of VENTOLIN HFA within 12 to 18 months of the start of their production scale-up (GSK comment at 7). The production scale-up would presumably start when we publish the final rule eliminating the essential use of ODSs in albuterol MDIs. GSK did not describe the circumstances that were presumed for their projection. GSK did not explain what they meant by ''adequate supplies and production capacity'' (GSK comment at 7). The manufacturer of PROVENTIL HFA, 3M Co. (3M), has not submitted any comments on the Stakeholders' petition and we have no information about their plans regarding future supplies and production capacity. With the relatively minimal amount of information on production capacity that we currently have, we have tentatively concluded that capacity to produce adequate supplies of non-ODS albuterol MDIs could be in place no sooner than 12 months after date of publication in the **Federal Register** of any final rule based on this proposed rule. We welcome the submission of additional information on the production and supply of alternative products, and the time it may take to put in place any additional production capacity that may be needed to meet projected U.S. needs.

In the 2002 rule, we stated that we ''generally will expect the non-ODS product to be manufactured at multiple manufacturing sites if the ODS product was manufactured at multiple manufacturing sites'' (67 FR 48370 at 48374). We do not require that replacement products be manufactured at multiple sites; the only requirement is that supplies and production capacity for the non-ODS product exist at levels sufficient to meet patient need. However, we did note in the 2002 rule that multiple manufacturing sites increase the likelihood that a manufacturer will be able to supply the replacement drug in the event of an

unforeseen circumstance that shuts down one site. (See 67 FR 48370 at 48377.) We do not believe that this issue is a concern in this proposed rulemaking. GSK and 3M will be making albuterol HFA MDIs at separate facilities. As an additional assurance in this regard, GSK said that the three European supply sites that manufacture albuterol HFA MDIs for non-U.S. markets could be used as an alternative in an emergency (GSK comment at 8).

C. Adequate U.S. Postmarketing Use Data Are Available for the Non-ODS Products

PROVENTIL HFA has been on the market 7 years, and VENTOLIN HFA has been on the market for more than 2 years. As with all new drug products, we have periodically examined reports made to our MedWatch system[4] and reports made to FDA by and for the sponsors of the NDAs for PROVENTIL HFA and VENTOLIN HFA. These reports do not reveal any unexpected adverse events, nor do they reveal any unanticipated problems with the safety, effectiveness, tolerability, and patient acceptance of albuterol HFA MDIs when the products are properly used.

We have read with interest a report of a study conducted in the United Kingdom of patients using VENTOLIN EVOHALER, a product substantially similar to VENTOLIN HFA.[5] This report supports our conclusion that albuterol HFA MDIs are well tolerated and accepted by patients.

While additional information is always welcome, we have tentatively determined that we do not need the results of additional studies to make a valid scientific assessment of the safety, effectiveness, tolerability, and patient acceptance of albuterol HFA MDIs. As we stated in the 1999 proposed rule, we will not require a postmarketing study if available data, including more traditional postmarketing surveillance data, are sufficient to support a finding that the CFC product is no longer essential (64 FR 47719 at 47730).

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

PROVENTIL HFA and VENTOLIN HFA were demonstrated to be safe and effective during the review of their NDAs. Data submitted with the NDAs showed that PROVENTIL HFA and VENTOLIN HFA are similarly tolerated compared to albuterol CFC MDIs, and patient compliance rates in the studies were comparable. All of the information available to us currently indicates that PROVENTIL HFA and VENTOLIN HFA will adequately serve all patient populations currently using albuterol CFC MDIs.

Albuterol CFC MDIs are only available in one strength, 0.09 milligrams per inhalation. PROVENTIL HFA and VENTOLIN HFA are available in strengths equivalent to 0.09 milligrams of albuterol base per inhalation. Because albuterol CFC MDIs are only available in one strength, alternative products need not be available in more than one strength to adequately serve patients. (See the 2002 rule (67 FR 48370 at 48374).)

In the preamble to the 2002 rule, we said we will ''consider whether a high-priced non-ODS product is effectively unavailable to a portion of the patient population because they cannot afford to buy the product'' (67 FR 48370 at 48374). As explained in section VIII.C.5 of this document, current retail prices of PROVENTIL HFA and VENTOLIN HFA are in excess of $20 more than the prices of generic albuterol CFC MDIs. This price difference is undesirable in that some patients whose drug expenditures are not covered by third parties may choose not to buy these MDIs that may be important to their health. However, FDA lacks adequate evidence to estimate precisely the number of MDIs that might not be bought as the result of this price increase or what the public health consequences of such decisions would be. The best evidence available to us indicates that the demand for prescription drugs is generally quite inelastic with respect to price changes, so even this relatively large price increase is likely to cause changes in the consumption of MDIs that are quite small relative to the market. When generic albuterol CFC MDIs first came on the market in 1995 and 1996, we did not see any clear indication that underserved patients who had not been purchasing the more expensive VENTOLIN ODS or PROVENTIL ODS began to purchase the lower-priced generics. Increases in total sales of albuterol MDIs around that time have been attributed to the continuing rising incidence of asthma and COPD. Still, given the number of albuterol canisters sold yearly in the United States, even a minor change could amount to as many as a million MDI canisters not purchased each year. Section VIII of this document describes the analysis we used in reaching this tentative conclusion.

Private and public health insurance should ameliorate some of the anticipated adverse impacts of price increases, though differences in co-payments between generics and branded products may make these inhalers more expensive for even insured patients. Programs run, or supported, by the pharmaceutical industry to provide low-cost or free drugs to less-affluent patients should also reduce the effect of price increases. Information on such programs has been submitted to FDA by GSK describing their ''Bridges to Access,'' ''Orange Card,'' ''Together Rx Card,'' and ''Promise'' Programs, as well as their commitment to provide 2 million free HFA canisters per year beginning at the time of the effective date of a final rule removing the essential-use designation of albuterol MDIs (see GSK comment at p. 15, and GSK's supplementary comment dated August 5, 2003 (Docket No. 2003P-0029/SUP 1).) At this time, FDA believes that the information provided by GSK is insufficient to fully evaluate the extent that these programs would assist low-income uninsured patients and seeks further details on how they would specifically address this issue. We seek comments from manufacturers and other interested persons on any similar efforts indicating how these programs might alleviate concerns over patient access for low-income, uninsured patients after the effective date.

We are particularly interested in receiving comments that provide more data on how the expected price increases for albuterol MDIs will affect the public health.

As described in section V of this document, the effects of any price increases on the availability of non-ODS products, and any potential resulting impacts on public health associated with such price increases, can, in theory, be reduced by adjusting the effective date of the rule to be closer to the time when low-cost generic copies of PROVENTIL HFA and VENTOLIN HFA will be available, which could be in either 2010 or 2015, depending on which patents control the availability of generic alternatives. We say ''in theory'' because such an outcome rests on the assumption that the United States can continue to successfully petition the Parties to the Montreal Protocol to grant the United States an essential use exemption for CFCs for use in albuterol MDIs for a time period up to 2010 or 2015. At present, the United States has received approval for an essential use exemption for 2005, and a request for an

[4] MedWatch is FDA's safety information and adverse event reporting program that allows health care professionals and consumers to report serious problems they suspect are associated with the drugs and medical devices they prescribe, dispense, or use.

[5] Craig-McFeely, P.M., L.V. Wilton, J.B. Soriano, et al., ''Prospective Observational Cohort Safety Study to Monitor the Introduction of a Non-CFC Formulation of Salbutamol with HFA134a in England,'' *International Journal of Clinical Pharmacology and Therapeutics*, 41:67-76, 2003.

exemption for 2006 is pending for consideration by the Parties to the Montreal Protocol in November 2004. The Parties will not approve U.S. essential use exemption requests indefinitely. Therefore the projected impacts in tables 2 and 3 of this document, may overestimate actual impacts because the analysis assumes approval of essential use exemptions through 2015. In fact, the Montreal Protocol's technical review group and many parties already have informally discussed a target date of 2005 for discontinuing exemptions for albuterol CFC MDIs. They may believe this target date is warranted because, for some time now, there have been at least two alternatives to albuterol CFC MDIs in the United States and other developed countries that appear to meet the medical needs of patients. However, in many countries, the price differential between the albuterol CFC MDIs and albuterol HFA MDIs is less than that in the United States, and medication reimbursement is handled differently in these countries. By virtue of having albuterol HFA alternatives available, many other developed countries have achieved a phaseout of albuterol CFC MDIs already and virtually all will do so earlier than 2010 or 2015. Therefore, these Parties to the Montreal Protocol have already questioned, and are likely to continue to question, why the United States has not made similar progress. This questioning on the part of other developed countries could affect future U.S. nominations for essential-use CFCs.

Another issue that should be considered in determining an appropriate effective date is the availability of pharmaceutical grade CFCs for use in MDIs. We have received a comment on the Stakeholder's petition from Honeywell (Docket No. 2003P-0029/C9). The comment states that Honeywell has been informed by the government of the Netherlands that production of CFCs will not be permitted at Honeywell's Weert, Netherlands plant past the end of 2005. The Weert plant is currently the only source of pharmaceutical grade CFCs used in the United States. Honeywell also said that they planned to renew production of certain pharmaceutical-grade CFCs this year at a plant in Baton Rouge, Louisiana that previously produced these CFCs and that they would be able to ship the pharmaceutical grade CFCs to customers this year also. We have no reason to disbelieve Honeywell's statements that they will have the capacity to supply the domestic demand for pharmaceutical grade CFCs from their Baton Rouge plant. However it is worth noting that Honeywell has not produced pharmaceutical grade CFC-11 or CFC-12 at Baton Rouge since 1995, and we cannot be certain that Honeywell will meet their goals.

Accordingly, the decision on what timeframe to use for removing the domestic essential-use status of albuterol must take into account several factors. On the one hand, it must consider the potential but uncertain health benefit that may result from ensuring a stable price for albuterol MDIs for a long period of time. Conversely, it must take into account several significant possibilities: that the United States will not be able to procure a long-term exemption for albuterol; that a unilateral U.S. action permitting use of albuterol CFC MDIs for up to a decade longer than other developed nations is likely to lead the parties to the Montreal Protocol to impose a more abrupt reduction in the exemption granted the United States; and that, in the near term, it is possible there may be a disruption in supply of pharmaceutical-grade CFCs. Based on our preliminary analysis, we have tentatively concluded that patients will be adequately served by albuterol HFA MDIs within the timeframes discussed in this document; therefore we are initiating rulemaking at this time. We hope that comments received on this proposed rule will further establish the adequacy of the HFA products to meet patients' needs (including issues of cost and access), as well as the potential risks to patients of misjudging the degree to which CFCs may continue to be available for albuterol MDIs, to help us establish an optimal effective date for albuterol CFCs no longer to be designated essential.

V. Potential Effective Dates

Setting an appropriate effective date for the elimination of the essential use designation for albuterol MDIs is one of the key aspects of this proposed rulemaking. No albuterol CFC MDIs can be legally marketed in the United States after the effective date of the final rule based on this proposal. We are particularly interested in receiving comments on what would be an appropriate effective date for this rulemaking.

As we discussed in section IV.B of this document, we have tentatively concluded that capacity to produce adequate supplies of non-ODS albuterol MDIs could be in place no sooner than 12 months after date of publication in the **Federal Register** of any final rule based on this proposed rule. An effective date that does not allow the creation of adequate production capacity would not be appropriate, and persons submitting comments on an effective date should keep this consideration in mind.

Section 505(b)(1) of the act (21 U.S.C. 355(b)(1)) requires that persons submitting NDAs to FDA include information about all patents that claim the drug for which the NDA is submitted. We publish that information in *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book). We note that the last listed patent for an albuterol HFA MDI expires in 2015. Another listed patent expires in 2010. Thus, lower priced generic versions of albuterol HFA MDIs can be expected to be marketed as early as 2010, or as late as 2015 depending on the validity of the patents involved. While we do not have the expertise to evaluate the validity of the patents, 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. We welcome comments from interested parties on when patents may cease to bar the marketing of generic albuterol HFA MDIs. In addition we seek comments on the feasibility of generic manufacturers obtaining rights to use patented technology before the expiration of the patents. While the availability of lower-priced generic albuterol HFA MDIs should remove any concerns that patients might not be adequately served by alternatives to albuterol CFC MDIs due to the higher prices of albuterol HFA MDIs, the future availability of generics may not be relevant to the ability of the United States to continue to receive exemptions for albuterol CFC MDIs (see section IV.D of this document).

The year 2010, in addition to its potential significance for patents on albuterol HFA MDIs, will be a major milestone in the regulation of ODSs under the Montreal Protocol. Beginning January 1, 2010, production and importation of new CFCs would be generally banned in all parties that are countries that are parties to the Montreal Protocol, both economically developed and less-developed countries (See paragraphs 4 and 8 of Article 2A of the Montreal Protocol (as amended)). There is an exception to this general ban for essential uses, but as we discussed in section IV.D of this document, the parties to the Montreal Protocol will be more reluctant to allocate CFCs for essential uses as time passes. We believe that the United States should take all appropriate action to support the global phaseout of CFCs, and eliminating the essential use for albuterol CFC MDIs,

before January 1, 2010, may be such an appropriate action.

Having weighed the public health, economic, and environmental impacts associated with this determination, we have tentatively concluded that currently no date after December 31, 2009, appears to be a practical effective date for this rulemaking, just as no date earlier than 12 months after publication of a final rule would appear to be a practical effective date. In any case, our current intention is to establish the earliest effective date that will adequately protect the public health of the United States. We invite comments on an appropriate effective date for the final rulemaking. Persons submitting comments on an appropriate effective date may wish to discuss how suggested effective dates would affect supplies and production capacity of non-ODS albuterol products and how different dates would affect the degree to which patients are adequately served by the non-ODS products. Interested persons may wish to comment on effective dates that are later than 2009 or earlier than 12 months after publication of the final rule.

VI. Decision XV/5

The parties to the Montreal Protocol held their 15th meeting at Nairobi, Kenya on November 10 through 14, 2003. The parties agreed to Decision XV/5, which states that no essential uses of CFCs will be authorized for parties that are developed countries at the 17th meeting of the parties (Autumn 2005), or thereafter, unless the party requesting the essential-use allocation has submitted an action plan. Among other items, the action plan is required to include a specific date by which the party will 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 [6] (Summer 2005).

In addition to fulfilling our obligations under the Clean Air Act and other provisions of the Montreal Protocol, this proposed rulemaking is intended to provide the specific date after which the United States will not request essential-use allocations of CFCs for albuterol MDIs. We realize that some comments received in response to this notice of proposed rulemaking may state that it is impractical to set a specific date for this purpose. However, based on the information we currently have, we believe that it will be both practical and desirable to establish a specific phaseout date for albuterol CFC MDIs.

VII. Environmental Impact

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

VIII. Analysis of Impacts

A. Introduction

We have examined the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4) (UMRA), 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). This proposed regulation is considered an economically significant regulatory action under Executive Order 12866.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in 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.'' Currently, such a statement is required if costs exceed about $110 million for any one year. The Congressional Review Act requires that regulations determined to be major must be submitted to Congress before taking effect.

The removal of the essential-use designation for ODS propellants used in albuterol MDIs will result in the elimination of low-priced generic versions of these products until protective patents for the HFA product expire. Assuming that the generics have otherwise received FDA approval, low-priced generic albuterol HFA MDIs can be expected to be marketed as soon as legally permissible, i.e., when the relevant patents for albuterol HFA MDIs expire or are successfully challenged. Currently, two versions of albuterol MDIs are available using an ozone-safe propellant, but at a price close to the higher prices of branded products using ODSs. Thus, we project that removal of the essential-use designation for albuterol MDIs before the albuterol HFA MDIs patents expire will result in higher consumer prices for this important medication for asthma and COPD unless and until generic versions of albuterol HFA MDIs become available. During this period, despite the relatively inelastic demand for medicines generally, the higher prices will discourage some patients from buying albuterol. Nonetheless, early removal of the essential-use designation for ODSs used in albuterol MDIs provide some marginal environmental and health gains related to reduced risk of skin cancers and cataracts and increase expected returns to research and development of new environmentally preferable technologies.

We note that the parties to the Montreal Protocol may decide to cease providing the United States and all other countries with exemptions for CFCs for albuterol prior to the time when the U.S. patents will expire (see discussion in section IV.D of this document). This decision may occur based on the simple availability of alternatives. In addition, a decision by the United States not to phase out promptly the use of CFCs in albuterol MDIs may be seen as discouraging greater efforts by other countries to comply with the Montreal Protocol.

Any economic analysis of prospective government actions needs to begin with a baseline from which to assess those actions. Standard practice is 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. In this world, generic albuterol MDIs containing CFCs might remain on the market indefinitely. To the extent

[6] 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 then be subsequently acted on by a meeting of the parties to the Montreal Protocol.

that consumers perceive generic albuterol HFA MDIs after they are introduced to be perfect substitutes to generic albuterol CFC MDIs, and generic producers also see the choice of propellant as immaterial, we can take a world with generic HFA MDIs as equivalent to the world where albuterol CFC MDIs are marketed indefinitely. Because the specific date by which generic albuterol HFA MDIs will be approved and marketed is uncertain, we have conducted our analyses using the dates of expiration of both the first (2010) and the last (2015) patents currently listed in the Orange Book for albuterol HFA MDIs as the likely dates for the reintroduction of generic competition. The choice of baseline for this analysis is in large part academic. The baseline does not affect the incremental costs and benefits of one phaseout date relative to another. Instead it affects only the characterization of the total benefits and costs associated with the choice of phaseout date.

Tables 2 and 3 of this document illustrate major quantifiable effects of alternative dates for removing the essential-use designation for the use of ODSs in albuterol MDIs. Table 2 of this document presents the effects assuming that generics do not enter the market until 2015, while table 3 of this document presents the same effects with an assumption that generics enter the market in 2010. In the second column of both tables 2 and 3 of this document, we present our estimates of the cumulative number of generic albuterol MDIs that would be marketed between the year the essential use is eliminated and 2015 or 2010. For example, in the 2015 scenario, elimination of the essential-use designation in the year beginning July 2006 would affect a total of 388 million generic MDIs of albuterol that would otherwise be sold between 2007 and 2015. Similarly in that scenario, elimination of the essential-use designation in July 2010 would affect 218.6 million generic MDIs of albuterol sales. In comparison, table 3 of this document shows that an estimated 169.4 million MDIs of generic albuterol would be affected by elimination of essential-use designation in 2006 and only 42.8 million in 2009. These estimates are adjusted for increases in current uses derived from projections of increased asthma prevalence based on age-adjusted population projections and stable incidence rates for the period. The estimates apply age-specific asthma incidence rates published by the Centers for Disease Control and Prevention (CDC) (Ref. 1) to mid-range population projections from the Bureau of Census. The resulting estimates of future increases in asthma prevalence were applied to the current quantity and market share of MDIs to result in projected increases in demand. The third and fourth columns in tables 2 and 3 of this document show the increased consumer expenditures associated with the purchase of branded, albuterol HFA MDIs rather than generic albuterol CFC MDIs for each year. We note that these expenditures represent primarily transfers from consumers and third-party payers to branded pharmaceutical manufacturers and are not societal costs. Since these estimates are based on average retail prices they include additional spending on parties other than the innovative drug manufacturers, including pharmaceutical distributors and the retail sector. These estimates are based on a current retail price difference of approximately $23 between branded and generic albuterol CFC MDIs derived below using data from the IMS National Prescription Audit *Plus*™; 1st Quarter 2004 (extracted April 2004). As we do not have a single ''best'' estimate of U.S. retail prices we discuss different data suggesting larger and smaller price differences. Future expenditures are discounted to 2006 using both 7 percent and 3 percent annual discount rates in accordance with Office of Management and Budget Circular A–4. For example, the present value of increased consumer expenditures in table 2 of this document is expected to be about $6.9 billion if essential-use designations are removed in 2006 (at 7 percent), but are $5.9 billion if 2007 is the date at which the essential use is ended. The present value of these expenditures (transfers) in table 3 of this document for a 2006 removal is $3.5 billion (at 7 percent), and $2.6 billion if 2007 is the decision year. As discussed in the following paragraphs, we expect that between 10 and 15 percent of these expenditures are out-of-pocket payments from patients, between 65 and 70 percent represent payments from private third-party payers, and the remainder (15 to 20 percent) represent increased government spending.

The fifth column in tables 2 and 3 of this document illustrates a potential reduction in therapies that may occur due to the price increase associated with the loss of cheaper generic competition. We estimate in the following paragraphs that the price increase could potentially reduce purchases and use of MDIs by several hundreds of thousands or more MDIs though there is substantial uncertainty about these estimates. We focus on a range from 400,000 to 1 million MDIs per year. The potential effect of the loss of medication on health outcomes is even more uncertain, and we have not attempted to quantify it. A recent article in the *Journal of the American Medical Association* has found, however, that increases in copayments for insured consumers can reduce utilization, and may thereby adversely attect health (Ref. 2). If it is assumed that generics cannot enter into the market until 2015, removal of essential-use designations in 2006 may result in between 3.9 and 9.7 million fewer MDIs sold over the entire period. This estimate assumes no price increase to branded HFA products for the entire period. If lower priced generic products are reintroduced in 2010, removal of essential-use designations in 2006 may result in between 1.6 and 4.0 million fewer MDIs being sold. Our estimates of reductions in canisters are based primarily on a response among the uninsured, although insured consumers may also reduce utilization in response to higher co-pays on the branded HFA albuterol MDIs (see Goldman et al., 2004 (Ref. 2)).

These estimates are based on very uncertain market responses to price changes and do not account for potential actions that may ameliorate this effect. For example, private programs such as GSK's ''Bridges to Access'' as well as its commitment to provide 2 million MDIs of HFA albuterol each year to physicians for distribution to patients are not explicitly accounted for in these estimates. We are unable to include the commitment to distribute free MDIs into our quantitative analysis because of uncertainty about the recipients. If the MDIs went exclusively to low income uninsured patients these estimates would likely be a large overstatement of expected effects. If the free MDIs went primarily to insured patients, the preceding estimates would remain valid.

The sixth column in tables 2 and 3 of this document illustrates the cumulative reduction in CFC emissions expected between each decision year and 2010. The cumulative reductions in CFC emissions are based on the 2004 allocation of approximately 1,400 metric tons of CFCs for albuterol MDIs that would no longer be available. If emissions were to be reduced by this amount, the levels of ozone in the stratosphere would be marginally higher, providing more protection from harmful UV–B radiation and resulting in reduced risks of skin cancers and cataracts because ozone reduces human exposure to UV–B radiation.

The final two columns of the tables present a measure of how the decision to remove essential-use designations would affect returns to the innovators of non-ODS albuterol MDI technology. We present the ratio of the value of U.S. sales discounted to 2006, relative to the value of U.S. sales if the phaseout were in 2006. This ratio also measures how returns to research and development (R&D) would be affected, as the R&D costs are independent of the phaseout date, so that their value is immaterial when the returns to R&D for one possible phaseout year are expressed relative to the returns if the phaseout were in a different year. This measure is expressed as a percent of the total returns in net gains investors would make given phaseout at the fastest possible rate, i.e., by March 2006. The numbers show the percent of that total return that investors would receive for each year's decision on essential uses.

To estimate the returns to innovative technology, we started our calculations using two manufacturers' total stated costs to research and develop non-ODS MDI technology worldwide and for all products. These expenditures were divided into the two manufacturers' share of the increased U.S. consumer expenditures for their branded products. (The National Association of Chain Drug Stores has estimated that manufacturers receive approximately 75 percent of branded prescription drug prices.) Thus, the innovating firms are expected to capture approximately 75 percent of the total annual expenditures for albuterol after the removal of the essential-use designation. The difference between this amount and their current estimated return was estimated for each year until generic competition is expected to return (2015 in table 2 of this document or 2010 in table 3 of this document). The present values of the increased streams of revenue are discounted (using both a 7-percent and a 3-percent annual discount rate) to 2006, then normalized to the present value of the increased revenues expected if 2006 is the decision year. For example, if generic competition is not expected until 2015 (table 2 of this document), a phaseout in 2007 would reduce the expected return on investment in this technology by 13 percent (using 7-percent discount rate) or 11 percent (using 3-percent discount rate). If generic competition returns in 2010, a phaseout in 2007 would reduce the expected return on investment by 27 percent (using 7-percent discount rate) or 26 percent (using 3-percent).

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 pricing agreements have depressed the potential returns to technological innovation. For example, we examined the relative prices of generic albuterol CFC MDIs and branded albuterol HFA MDIs in three European markets (United Kingdom, France, and Germany). The price difference ranged between $0.30 and $0.85 per MDI. These differences are much less than the U.S. price difference. The U.S. decision to eliminate albuterol CFC products is complicated, not only because the U.S. price difference is so large that the phaseout may limit some consumers' access to albuterol, but also because the U.S. decision has a disproportionately large effect on the returns to R&D.

TABLE 2.—MAJOR QUANTIFIABLE EFFECTS OF ALTERNATIVE DATES FOR ENDING THE ESSENTIAL-USE DESIGNATION FOR CFCS[1] FOR ALBUTEROL MDIS WITH GENERIC COMPETITION IN 2015

Year of Removal of Essential-Use Designation	Number of Affected Canisters of Albuterol (millions)	Increased Expenditures on albuterol. Present Value in 2006; (billions)		Possible Reduction in MDIs (millions)	Reduced Aggregate CFC Emissions Relative to a Phaseout in 2015 (metric tons)	Discounted Innovators' Revenue from U.S. Sales, Relative to Discounted Revenue With 2006 Phaseout	
		7-percent discount rate	3-percent discount rate			7-percent discount rate	3-percent discount rate
2006	388.0	$6.9	$7.9	3.9 to 9.7	12,600	100	100
2007	346.1	$5.9	$7.0	3.5 to 8.7	11,200	87	89
2008	303.9	$5.0	$6.0	3.0 to 7.6	9,800	75	78
2009	261.4	$4.2	$5.1	2.6 to 6.5	8,400	63	68
2010	218.6	$3.4	$4.2	2.0 to 5.5	7,000	53	57
2011	175.5	$2.6	$3.3	1.8 to 4.4	5,600	42	47
2012	132.1	$1.9	$2.5	1.3 to 3.3	4,200	33	37
2013	88.4	$1.2	$1.6	0.9 to 2.2	2,800	24	28
2014	44.4	$0.6	$0.8	0.4 to 1.1	1,400	15	18
2015	None	None	None	None	None	None	None

[1] CFC means chlorofluorocarbons.

TABLE 3.—MAJOR QUANTIFIABLE EFFECTS OF ALTERNATIVE DATES FOR ENDING THE ESSENTIAL USE DESIGNATION FOR CFCS FOR ALBUTEROL MDIS WITH GENERIC COMPETITION IN 2010

Year of Removal of Essential-Use Designation	Number of Affected MDIs of Albuterol (millions)	Increased Expenditures on albuterol. Present Value in 2006; (billions)		Possible Reduction in MDIs (millions)	Reduced Aggregate CFC Emissions Relative to a Phaseout in 2015 (metric tons)	Discounted Innovators' Revenue from U.S. Sales, Relative to Discounted Revenue With 2006 Phaseout	
		7-percent discount rate	3-percent discount rate			7-percent discount rate	3-percent discount rate
2006	169.4	$3.5	$3.7	1.6 to 4	5,600	100	100
2007	127.5	$2.6	$2.8	1.2 to 3	4,200	73	74
2008	85.3	$1.7	$1.8	0.8 to 2	2,800	47	49
2009	42.8	$0.8	$0.9	0.4 to 1	1,400	23	24
2010	None	None	None	None	None	None	None

B. Objective of the Proposed Rule

The objective of the proposed rule is to reduce emissions of ODSs, specifically CFCs. CFCs and other ODSs deplete the stratospheric ozone that protects the Earth from ultraviolet solar radiation. FDA is proposing to end the essential-use designation for ODSs to be used in albuterol MDIs, given that two ODS-free albuterol MDIs have been successfully marketed in the United States for more than 2 years, and these MDIs may provide patients with adequate access to these medications. Under this proposal, albuterol CFC MDIs would no longer qualify for an essential use, so the essential use designation will cease when the rule goes into effect.

C. Current Conditions

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 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. As a result, environmental scientists advocated ending the use of these chemicals. An effort to craft a coordinated international response to this global environmental problem culminated in the historic 1987 Montreal Protocol. This Protocol now has been ratified by 186 parties. The current procedures to nominate essential uses and allocation of CFCs under the Montreal Protocol are described in section III.B of this document. At the November 2003 meeting, the parties to the Protocol decided that all parties must announce prior to the Open-Ended Working Group meeting in summer 2005, a date by which they would no longer seek an essential-use designation for CFCs for albuterol MDIs.

2. Effects of the Montreal Protocol

Since the Montreal Protocol has been in place, overall usage of CFCs has been dramatically reduced. In 1986, global consumption of CFCs totaled 1,078,634 metric tons. By 2000, global consumption had fallen to 96,058 metric tons (Ref. 3). This decline amounts to about a 90-percent drop and is a key measure of the success of the Protocol. Within the United States, emissions of CFCs have also fallen sharply—about 80 percent from 1990 to 2000 when measured as the sum of CFC-11 and CFC-12.[7]

EPA has generated a series of estimates of the public health benefits of the Montreal Protocol (see The Benefits and Costs of the Clean Air Act: 1990–2010, *http://www.epa.gov/air/sect812/1990-2010/fullrept.pdf* (Benefits and Costs) (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document has published in the **Federal Register**)). These include hundreds of millions of nonfatal avoided skin cancers, 6 million fatal avoided skin cancers, and 27.5 million avoided cataracts, all between the years 1990 and 2165 (see Benefits and Costs, Table G–4). In dollar terms EPA estimated these and related benefits to sum to $4.3 trillion in present value when discounted at 2 percent over the period of 175 years (see Benefits and Costs, Table G–7). This amount is equivalent to $6 trillion after adjusting for inflation between 1990 and 2003. These estimates include all the benefits of total worldwide emission reductions expected from the Montreal Protocol, and are based on reductions from a baseline that assumes future increases in emissions of CFC and all other ozone depleting substances in the absence of the protocol (see Benefits and Costs, page G–13). EPA does not report, however, any information about the magnitude of the emissions reductions associated with its benefits estimates. Thus, these estimates are of little help in evaluating the economic impacts of this rulemaking.

We believe that a reduction in emissions of CFCs from MDIs would result in public health gains in the United States, and that these gains could be magnified if other countries follow suit and further reduce emissions.

3. Asthma

Asthma is 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.

[7] This sum is valid, as their ozone depleting potentials are equal. See *http://www.epa.gov/ozone/ods.html*. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document has published in the **Federal Register**.)

According to the National Health Interview Survey (NHIS), 31.3 million people in the United States have been diagnosed with asthma during their lifetime, and 20.3 million of them are currently being treated for asthma (National Center for Health Statistics, 2003). The prevalence of current asthma decreases with age, with the prevalence being 87 per 1,000 children ages 0-17 years (6.3 million children) compared to 69 per 1,000 adults 18 years and over (14 million adults).

Asthma attack prevalence, or the number of people who had at least one asthma attack during the previous year, is considered by CDC to be a crude indicator of how many people have uncontrolled asthma and are at risk for a poor outcome from asthma, such as hospitalization. In 2001, 12 million people (about 60 percent of the people who had asthma) reported experiencing an asthma attack in the previous year. Asthma attack prevalence tends to decrease with age; 57 per 1,000 children ages 0-17 years (4.2 million children) had an asthma attack during the previous year compared to 38 per 1,000 adults (7.8 million adults).

NHIS reported there were 10.4 million outpatient asthma visits to physician offices and hospital clinics during 2000. In addition, there were 1.8 million emergency room visits; 465,000 hospital admissions; and 4,487 mortalities associated with asthma. The estimated direct medical cost of asthma (hospital services, physician care, and medications) was $10.4 billion (Ref. 4).

While the prevalence of asthma, or the proportion of the U.S. population with asthma, has been increasing, the incidence of asthma, the rate of new diagnoses of asthma, has remained fairly constant since 1997, according to CDC (Ref. 1). Non-Hispanic blacks, children under 17 years, and females have higher incidence rates than the general population and also have higher asthma attack prevalence. CDC notes that although a numeric increase has occurred in the numbers and rates of physician office visits, hospital outpatient, 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.

4. COPD

COPD has been defined as the physiologic finding of non-reversible impairment of lung function. 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 (e.g., chronic coughing, expectoration, and wheezing). COPD is generally associated with cigarette smoking and is extremely rare in persons younger than 25 years of age.

According to CDC, an estimated 10 million adults were diagnosed with COPD during 2000 (Ref. 5). Because such diagnoses have usually been based on patient-reported symptoms, the NHIS suggests that as many as 24 million Americans are actually affected by the disease. Between 1980 and 2000, the rate of COPD in females increased relative to males. However, the proportion of the U.S. population with mild or moderate COPD has declined over the last quarter century, suggesting increases seen in recent decades may not continue indefinitely. The most effective intervention in modifying the course of COPD is smoking cessation. However, symptoms, such as coughing, wheezing, and sputum production are treated with medications.

5. Current U.S. MDI Market

Patients in the United States currently use MDIs with 12 approved medications—active ingredients—for treatment of asthma and COPD. According to updated data originally presented in 64 FR 47719, approximately 120 million prescription MDIs are sold per year. Albuterol is the only ingredient available in both CFC and HFA MDIs and is also the only prescription MDI available from generic manufacturers, although patents have expired for 9 of the 12 medications (Ref. 6).

Branded, private-label branded, and generic versions of albuterol MDIs account for about 40 percent of all MDI prescriptions, or about 50 million per year. During 2002, about 40 million prescriptions were for private label branded and generic versions of the product.

Two versions of albuterol MDIs are now available with HFA as a propellant. The first patent for albuterol HFA MDI technology will expire on July 6, 2010. Additional patents expire through June 16, 2015. We are not currently aware of any other marketing exclusivities.

We use price data from several sources because we lack comprehensive detailed data that are representative of prices faced by consumers whose behavior is most likely to be affected by this rule—uninsured and underinsured asthma and COPD patients of low to modest incomes. A key source is a private company, IMS Health, which provides marketing data on drug products. A recent FDA analysis of the average national retail price of drugs in ''brick-and-mortar'' pharmacies (i.e., chain, independent, and foodstore pharmacies, excluding Internet, mail order and long-term care pharmacies) found that median prices for generic albuterol MDIs are about 48 percent of the brand price for VENTOLIN (ODS), when prices are measured using the average pharmacies' revenues from uninsured customers, insured customers, and Medicaid beneficiaries alike. See *http://www.fda.gov/cder/consumerinfo/savingsfromgenericdrugs.htm*. We have analyzed the same IMS data set, National Prescription Audit *Plus*™; 1st Quarter 2004 (extracted April 2004), and find that the median price per MDI for generic albuterol MDIs is $19.70, and that the price per MDI for albuterol HFA MDIS is $43.00.[8] These prices imply a price difference of $23.00 and should be seen as approximate in part, because they change over time. Over the preceding year HFA MDI prices rose by almost 8 percent. Therefore, these prices are not necessarily comparable to prices for cash-paying customers because they reflect the average price for all payer types.

Manufacturers also report price data in the form of average wholesale prices (AWP) per prescription as noted in the Red Book (Ref. 7). For generic albuterol MDIs, the AWP reported from this reference was about $25 in 2002. However, according to utilization data from the Medicaid drug rebate program, the average Medicaid reimbursement for generic albuterol MDIs during 2002 was $27.29.[9] The AWP for branded albuterol CFC MDIs was approximately $35 per MDI during 2003. The reported AWP for albuterol HFA MDIs is also approximately $35. These prices have remained fairly constant since 2000.

The federal supply schedule (FSS) established by the Department of Veterans Affairs (*http://www.vapbm.org/PBM/prices.htm*) provides yet another source of information on prices (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document has published in the **Federal Register**). It indicates that the HFA MDI with the larger market share is priced

[8] We calculate the HFA price as follows: Retail revenues for PROVENTIL HFA and for VENTOLIN HFA for the quarter ending in March 2004, divided by total canisters dispensed. We calculate the number of canisters dispensed as the number of grams of active ingredient times the grams per canister (6.7 grams for PROVENTIL HFA, and 18 for VENTOLIN HFA).

[9] Utilization Data from the Medicaid Drug Rebate Program, Centers for Medicare and Medicaid Services. July 28, 2003.

significantly lower than the other HFA MDI: $14.30 versus $26.50 per MDI. The other FSS prices are all lower than the IMS prices by various amounts. Ten products, however, have no FSS price, so that broader generalizations about these prices are very problematic.

Alternative medications for the treatment of asthma and COPD available in MDIs have reported average wholesale prices between $30 and $50 per prescription (Ref. 7).

Finally, we have conducted an informal assessment of retail MDI prices that offers evidence of price differences at the retail level for uninsured customers. A March 24, 2004, examination of *http://www.drugstore.com*'s (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document has published in the **Federal Register**) prices revealed that a generic albuterol MDI was 60 percent less expensive than branded PROVENTIL (ODS) or VENTOLIN (ODS) MDIs ($13.99 versus $38.10 and $35.99, respectively). PROVENTIL HFA and VENTOLIN HFA were priced at a small premium of 4 to 8 percent over the branded CFC equivalents (e.g., one MDI of PROVENTIL HFA was $39.60 and one MDI of VENTOLIN HFA was $38.99).

For our analysis we use a range of price differences for the ratio of the branded HFA MDI price to the generic MDI price. As a lower bound we use 1.2, reflecting the price difference based on IMS data and as an upper bound we use 1.8, reflecting the price differences reported using Internet price data. Note that the first estimate reflects all retail prices in all brick and mortar pharmacies, including uninsured and insured patients. The second estimate reflects only prices for cash-paying customers on the Internet.

D. Benefits of Earlier Phaseout Dates

There are four categories of benefits of earlier dates to eliminate the essential-use designation for ODSs in albuterol MDIs: controlled transition from CFC MDIs to HFA MDIs that avoids any ambiguity in the authorization of the parties to produce and market CFCs and MDIs containing CFCs, the environmental and human health benefits of ODS emissions reductions by the United States, the environmental and human health benefits of continued compliance by other countries with the phaseout targets of the Montreal Protocol, and perceived improvements in incentives to research and develop new and better technologies to solve environmental problems. We address these items in turn.

1. Controlled Transition to Non-CFC MDIs

Under the Montreal Protocol, manufacture of CFCs is allowed only for export to economically less-developed countries and for purposes designated as ''essential,'' including MDIs. As discussed in section IV. D of this document, one manufacturer of pharmaceutical grade CFCs has announced plans to cease production at the current site in the Netherlands in 2005. We do not have information that conclusively shows that the Baton Rouge facility can produce adequate quantities of pharmaceutical grade CFC-11 and CFC-12. Consequently, a benefit of a 2006 phaseout date is that it would avoid a possibility of a shortfall in MDI production due to the unavailability of CFCs after the plant in the Netherlands ceases production in 2005.

2. Value of Reduced ODS Emissions

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 $6.0 trillion.[10] However, EPA's report provides no information about the tons of emissions reduced or the value of reducing CFC emissions by one more ton. Moreover, EPA's reports provide no information about the total emissions reductions associated with its benefits estimates. Therefore we cannot use those reports as a basis for estimating benefits of reducing ODS emissions from MDIs. As a share of total global emissions, a few years' of CFC emissions from MDIs in the United States would represent only a small fraction of a percent. In fact, the current U.S. allocation of CFCs for albuterol MDIs accounts for about 0.1 percent of the total 1986 global consumption of CFCs.[11] Furthermore, current U.S. CFC emissions from MDIs represent a much smaller but unknown share of the total emissions reduction associated with EPA's estimate of $6 trillion in benefits from the Montreal Protocol, because that estimate reflects avoided growth in emissions over many decades. FDA solicits comment on how to analyze further the benefits of CFC and other ODS emission reductions. We believe that the direct benefits of this proposed regulation are small relative to the overall benefits of the Montreal Protocol. More importantly, however, we have been unable to assess how these reduced UV–B radiation related health effects would compare to the possible negative public health impacts associated with more years of reduced access to inexpensive generic albuterol.

3. International Cooperation

The Montreal Protocol, like most international environmental treaties, relies primarily on a system of national self-enforcement. However, it does include significant trade sanctions for noncompliance. Moreover, execution of its directives is in many respects subject to differences in national implementation procedures. Economically less-developed nations, which have a more protracted phaseout schedule, have emphasized in previous meetings of the parties the importance to their own national programs of continued progress by developed nations (such as the United States) in eliminating CFC production. As noted previously, if the United States adopts a relatively later phaseout date, other parties to the Montreal Protocol may decide to alter their own adoption of control measures. Conversely, parties that have already achieved an early phaseout of albuterol CFC MDIs by conversion to the same alternatives currently available in the United States may promote a decision to phase out albuterol CFC MDIs in all developed countries by a specified date in the near future, which could prevent an orderly transition away from CFC MDIs and could also raise compliance issues for the United States under the Montreal Protocol. Thus, the advantages of selecting a date that maintains international cooperation in implementing the remaining measures required by the Montreal Protocol are potentially substantial. Selection of a date seen to be unsuitable could have adverse environmental and human health consequences (e.g., if all countries interpret U.S. action as a license to consume 1,400 additional tons of CFCs per year).

4. Encouraging Innovation

Earlier phaseout dates not only reward the developers of the HFA technology, but also would serve as a signal to potential developers of other environmentally benign technologies. In particular, earlier phaseout dates would promote the perception that the incentives to research and develop such technologies are relatively high.

Newly developed technologies to reduce ODS emissions have resulted in more environmentally ''friendly'' air conditioners, refrigerants, solvents, and propellants. Several manufacturers have

[10] See *http://www.epa.gov/air/sect812/1990-2010/ch_apg.pdf*. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document has published in the **Federal Register**.)

[11] See United Nations Environmental Programme; ''Production and Consumption of Ozone Depleting Substances: 1986–2000''; 2003 (Ref. 1).

claimed development costs that total between $250 and $400 million to develop HFA MDIs and new propellant free devices for the global market (Ref. 8).

These investments have resulted in several innovative products in addition to albuterol HFA MDIs. For example, breath-activated delivery systems, dose counters, dry-product inhalers, and mini-nebulizers have also been successfully marketed. This technology could also affect other medications used for the treatment of asthma and COPD because of the likelihood that all CFC allocations may be revoked at some future date. However, currently only two albuterol HFA MDIs are marketed in the United States, accounting for less than 5 percent of albuterol MDI prescriptions.

Earlier removal of the essential-use designation for albuterol MDIs will increase the overall returns on these investments, thereby serving to encourage future research in related areas.

The expected revenue increases for HFA MDIs that would follow the removal of the essential-use designation for ODSs in albuterol MDIs in the United States would be large. With an estimated $43 per MDI cost for albuterol HFA MDIs, manufacturers of branded HFA MDIs would increase revenues by about $850 million per year, based on historical returns to manufacturers of branded products. These revenue gains are based on innovating firms capturing the current generic market for albuterol and receiving 75 percent of the retail price of the HFA product with the remainder kept by distributors and retailers. Innovating firms have claimed total costs of R&D for non-ODS MDIs globally and for all products to be between $250 and $400 million per firm. No other market provides the potential for such significant returns on investment because of the low difference between generic and branded prices. European prices have typically shown differences of less than $1.00, which limit the potential gains on investment from these markets.

E. Costs of Earlier Phaseout Dates

The key cost of earlier dates to discontinue use of albuterol CFC MDIs is the potential decline in consumption of such MDIs that may result from the price increase that would accompany loss of generic products. Patients respond to price increases of medicines for chronic conditions in a way that may adversely affect their health. A recent paper by Goldman et al. reported 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* * *,

though they characterize these results as ''not definitive'' (Ref. 2). These data suggest that increased prices for albuterol medication may lead to some adverse public health effects in the United States among populations who would pay increased prices. This evidence is insufficient, however, to permit us to quantify the adverse effects of an albuterol price increase on public health. We adopt two complementary approaches to estimate the potential change in MDI use that may result from the expected increase in market price of albuterol MDIs when albuterol CFC MDIs are taken off the market. In both instances, we focus on aggregate MDI use because it provides an overall measure of whether patients are adequately served, that is, whether high-priced non-ODS products may be effectively unavailable to a portion of the patient population because the high price discourages them from buying MDIs.

Our first approach simply assumes that the only effect of an elimination of albuterol CFC MDIs from the market would be an increase in the average price of albuterol MDIs. We ignore any changes in the price of albuterol HFA MDIs that removal of the essential use designation for albuterol may cause. Given the projected price increase and existing estimates of the market response to the price increase, we project how the quantity of albuterol MDIs consumed may decline.

Our second approach assumes that the effects of removing albuterol CFC MDIs from the market can be inferred from the effects of the introduction of generic products. We describe these two approaches in turn.

To apply the first approach, we need to start with estimates of market price. As previously discussed, the Internet prices and the IMS retail prices suggest that delisting albuterol as an essential use would imply price increases of 180 and 120 percent, respectively.

We have no information about how consumers react to increases in the price of MDIs per se, and the price of ''rescue'' type MDIs such as albuterol bronchodilators in particular, which are used in more emergency cases. Economists have written many articles about the response of consumers to higher insurance copayments for drugs generally, however, and these appear to be concentrated 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. 9). One recent paper suggests a somewhat larger estimate for antiasthmatic medications. Based on an analysis of nearly 530,000 people enrolled in 52 health plans over 4 years, Goldman et al., 2004, report that as the average copayment for antiasthmatics doubles, the average number of days of treatment supplied fell by more than 30 percent. Albuterol was one of the most common antiasthmatic drugs in their sample (Ref. 10). Given that a doubling of the copayment amounts to a 100 percent increase in the effective (out of pocket) price, this results suggests an elasticity for antiasthmatics of -.3. The authors also report, however, that the effect of price of consumption falls as fewer substitutes are available. For drugs with no over the counter substitutes—a set that presumably includes albuterol—the effect is only 0.15, while for drugs with close substitutes available over the counter the effect rises to 0.32. A doubling of the average copayment of $12.85 is a slightly smaller price increase in both absolute and relative terms than might be expected from the delisting of albuterol, as explained in the following paragraphs.

We assume that elasticity estimates derived from increases in copayments are applicable to forecasting the demand response among uninsured patients. Assuming that 15 percent of the 40 million generic albuterol MDIs now marketed annually are sold to uninsured patients, and a price elasticity of demand of 0.05, a 120 increase in price would lead to a reduction in demand in this population of about 360,000 MDIs per year (40 million x 15 percent x .05 price elasticity x 120 percent price increase). Given the obvious uncertainty we round this estimate to 400,000 MDIs per year. A similar calculation using the price difference observed on the Internet and assuming that demand is more sensitive to price would yield a higher estimate. In particular the sale of albuterol MDIs would drop by slightly more than a million MDIs annually given a price difference of 1.8 and a price elasticity of demand of 0.1. The elasticity consistent with the Goldman paper for products without substitutes available OTC—0.15-would imply a market effect of 1.6 million MDIs not sold.

These forecasts require several caveats. First, they apply estimates of consumer behavior developed from very small price changes to a large price change. This application may not be warranted. Second, these forecasts

assume that the elimination of albuterol CFC MDIs from the market would not affect other factors, such as advertising. Finally, and most importantly, these estimates ignore the GSK plan to distribute 2 million free MDIs per year. Clearly, GSK's plan could substantially reduce the projected loss in consumption of MDIs if its 2 million free MDIs were distributed to the patients whose consumption of MDIs is most sensitive to price. Given the limitations in the data, we cannot develop an estimate free from these caveats.

In an effort to corroborate this estimate, we tried to develop a completely independent approach borrowing from the experience of markets when generics are first introduced. Estimates of the market response to the introduction of a generic product should provide information about how markets respond when a generic product is eliminated. One study (Ref. 10) examined the effects of generic competition on pharmaceutical markets, and offers suggestive, but not definitive, evidence. It estimates how the prices and quantity of drugs sold vary with the number of generic competitors. The authors note that the total quantity of drugs sold after generic competition began initially increased and then decreased. The authors note that the variable response reflects both the impact of lower prices and the decline in advertising by the manufacturer of the branded product. The largest identified response, a 3-percent increase in the quantity of drugs sold, occurs after four to five generic products have been introduced. With further entry, consumption falls relative to the level it had with no generics because the effect of greater competition on increasing consumption is more than offset by the effect of diminished advertising.

This research suggests that any effect on consumption by the removal of generic albuterol MDIs may be quite small. However, there are several limitations. First, the peak response in terms of the increase in the number of prescriptions (3 percent) is dependent on a statistically insignificant response. Second, the number of generic albuterol CFC MDIs currently marketed exceeds the four to five entries associated with the peak quantity response relative to the no-generics scenario.

These analyses suggest that a reasonable range of estimates for the potential reduction in the quantity of albuterol MDIs sold could range from about 400,000 per year to more than 1 million per year. We derive the estimate of 400,000 fewer MDIs as a reduction of 1 percent of the 40 million generic albuterol MDIs currently sold each year. We present 1 million as a reasonable upper bound but note that the research allows the possibility that the true response will be greater.

We also note that the assumption that prices of HFA MDIs would remain constant may be inappropriate. Many economic models suggest that reducing the number of products that compete in a market will tend to raise prices, other things remaining equal. However, since one manufacturer (GSK) has announced a voluntary price freeze on its albuterol HFA MDIs (i.e., it voluntarily agreed to not change its price), we have assumed stable prices for this analysis.

The withdrawal of ODSs as propellants for albuterol MDIs may affect pricing of the 15 active moieties available for treatment of asthma and COPD, including albuterol HFA MDIs. However, generic albuterol HFA MDIs will not be available until current patents no longer bar generic competition. We believe the albuterol market is attractive to potential generic marketers and competition will reenter this market as soon as possible. Until generic albuterol HFA MDIs enter the market, however, the average price for albuterol MDIs in the event that albuterol CFC MDIs are discontinued will be significantly higher than the current price. The availability of other therapies for the treatment of asthma and COPD (such as dry powder inhalers) may provide sufficient competition to avoid any additional price effects.

GSK has stated that sufficient supplies of albuterol HFA MDIs would be available within 12 to 18 months of notification of removal of the essential-use designation. Therefore, we do not believe inadequate supplies of these products would occur after the removal of essential-use designations through notice-and-comment rulemaking.

F. Insurance and Third Party Payers

According to the Department of Census, about 85 percent of the population has some health insurance coverage (Ref. 11), while according to the National Council of Prescription Drug Plans (NCPDP), about 80 percent of all health plans offer drug coverage (Ref. 12). Together, these imply that about 35 percent of the population has no prescription drug coverage and must pay for medications out of pocket. However, the recent Medicare Prescription Drug Improvement and Modernization Act increased the proportion of the population covered by a prescription drug insurance plan. Overall, based on discussions with NCPDP, we expect that the patient population will consist of approximately 15 percent uninsured, 20 percent insured by public sources (Medicare, Medicaid, Department of Veterans Affairs, etc.), and 65 percent insured privately. (These estimates are for analysis purposes and are rounded for ease of estimation. They are not meant to be precise estimates of coverage.) The uninsured sector of the population may be particularly affected by the expected increase in price with the loss of generic competition.

This effect has been noted by the innovating manufacturers. GSK has pledged to supply up to 2 million albuterol HFA MDIs to physicians for free distribution to low income patients. They also have long provided private programs, such as ''Bridges to Access'' and others to provide access to needed medications. We believe that any potential access problems may be ameliorated by programs such as these and specifically request comment on them in order to better analyze their potential impact on maximizing patient access to therapies.

Patients who use more MDIs than average may incur greater than average costs as a result of the expected price increase. Extrapolating data from one long-term Canadian study that tracked asthma patients over many years, and included information on the number of MDIs used by asthmatics who had received at least 3 prescriptions for asthma during any one period from 1975 to 1991 (Ref. 13), about 1 million patients may use 6 or more MDIs of medication a year. Assuming that 15 percent of these are uninsured, and face a conservative out-of-pocket price increase of $23 per MDI, then about 150,000 patients would pay $138 or more per year for their medications. Higher differences in prices, such as the $25 difference in Internet prices reported above would lead to proportionately much greater increases in spending.

The loss of generic products may also affect co-payment rates in that most carriers require a higher per prescription copayment for branded rather than generic products. For example, a patient may pay $22 per prescription for a branded drug, but only $10 for a generic substitute. However, if there is no generic substitute, most plans provide the lower copayment (Ref. 12). Patients in plans that offer co-insurance rates for prescription coverage would face higher out-of-pocket costs because of the loss of generic products.

To assess the population of users of albuterol we asked the Agency for Healthcare Research and Quality

(AHRQ) to use the Medical Expenditure Panel Survey (MEPS) for 2000 and 2001 to estimate how many low- or moderate-income people without health insurance or with inadequate used albuterol MDIs. The results of that assessment suggest the following.

• There are about 620,000 low and moderate income users of albuterol MDIs that have no health insurance or that have no group health insurance. The 95 percent confidence interval for this estimate is approximately 470,000 to 770,000 users. Low and moderate income in this context means belonging to a family whose income is less than 400 percent of the Federal poverty line.

• The prescriptions per user per year among low- and moderate-income users who have no insurance or no group insurance are about 3.8, somewhat greater than the 2.9 prescriptions among all users irrespective of income or insurance status.

• The average price per prescription for users of albuterol MDIs who were low or moderate income and either uninsured or without group health insurance, was $25.40, but only $22 if they bought generic. AHRQ did not report the price of branded products, or the price of the HFA MDIs, however, so no comparison between generic and branded prices is possible.

• Of all users of albuterol MDIs, approximately 88 percent use generics, while for the low and moderate income patients with non-group insurance or no insurance, only 80 percent use generics.

The average expenditures on albuterol MDIs for the low or moderate income user without group health insurance or any insurance were $97 per year. An increase in price of $23 per MDI would mean additional out of pocket health care costs of about $43 million per year for this group.

G. Small Business Impact

We believe the proposed rule is likely to have a significant impact on a substantial number of small entities. Current HHS guidance suggests that 3 to 5 percent impact of small entity's revenues could constitute a significant regulatory impact (Guidance on Proper Consideration of Small Entities in Rulemakings of the U.S. Department of Health and Human Services; May 2003). Because of this, we have prepared an initial Regulatory Flexibility Analysis (IRFA) and invite comment from any affected entities. In addition, the proposed rule is considered a significant rule under UMRA, and alternatives are examined and briefly discussed here.

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 proposed rule on generic manufacturers is the lost revenues 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.

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. Of the 40 million generic or relabeled prescriptions for albuterol, about 30 million were dispensed by a large innovative firm under a different label (Warrick). According to IMS, the remaining 10 million dispensed generic or relabeled prescriptions were marketed by eight different companies. Each company sold an average of about 1.25 million MDIs. According to data collected by the Congressional Budget Office (Ref. 14), the value of shipments from manufacturers of generic drug products accounts for approximately 35 percent of the retail price of the product. If so, revenues from 1.25 million MDIs would approximate $10 million per year, or about 40 percent of annual revenues for a small entity. We believe this constitutes a significant impact on a substantial number of small entities.

2. Alternatives

We are considering the effect of removing the essential-use designation for ODSs in albuterol MDIs for each year between 12 months after issuance of a final rule on this subject and December 31, 2009. There is no difference in the expected annual effect on small entities in any of the examined years. However, if generic competition with HFA albuterol was available prior to the removal of the essential-use designation any impact on small entities would be eliminated. But this alternative is not being considered at this time because it would not meet the objective of meeting the requirements of the Montreal Protocol.

3. 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. However, we will specifically solicit comments from small entities on ways the proposed rule may affect their businesses.

H. Conclusion

The proposed rule could result in increased health care expenditures of about a billion dollars for each year between the reintroduction of generic competition in this market and the selected year for removing the essential-use designation.

We project that higher prices may reduce the MDIs sold by between 400,000 and 1 million per year for each year without generic competition, though this estimate ignores GSK's offer to distribute free MDIs because we are unable to quantify how many of these MDIs would go the people who would otherwise reduce MDI purchases because of the higher prices. In addition, each earlier year after removing the essential-use designation will avoid about 1,400 metric tons of CFC emissions and provide increased investment returns for innovators of ODS-free technology. Removing the essential-use designation will also meet requirements of international agreements and avoid the potential disruption of complete withdrawal of CFC allocation. Finally, we believe the removal of the essential-use designation for this purpose will result in a significant impact on a substantial number of small entities, but this impact can be ameliorated by adjusting the effective date of the rule.

IX. 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.

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

2. Goldman, J. et al., ''Pharmacy Benefits and the Use of Drugs by the Chronically Ill,'' *The Journal of the American Medical Association*, May 19, 2004; 291:2344–2350, 2349.

3. United Nations Environmental Programme, ''Production and Consumption of Ozone-Depleting Substances 1986–2000,'' 2003.

4. Weiss, K.B. et al., ''Trends in the Costs of Illness for Asthma in the United States,

1985–1994,'' *Journal of Allergy and Clinical Immunology*, 106(3):493–499, September 2000.

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

6. Food and Drug Administration, Center for Drug Evaluation and Research, *Approved Drug Products with Therapeutic Equivalent Evaluations*, 23rd Edition, 2003.

7. Drug Topics, *Red Book*, Thomson Medical Economics, 2002.

8. Rozek, R.P., and E.R. Bishko, ''The Impact on Patients and Payers of Designating Albuterol a Non-Essential Use of an Ozone-Depleting Substance,'' National Economic Research Associates, September 8, 2003.

9. Ringel J.S. et al., ''The Elasticity of Demand for Health Care,'' National Defense Research Institute, Rand Health, 2002.

10. Goldman, Dana, private communication, May 29, 2004.

11. Caves, R.E. et al., ''Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry,'' *Brookings Papers on Economic Activity*, *Microeconomics*, 1991.

12. Bureau of Census, ''Health Insurance Coverage: 2001,'' Current Population Reports, U.S. Department of Commerce, September 2002.

13. Communication between Mr. Thomas Bizzaro, Vice-President of the National Council of Prescription Drug Plans, and Mr. Steven A. Tucker, Food and Drug Administration, June 23, 2003.

14. Suissa, S. et al., ''Low-Dose Inhaled Corticosteroids and the Prevention of Death from Asthma,'' *New England Journal of Medicine*, 343(5):332–336, 2000.

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

X. The Paperwork Reduction Act of 1995

We have tentatively concluded that this proposed rule contains no collection of information. Therefore clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

XI. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have tentatively 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. Consequently, we do not currently plan to prepare a federalism summary impact statement for this rulemaking procedure. We invite comments on the federalism implications of this proposed rule.

XII. Request for Comments

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

List of Subjects in 21 CFR Part 2

Administrative practice and procedure, Cosmetics, Drugs, Foods.

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

PART 2—GENERAL ADMINISTRATIVE RULINGS AND DECISIONS

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

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

§ 2.125 [Amended]

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

Dated: June 8, 2004.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 04–13507 Filed 6–9–04; 4:09 pm]

BILLING CODE 4160–01–S