DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 2

[Docket No.]

RIN 0910-AF92

8/07
ams changes

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA), after consultation with the Environmental Protection Agency (EPA), is proposing to amend FDA's regulation on the use of ozone-depleting substances (ODSs) in self-pressurized containers to remove the essential-use designation for epinephrine used in oral pressurized metered-dose inhalers (MDIs). The Clean Air Act requires FDA, in consultation with the EPA, to determine whether an FDA-regulated product that releases an ODS is an essential use of the ODS. FDA has tentatively concluded that there are no substantial technical barriers to formulating epinephrine as a product that does not release ODSs, and therefore epinephrine would no longer be an essential use of ODSs. If the essential-use designation is removed, epinephrine MDIs containing an ODS could not be marketed after a suitable transition period. We will hold an open public meeting on the essential use of epinephrine on a date to be announced later.

DATES: Submit written or electronic comments by [insert date 60 days after date of publication in the FEDERAL REGISTER].

ADDRESSES: You may submit comments, identified by Docket No. _____ and/or RIN number 0910-AF92, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

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

Written Submissions

Submit written submissions in the following ways:

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

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

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

heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents, comments, a transcript of, and material submitted for, the joint meeting of the Nonprescription Drugs and Pulmonary-Allergy Drugs Advisory Committee held on January 24, 2006, go to http://www.fda.gov/ohrms/dockets/default.htm and insert the docket number(s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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

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I. Background

A. CFCs

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

CFCs are very stable in the troposphere, the lowest part of the atmosphere. They move to the stratosphere, a region that begins about 10 to 16 kilometers (km) (6 to 10

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

B. Regulation of ODSs

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

1. The 1978 Rules

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

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

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

2. The Montreal Protocol

On January 1, 1989, the United States became a Party to the Montreal Protocol on Substances that Deplete the Ozone Layer (Montreal Protocol) (September 16, 1987, 26 I.L.M. 1541 (1987)), available at http://www.unep.org/ozone/pdfs/Montreal-Protocol2000.pdf.[1] The United States played a leading role in the negotiation of the Montreal Protocol, believing that internationally coordinated control of ODSs would best protect both the U.S. and global public health and the environment from potential adverse effects of depletion of stratospheric ozone. Currently, there are 191 Parties to this treaty.[2]

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

[2]The summary descriptions of the Montreal Protocol and decisions of Parties to the Montreal Protocol contained in this document are presented here to help you understand the background of the action we are taking. These descriptions are not intended to be formal statements of policy regarding the Montreal Protocol. Decisions by the Parties to the Montreal Protocol are cited in this document in the conventional format of "Decision IV/2," which refers to the second decision recorded in the Report of the Fourth Meeting of the Parties to the Montreal Protocol on Substances That Deplete the Ozone Layer. Reports of

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, by which, following assessment of the existing control measures, the Parties could adjust the scope, amount, and timing of those control measures for substances already subject to the Montreal Protocol. As the evidence regarding the impact of ODSs on the ozone layer became stronger, the Parties used this adjustment procedure to accelerate the phase-out of ODSs. At the fourth Meeting of the Parties to the Montreal Protocol, held at Copenhagen in November 1992, the Parties adjusted Article 2 of the Montreal Protocol to eliminate the production and importation of CFCs by January 1, 1996, by Parties that are developed countries (Decision IV/2).[3] The adjustment also indicated that it would apply, "save to the extent that the Parties decide to permit the level of production or consumption that is necessary to satisfy uses agreed by them to be essential" (Article 2A(4)).

One of the most important essential uses of CFCs under the Montreal Protocol is their use in MDIs for the treatment of asthma and chronic obstructive pulmonary disease (COPD). The decision on whether the use of CFCs in MDIs is "essential" for purposes of the Montreal Protocol turns on whether "(1) It is necessary for the health, safety, or is critical for the functioning of society (encompassing cultural and intellectual aspects) and (2) there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health" (Decision IV/25).

Each request and any subsequent exemption is for only 1 year's duration

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Meetings of the Parties to the Montreal Protocol may be found on the United Nations Environment Programme's Web site at http://ozone.unep.org/Meeting_Documents/mop/index.shtml.

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

(Decision V/18). Since 1994, the United States and some other Parties to the Montreal Protocol have annually requested, and been granted, essential-use exemptions for the production or importation of CFCs for their use in MDIs for the treatment of asthma and COPD (see, among others, Decisions VI/9 and VII/28). The exemptions have been consistent with the criteria established by the Parties, which make the grant of an exemption contingent on a finding that the use for which the exemption is being requested is essential for health, safety, or the functioning of society, and that there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of health or the environment (Decision IV/25).

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

- Decision VIII/10 stated that the Parties that are developed countries would take various actions to promote industry's participation in a smooth and efficient transition away from CFC-based MDIs (San Jose, Costa Rica, 1996).
- Decision IX/19 required the Parties that are developed countries to present an initial national or regional transition strategy by January 31, 1999 (Montreal, Canada, 1997).
- Decision XII/2 elaborated on the content of national or regional transition strategies required under Decision IX/19 and indicated that any MDI for the treatment of asthma or COPD approved for marketing after 2000 would not be an "essential use" unless it met the criteria laid out by the Parties for essential uses (Ouagadougou, Burkina

Faso, 2000).

- Decision XIV/5 requested that each Party report annually the quantities of CFC and non-CFC MDIs and dry-powder inhalers (DPIs) sold or distributed within its borders and the approval and marketing status of non-CFC MDIs and DPIs. Decision XIV/5 also noted "with concern the slow transition to CFC-free metered-dose inhalers in some Parties" (Rome, Italy, 2002).

- Decision XV/5 stated that, at the 17th Meeting of the Parties (in December 2005) or thereafter, no essential uses of CFCs will be authorized for Parties that are developed countries, unless the Party requesting the essential-use allocation has submitted an action plan for MDIs for which the sole active ingredient is albuterol. Among other items, the action plan should include a specific date by which the Party plans to cease requesting essential-use allocations of CFCs for albuterol MDIs to be sold or distributed in developed countries[4] (Nairobi, Kenya, 2003).

- Decision XVII/5 stated that Parties that are developed counties should provide a date to the Ozone Secretariat[5] before the 18th Meeting of the Parties (October 30 to November 3, 2006) by which time a regulation or regulations will have been

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

[5]The Ozone Secretariat is the Secretariat for the Montreal Protocol and the Vienna Convention for the Protection of the Ozone Layer (the Vienna Convention) (March 22, 1985, 26 I.L.M. 1529 (1985)), available at http://hq.unep.org/ozone/pdfs/viennaconvention2002.pdf. Based at the United Nations Environment Programme (UNEP) offices in Nairobi, Kenya, the Secretariat functions in accordance with Article 7 of the Vienna Convention and Article 12 of the Montreal Protocol.

The main duties of the Secretariat include the following:

•Arranging for and servicing the Conference of the Parties, Meetings of the Parties, their Committees, the Bureaux, Working Groups, and Assessment Panels;

•Arranging for the implementation of decisions resulting from these meetings;

•Monitoring the implementation of the Vienna Convention and the Montreal Protocol;

•Reporting to the Meetings of the Parties and to the Implementation Committee;

•Representing the Convention and the Protocol; and

•Receiving and analyzing data and information from the Parties on the production and consumption of ODSs.

proposed to determine whether MDIs, other than those that have albuterol as the only active ingredient, are nonessential (Dakar, Senegal, 2005).

3. The 1990 Amendments to the Clean Air Act

In 1990, Congress amended the Clean Air Act to, among other things, better protect stratospheric ozone (Public Law No. 101-549, November 15, 1990) (the 1990 amendments). The 1990 amendments were drafted to complement, and be consistent with, our obligations under the Montreal Protocol (see section 614 of the Clean Air Act (42 U.S.C. 7671m)). Section 614(b) of the Clean Air Act provides that, in the case of a conflict between any provision of the Clean Air Act and any provision of the Montreal Protocol, the more stringent provision will govern. Section 604 of the Clean Air Act requires the phase-out of the production of CFCs by 2000 (42 U.S.C. 7671c),[6] while section 610 of the Clean Air Act (42 U.S.C. 7671i) required EPA to issue regulations banning the sale or distribution in interstate commerce of nonessential products containing CFCs. Sections 604 and 610 provide 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

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

(B) if such device, product, drug, or drug delivery system, has, after notice and opportunity for public comment, been approved and determined to be essential by the Commissioner [of Food and Drugs] in consultation with the Administrator [of EPA].

4. EPA's Implementing Regulations

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

The prohibition on production and import of CFCs contains an exception for essential uses and, more specifically, for essential MDIs. The definition of essential MDI at 40 CFR 82.3 requires that the MDI be intended for the treatment of asthma or COPD, be essential under the Montreal Protocol, and if the MDI is for sale in the United States, be approved by FDA and listed as essential in FDA's regulations at § 2.125 (21 CFR 2.125).

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

5. FDA's 2002 Regulation

In the 1990s, we decided that § 2.125 required revision to better reflect our obligations under the Montreal Protocol, the 1990 amendments, and EPA's regulations, and to encourage the development of ozone-friendly alternatives to medical products containing CFCs. In particular, as acceptable alternatives that did not contain CFCs or other ODSs came on the market, there was a need to provide a mechanism for removing essential uses from the list in § 2.125(e). In the FEDERAL REGISTER of March 6, 1997 (62 FR 10242), we published an advance notice of proposed rulemaking (the 1997 ANPRM) in which we outlined our then-current thinking on the content of an appropriate rule regarding ODSs in products FDA regulates. We received almost 10,000 comments on the 1997 ANPRM. In response to the comments, we revised our approach and drafted a proposed rule published in the FEDERAL REGISTER of September 1, 1999 (64 FR 47719) (the 1999 proposed rule). We received 22 comments on the 1999 proposed rule. After minor revisions in response to these comments, we published a final rule in the FEDERAL REGISTER of July 24, 2002 (67 FR 48370) (the 2002 final rule) (corrected in 67 FR 49396, July 30, 2002, and 67 FR 58678, September 17, 2002). The 2002 final rule listed as a separate essential use each active moiety[7] marketed under the 1978 rule as essential uses for metered-dose steroid human drugs for oral inhalation and metered-dose adrenergic bronchodilator human drugs for oral inhalation; eliminated the essential-use

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

designations in § 2.125(e) for metered-dose steroid human drugs for nasal inhalation and for products that were no longer marketed; set new standards to determine when a new essential-use designation should be added to § 2.125; and set standards to determine whether the use of an ODS in a medical product remains essential.

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

II. Criteria

Among other changes, the 2002 final rule, in revised 21 CFR § 2.125(g)(2), establishes a standard for removing an essential-use designation for any drug after January 1, 2005, that would apply to a drug for which there is no acceptable non-ODS alternative with the same active moiety. The process for removing the essential-use designation for such a drug must include a consultation with a relevant advisory committee and an open public meeting, in addition to a proposed rule and a final rule. The criterion established for removing the essential use in such circumstances is that it no longer meets the criteria specified in revised § 2.125(f) for adding a new essential use (21 CFR § 2.125(g)(2)). The criteria in § 2.125(f) are: "(i) Substantial technical barriers exist to formulating the product without ODSs; (ii) The product will provide an unavailable important public health benefit; and (iii) Use of the product does not release cumulatively significant amounts of ODSs into the atmosphere or the release is warranted in view of the unavailable important public health benefit."

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

criteria are linked by "and" (as opposed to "or"), failure to meet any single criterion results in a determination that the use is not essential.

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

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

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

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

In determining whether a drug product provides an otherwise unavailable important public health benefit, our primary focus is on the availability of non-ODS products that provide equivalent therapeutic benefits for patients who are currently using the CFC MDIs. If therapeutic alternatives exist for everyone using the CFC MDI, we would then determine that the CFC MDI does not provide an otherwise unavailable important public health benefit. In the case of epinephrine MDIs, the fact that they are marketed over-the-counter (OTC), while the therapeutic alternatives for epinephrine MDIs are prescription drugs, makes the analysis of whether everyone is adequately served by the therapeutic alternatives more complicated.

Under the third criterion, the essential use must be eliminated unless we find either: (1) The use of the product does not release cumulatively significant amounts of ODSs into the atmosphere; or (2) the release, although cumulatively significant, is warranted in view of the otherwise unavailable important public health benefit that the use of the drug product provides. In evaluating whether continuing the essential-use designation of an MDI would result in the product releasing significant quantities of ODSs, in light of past policy statements (2002 final rule p. 48380) and the current state of the phase-out of ODSs, the release of CFCs from epinephrine MDIs is currently significant and as the phase-out of ODSs continues throughout the world, the significance of the quantities of CFCs released by epinephrine MDIs will increase in significance.

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In applying the first part of the third criterion, we are guided by previous policy statements. The United States evaluated the environmental effect of eliminating the use of all CFCs in an environmental impact statement in the 1970s (see 43 FR 11301, March 17, 1978). As part of that evaluation, FDA concluded that the continued use of CFCs in

medical products posed an unreasonable risk of long-term biological and climatic impacts (see Docket No. 96N-0057). Congress later enacted provisions of the Clean Air Act that codified the decision to fully phase out the use of CFCs over time (see 42 U.S.C. 7671 et seq. (enacted November 15, 1990)). We note that the environmental impact of individual uses of nonessential CFCs must not be evaluated independently, but rather must be evaluated in the context of the overall use of CFCs. Cumulative impacts can result from individually minor, but collectively significant, actions that take place over a period of time (40 CFR 1508.7). Significance cannot be avoided by breaking an action down into small components (40 CFR 1508.27(b)(7)). Currently, MDIs for the treatment of asthma and COPD are the only legal use for newly produced or imported CFCs (see 71 FR 58504 (October 4, 2006)). Although it may appear to some that the CFCs released from MDIs represent insignificant quantities of ODSs, and therefore should be exempt, the elimination of CFC use in MDIs is one of the final steps in the overall phase-out of CFC use. The release of ODSs from some of the MDIs may be relatively small compared to total quantities that were released 2 or 3 decades ago, but if each use that resulted in the release of relatively small quantities of ODSs were provided an exemption, the cumulative effect would be to prevent the elimination of ODS releasing products. This would prevent the full phase-out envisioned by the Clean Air Act and the Montreal Protocol. Therefore, we tentatively conclude that the release of ODSs from epinephrine MDIs is cumulatively significant.

Given this proposed finding that the first part of the third criterion is not satisfied, the essential use for epinephrine must be eliminated under § 2.125(f)(1)(iii) if we also find that the second part of the third criterion is not satisfied: it provides an otherwise

unavailable important public health benefit which warrants the cumulatively significant release of the ODS.

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

The criteria in § 2.125(g)(2) (which refers to those found in § 2.125(f)(1)) that we are using in this rulemaking are different from those in § 2.125(g)(3) and (g)(4). Section 2.125(g)(2) specifically addresses the situation where there is no marketed non-ODS product containing the active moiety listed as an essential use, while § 2.125(g)(3) and (g)(4) apply to situations where there is at least one marketed non-ODS product with the listed active moiety. Section 2.125(g)(2) permits FDA to remove an essential use even if a current essential-use active moiety is not reformulated, provided that sufficient alternative products exist to meet the needs of patients, because the essential use would no longer provide an otherwise unavailable important health benefit. Therefore, the

analysis we use here is not identical to the analysis we used under § 2.125(g)(4) in the recent rulemaking to remove the essential use for albuterol (70 FR 17168, April 4, 2005). However, the basic concern of protecting the public health underlies all of the criteria. Therefore, our analyses are similar, and we have found it useful to borrow concepts from the more specific provisions of § 2.125(g)(3) and (g)(4) to help give more structure to our analysis under the broader language of § 2.125(f)(1).

III. Effective Date

We are proposing that any rule finalizing the removal of the essential use for OTC epinephrine MDIs have an effective date of December 31, 2010. Because there are therapeutic alternatives which are marketed as prescription drugs, in determining the appropriate effective date for this rulemaking, we will consider both: (1) Whether adequate time exists to provide patient education for users of OTC epinephrine MDIs, particularly those who do not consult doctors, pharmacists, and other health care professionals; and (2) whether adequate production capacity and supplies are available to meet the new, presumably increased, demand for the therapeutic alternatives once OTC epinephrine MDIs are no longer sold.

Patient education for any transition away from OTC epinephrine MDIs presents unique concerns. Much of the thinking about patient education on the transition from CFC MDIs has focused on the dissemination of information through physicians, pharmacists, and other health care professionals. This information could be given orally by health care professionals, or the information could be available in the professionals' offices or pharmacies for patients to read. Because epinephrine MDIs are sold OTC, many purchasers will not interact with a health care provider. New avenues of

communication will have to be opened to reach all OTC epinephrine MDI users. Many OTC epinephrine MDI users may need to be provided information to help them select a physician. Some OTC epinephrine MDI users who face economic barriers to appropriate health care may need even more time to find and avail themselves of free or low-cost health care and prescription drug programs (see section V.B.2.b of this document). These factors have led us to believe that a transition away from OTC epinephrine MDIs may be more difficult than transitions in which patients change from one prescription drug to another prescription drug, and accordingly that any effective date for such a rulemaking should provide for a longer transition period than the transition period for the recently published proposed rule to eliminate the essential-use designation for MDIs containing flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil (72 FR 32030, June 11, 2007). We have, therefore, tentatively concluded that the December 31, 2010, effective date would be appropriate for a final rule removing the essential-use designation for OTC epinephrine MDIs. We invite comment on the proposed effective date of December 31, 2010, as well as possible alternative effective dates, such as December 31, 2011 or 2012.

In determining an appropriate effective date, we have kept in mind that albuterol MDIs that use the hydrofluoroalkane HFA-134a (HFA) as a propellant are a primary therapeutic alternative to OTC epinephrine MDIs, because both drugs are in the same therapeutic class (short-acting inhaled beta-agonist bronchodilators), albuterol is the only member of the class available in an HFA MDI, and no members of the class are available as a DPI.[8] Sales of OTC epinephrine MDIs have totaled approximately 4.5 million MDIs

[8]Neither HFA MDIs nor DPIs release ODSs. HFA MDIs and DPIs are generally considered to be the non-ODS drug products that are most comparable to CFC MDIs in terms of portability and ease of use.

a year. We are confident that there will be adequate supplies of albuterol HFA MDIs to meet the needs of all users of albuterol CFC MDIs by December 31, 2008 (the date on which albuterol MDIs will no longer be designated an essential use).[9] Although we have limited data on production increases above current demand for 2009, 2010, and later, we believe that by December 31, 2010, albuterol HFA production will be able to meet any increased demand caused by this rulemaking. This proposed effective date is 1 year later than the effective date that we proposed in the recently published proposed rule to eliminate the essential-use designation for MDIs containing flunisolide, triamcinolone, metaproterenol, pirbuterol, albuterol and ipratropium in combination, cromolyn, and nedocromil (72 FR 32030, June 11, 2007). As we said in that proposed rule, many of the patients using some of those drugs would switch to albuterol HFA inhalers. We believe that the additional time required for the needed patient education on alternatives to OTC epinephrine MDIs will also provide additional time to scale up production of albuterol HFA MDIs. This additional time should provide greater assurance that there will be adequate supplies of albuterol HFA MDIs for all patients who use them. We specifically invite comments from manufacturers of albuterol HFA MDIs on this issue.

In proposing a December 31, 2010, effective date, we expect that 2010 would be a transition year characterized by declining production of OTC epinephrine MDIs. If a December 31, 2010, effective date is established by this rulemaking, we anticipate that other administrative actions taken by EPA and FDA would reflect the concept of 2010 being a transition year.

The sale of remaining stocks of CFC MDIs by manufacturers, wholesalers, and

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

retailers was a consideration in setting the effective date of the albuterol rule (70 FR 17168, 17179, April 4, 2005). We believe that this consideration is appropriate for this rulemaking also. In evaluating the period of time needed to sell remaining stocks of OTC epinephrine MDIs, a factor that must be considered is the expiration dating for the relevant products. Both PRIMATENE MIST and the OTC epinephrine MDIs made by Armstrong Pharmaceuticals, Inc. (Armstrong) have expiration dates set at 24 months after manufacture. Drug products are not generally sold right up to the expiration date. Drugs are generally sold well before the expiration date, allowing the purchasers a significant amount of time to use the drug before it reaches its expiration date; therefore, we believe that all OTC epinephrine MDIs manufactured prior to publication of a final rule based on this proposal should be sold by December 31, 2010.

We are proposing a December 31, 2010, effective date based on the assumption that there will not be an inhaled epinephrine OTC drug product that does not contain ODSs on the market in the foreseeable future. If persuasive evidence is presented to the agency that a non-ODS inhaled epinephrine drug product will be marketed in the foreseeable future, we may take this into consideration in finalizing this proposed rule with a different and, presumably, later effective date that would allow a smooth transition to the non-ODS product. We strongly urge that interested individuals submit detailed information on whether inhaled-epinephrine will be available in a non-ODS formulation and when a non-ODS inhaled epinephrine product can reasonably be expected to be on the market.

IV. 2006 NDAC/PADAC Meeting

Section 2.125(g)(2) requires that we consult an advisory committee before we

remove an essential-use designation when there is no non-ODS product with the same active moiety. We consulted the Nonprescription Drug Advisory Committee (NDAC) and the Pulmonary-Allergy Drugs Advisory Committee (PADAC) on the essential-use status of OTC MDIs containing epinephrine at a joint committee meeting held on January 24, 2006 (NDAC/PADAC meeting).[10] Presentations were made by representatives of Wyeth Consumer Health (Wyeth), two patient advocacy and public policy groups, and physician organizations. Seven of the joint committee members recommended that epinephrine be retained as an essential use, while eleven members recommended that the essential-use designation be removed. The opinions expressed by the NDAC and PADAC (NDAC/PADAC) members and other participants in the NDAC/PADAC meeting will be discussed below.

This NDAC/PADAC meeting should not be confused with the open public meeting on the essential-use status of OTC MDIs containing epinephrine we will be holding in the near future. We will publish a notice for that meeting in the FEDERAL REGISTER shortly.

V. Epinephrine

Epinephrine is a short-acting adrenergic bronchodilator used in the treatment of asthma. A new drug application (NDA) for OTC epinephrine MDIs was approved in 1956. Epinephrine was included in the 1978 rule under the provision designating "[m]etered-dose adrenergic bronchodilator human drugs for oral inhalation" as an essential use. Approved NDAs for OTC epinephrine MDIs are currently held by Wyeth and Armstrong, (a subsidiary of Amphastar Pharmaceuticals, Inc.). Wyeth markets their

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

OTC epinephrine MDIs as PRIMATENE MIST, while Armstrong labels their product as "house brands" for certain retail pharmacies. Epinephrine MDIs are the only MDIs for treatment of asthma (or any other disease) that are approved for OTC use.[11] Customers do not need a prescription from a health care provider to purchase OTC epinephrine MDIs. Wyeth presented data at the NDAC/PADAC meeting estimating that 2 to 3 million people with asthma use OTC epinephrine MDIs (meeting transcript p. 51, Wyeth slide 19). Based on the 2005 National Health Interview Survey (NHIS), the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS) has estimated that 7.7 percent of the U.S. population currently has asthma (Ref. 1). Using an estimate of the U.S. population of 300 million,[12] we can estimate that approximately 23 million people in the United States currently have asthma.

Epinephrine is also an active ingredient in many other drug products. It is used in a self-injectable dosage form for treatment of severe allergic reactions. EPIPEN is an example of epinephrine in this dosage form. Epinephrine is also available OTC as a solution for use in an electrically powered nebulizer for the treatment of asthma. This rulemaking will not affect the availability of these non-MDI drug products.

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

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

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

As we said in the 2002 final rule, we intend the term "technical barriers" to refer to difficulties encountered in chemistry and manufacturing. To demonstrate that substantial technical barriers exist, it will have to be established that all available alternative technologies have been evaluated and why each alternative is unusable (2002 final rule at 48373). Wyeth did not present any significant data on technical barriers to formulating an inhaled epinephrine product without ODSs at the NDAC/PADAC meeting. At the NDAC/PADAC meeting, Wyeth said that they had been trying to reformulate or outsource their product for over a decade and mentioned unacceptable prototypes, but they mentioned that a significant difficulty in reformulation was avoiding designs that would infringe patents held by 3M Co. (3M) and GlaxoSmithKline (GSK) (meeting transcript, pp. 86-88). A patent is a legal barrier, not a technical barrier. Wyeth and Armstrong are free to engineer around the patent if they can. It should also be kept in mind that patent licenses and contract manufacturing by patent holders have been very frequently used during the current transition away from CFC MDIs. An example of this is 3M's manufacture of, and patent licensing for, albuterol HFA MDIs. 3M holds patents on HFA MDI technology and it also manufactures PROVENTIL HFA (albuterol) MDIs for sale by Schering Corporation (Schering). Ivax Corp. has licensed HFA MDI technology patents from 3M and manufactures PROAIR HFA (albuterol) MDIs. We have not been presented with any evidence that Wyeth could not obtain patent licenses or arrange for contract manufacturing by a patent holder.

At least nine different active moieties have been formulated as HFA MDIs for the treatment of asthma and COPD in the United States and abroad.[13] HFA MDIs have been

[13]The nine moieties formulated as HFA MDIs are albuterol, beclomethasone, budesonide, fenoterol, fluticasone, flunisolide, formoterol, ipratropium, and salmeterol. While a salmeterol DPI (SEREVENT)

formulated with both suspensions and solutions. Albuterol and levalbuterol are close chemical analogs of epinephrine. Given the chemical similarity between them and the success with reformulating albuterol (as albuterol sulfate in PROAIR HFA, PROVENTIL HFA, and VENTOLIN HFA) and levalbuterol (as levalbuterol tartrate in XOPENEX), there appears to be no technical reason why epinephrine cannot be successfully reformulated into an HFA MDI. Wyeth said at the NDAC/PADAC meeting that early attempts to formulate an epinephrine HFA MDI were characterized by higher pressures and quantities of alcohol that provided unacceptable sensations to users of the product, including an unpleasant taste of alcohol[14] (Wyeth briefing material, p. 1-7; meeting transcript, p.87). These do not seem to represent technical barriers; rather they seem to be the type of problems routinely encountered in the development of a new product that require prototypes to be reengineered. Indeed, Wyeth did not seem to truly believe that there were technical barriers to development of an epinephrine HFA MDI, predicting that they would have a product developed and clinically tested by 2011, and attributing their earlier difficulties to a lack of in-house expertise (Wyeth briefing material, p. 1-7). FDA has had experience with several firms reformulating products from ODS containing MDIs to non-ODS products. Based on our experience with those reformulation efforts, it seems highly unlikely that a non-ODS inhaled epinephrine will be developed and clinically tested until well after 2011. As we mentioned before, we are particularly interested in receiving comment on current efforts on developing non-ODS inhaled

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has been approved in the United States, salmeterol HFA MDIs have only been approved overseas. There are no approved fenoterol or formoterol products in the United States, but fenoterol HFA MDIs and formoterol HFA MDIs have been approved in several foreign countries.

[14]PRIMATENE MIST contains 35 percent alcohol and other MDIs also contain alcohol. Wyeth did not reveal the amount of alcohol in their prototype or explain why the amount of alcohol could not be reduced or the taste otherwise minimized.

epinephrine drug products that would be suitable for OTC sale.

Wyeth said that an epinephrine DPI was not a viable alternative to the epinephrine MDI, but without any elaboration (Wyeth briefing material, p. 1-7). The DPI has proven to be a very successful dosage form. At least nine different moieties have been formulated as DPIs for treatment of asthma and COPD in the United States or overseas.[15] Alkermes, Inc., developed a large dose epinephrine DPI for investigations into using an epinephrine DPI for treatment of anaphylaxis. While this product has not been approved by FDA and it is not intended for the treatment of asthma, it does show that epinephrine can be formulated into a DPI (Refs. 2 and 3).

Thus, all of the evidence before us strongly indicates that epinephrine can be formulated into a drug product that does not release ODSs. The facts presented by Wyeth at the NDAC/PADAC meeting did not indicate that there are technical barriers to the development of a non-ODS epinephrine product, despite the conclusions that Wyeth presented at the meeting.

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

Because we have reached a tentative conclusion that there are no substantial technical barriers to formulating epinephrine into a non-ODS product, we do not believe it is necessary at this time to reach a conclusion on the public health benefits of OTC epinephrine MDIs. However, this issue was discussed at length at the NDAC/PADAC

[15]The nine moieties formulated as DPIs are albuterol, beclomethasone, budesonide, fluticasone, formoterol, mometasone, salmeterol, terbutaline, and tiotropium. While albuterol HFA MDIs have been approved in the United States, albuterol DPIs are not currently marketed in the United States, but are approved overseas. A terbutaline CFC MDI and other terbutaline products have been approved in the United States, but terbutaline DPIs have only been approved overseas. There are no approved formoterol products in the United States, but formoterol DPIs have been approved in several foreign countries.

meeting and we are keenly interested in the potential public health benefits of having epinephrine MDIs available OTC. We will evaluate those public health benefits before issuing any final rule on the essential-use designation for epinephrine. Additionally, if, as a result of public comments received in response to this proposed rule, FDA reconsiders its tentative conclusion regarding substantial technical barriers to reformulation, we would need to fully evaluate and reach a conclusion on the public health benefits of OTC epinephrine at that time. Accordingly, we will discuss some of the questions on which we would be particularly interested in receiving comments that would be relevant in reaching a conclusion on the public health benefits of OTC epinephrine MDIs.

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

During the last several years, four prescription HFA MDIs with two different forms of albuterol have come onto the market:

- Albuterol sulfate MDI (PROAIR HFA);
- Albuterol sulfate MDI (PROVENTIL HFA);
- Albuterol sulfate MDI (VENTOLIN HFA); and
- Levalbuterol tartrate MDI (XOPENEX HFA).

These products use HFA as a replacement for ODSs, which does not affect stratospheric ozone. Albuterol and epinephrine are both adrenergic bronchodilators. Albuterol MDIs are therapeutic alternatives to OTC epinephrine MDIs and are, by far, the most widely prescribed short-acting bronchodilators. To determine whether epinephrine provides an otherwise unavailable important public health benefit, we should compare OTC epinephrine MDIs to albuterol HFA MDIs. The labeled indication for the

OTC epinephrine MDIs is "for temporary relief of occasional symptoms of mild asthma." The comparable labeled indication for the albuterol HFA MDIs is "for treatment or prevention of bronchospasm with reversible obstructive airway disease." OTC epinephrine MDIs and three of the albuterol HFA MDIs are indicated for adults and children 4 years of age and older.[16] The labeled indications for the albuterol HFA MDIs cover all patients described in the labeled indication for OTC epinephrine MDIs.

Clinical data presented by a representative of Wyeth at the NDAC/PADAC meeting indicated that OTC epinephrine MDIs may be slightly quicker to onset of action than albuterol MDIs, but they have a significantly shorter duration of action (Wyeth briefing statement at p. 1-9). The slightly quicker onset of action may explain why some people with asthma describe OTC epinephrine MDI as working better than prescription drugs. The slightly quicker onset of action is a pharmacodynamic assessment, but there are no clinical data to support a conclusion that this perceived quicker relief provided by epinephrine leads to better outcomes. Therefore, we do not believe that this represents a "otherwise unavailable important public health benefit."

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Wyeth presented another study of the treatment of nocturnal asthma that concluded that OTC epinephrine MDIs can "achieve the same benefit as albuterol" MDIs (Ref. 4, p. 533).[17] However, as pointed out by NDAC/PADAC members, the frequency of doses of epinephrine used in this study were several times the amount approved in

[16]PROAIR HFA is indicated for adults and children 12 years of age and older.

[17]The author of the study report did not appear to view the study as supporting the OTC use of epinephrine MDIs, stating that the results of the study do not imply that it is safe for people with asthma to self-medicate without physician intervention and that results of the study indicate that nonprescription epinephrine presents the same risk of delaying patients from seeking medical care as other beta-agonists. The report concluded with a statement that a larger study is required before epinephrine can be recommended as rescue therapy when a prescription $beta_2$-agonist MDI is not accessible (Ref. 3).

labeling (this was also true, but to a smaller degree, for albuterol in this study).[18] Further, this was a limited study with only eight subjects completing the evaluations. These elements made the utility of this study for purposes of this rulemaking very questionable, and even if these questions were ignored, the study shows, at best, that epinephrine is roughly as effective as, but not more effective than, albuterol.

In the United States, the generally recognized standard of care for asthma is set forth in the National Heart, Lung, and Blood Institute's Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma (EPR-2) (Ref. 5).[19] The National Heart, Lung, and Blood Institute is one of the National Institutes of Health. In the 2002 update to EPR-2 (Ref. 6), we find the latest updates to the standard.

In several points in Wyeth's written, oral, and visual presentation for the NDAC/PADAC meeting, it was stated that use of epinephrine was consistent with the National Heart, Lung and Blood Institute's asthma treatment guidelines (Ref. 5) (frequently called the second Expert Panel Report or EPR-2), issued as part of the National Asthma Education and Prevention Program.[20] The EPR-2, as updated, is widely seen as representing the generally recognized standard of care for asthma in the United States.[21] Wyeth stated in its written materials that epinephrine is not mentioned specifically in the EPR-2 (Wyeth briefing material, p. 1-8; meeting transcript, pp. 50-51;

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[18]The author of the study report recognized that the large number of actuations might be impractical (Ref. 43).

[19] The Guidelines represent best practices and are recognized as the clinical standard of care for treatment of asthma. See, e.g., http://www.asthmanow.net/care.html; http://www.colorado.gov/bestpractices/index.html; http://www.doh.wa.gov/CFH/asthma/publications/plan/health-care.pdf.

[20]EPR-2 was updated in 2002 (Ref. 6) (EPR—Update 2002). References to outside publications or any other statements of fact or opinion in this document concerning a drug product are not intended to be equivalent to statements in labeling approved under section 505 of the act (21 U.S.C. 355) and part 314 of FDA regulations (21 CFR part 314).

[21]The EPR-2 is very similar to other published standards of care (See the Australian Asthma Management Handbook: 2002 (Ref. 7) and the "Canadian Asthma Consensus Report, 1999" (Ref. 8).

Wyeth slide 18). FDA disagrees with these statements. The 2002 update to the EPR-2 states that "[n]onselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses" (Ref. 6, p. 120). While recognizing the possibility that the concerns expressed in the EPR-2 about cardiovascular risk may be overstated (see Refs. 4 and 9), we do not need to reach a conclusion on the relative cardiovascular risk of the use of epinephrine compared to the use of albuterol. FDA is unaware of any evidence comparing epinephrine and albuterol at recommended doses indicating that the cardiovascular safety of epinephrine is better than that of albuterol.

A voting consultant with NDAC characterized the OTC epinephrine MDI as an "inferior medicine" (meeting transcript, p. 181). She admitted there was an absence of good data on the safety and efficacy of OTC epinephrine MDIs. Her opinions were shared by many members of the committees. NDAC/PADAC members who recommended that the essential use for OTC epinephrine MDIs be retained did not state that epinephrine was safer or more effective than albuterol. The evidence before us indicates that epinephrine is not safer or more effective than albuterol. The EPR-2 recommends against epinephrine's use. The consensus opinion at the NDAC/PADAC meeting was that OTC epinephrine MDIs presented no significant therapeutic advantage over albuterol MDIs. This leads us to tentatively conclude that OTC epinephrine MDIs do not provide a clinical benefit that is otherwise unavailable. If we intended to draw a conclusion about the public health benefits of OTC epinephrine MDIs, and if OTC epinephrine MDIs were prescription drugs, as albuterol HFA MDIs are, our analysis would be nearly complete. However, the epinephrine MDIs, PRIMATENE MIST and

the Armstrong products, are the only MDIs for treatment of asthma that are marketed OTC. We, therefore, have to examine more questions on the possible public health benefits of the continued OTC marketing of epinephrine CFC MDIs.

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

Our discussion on the public health benefit of OTC marketing of epinephrine is largely informed by the data presented and the opinions expressed at the NDAC/PADAC meeting.

a. Is patient convenience an important public health benefit? Wyeth asserted at the NDAC/PADAC meeting that the convenience of patients having an OTC MDI for asthma provides an "important public health benefit" (meeting transcript, p. 66). Having this OTC product available would allow patients who run out of their prescribed medication and cannot get a refill authorization from their physician to go to the local store and purchase OTC epinephrine MDI. Wyeth presented data from a survey they had conducted indicating that one-third of OTC epinephrine MDI users use it as their sole asthma medication, while two-thirds use it in addition to prescription drugs. The survey indicated that 55 percent of people with asthma who solely use OTC epinephrine MDIs for their asthma said that the OTC product is "easier and quicker to obtain." Fifty-eight percent of asthma patients who use both prescription drugs and OTC epinephrine MDIs say they purchase the OTC MDI when they either "run out of my prescription medication" or "have an asthma attack and I don't have my prescription with me" (Wyeth slide 36).

Maintaining current valid prescriptions and supplies of prescribed drugs is a

regular and sometimes onerous, but necessary, task for many patients with chronic diseases. It would certainly be more convenient for all of these patients if some sort of therapeutic alternative were available OTC. However, there are no OTC remedies for most serious diseases. Of note, patients with anaphylaxis to bee stings or peanuts can face sudden, life-threatening attacks if exposed to their relevant triggers. Yet epinephrine autoinjectors, such as EPIPEN, are not OTC products because of considerations that include the proper evaluation and treatment of such patients. No evidence has been presented to us, in the course of this rulemaking, to indicate how asthma differs from other serious diseases in a way that warrants having an OTC treatment available.

These facts would support a conclusion that any added convenience of OTC availability of epinephrine for patients who have been prescribed drugs for the treatment of asthma, such as albuterol MDIs, does not provide an "important public health benefit."

b. Do OTC epinephrine MDIs provide an important health benefit for people who have poor access to adequate health care? Wyeth and several members of NDAC and PADAC have stated that a significant number of people with asthma do not have adequate access to health care, and a significant number of these people with asthma use OTC epinephrine MDIs. To examine the public health benefit of OTC marketing of epinephrine MDIs we must examine (1) The number of people with asthma who use epinephrine because of inadequate access to health care providers able to diagnose asthma and prescribe treatments other than epinephrine, and (2) the extent that OTC epinephrine benefits these people. We are particularly interested in the public health benefits that may be provided to this population by having epinephrine MDIs available OTC. Any final conclusion we reach on the essential-use designation of epinephrine

could be affected by data on the public-health benefit contained in comments submitted in response to this proposed rule.

Wyeth presented information at the NDAC/PADAC meeting from their 2005 survey indicating that 22 percent of people with asthma did not have health insurance (Wyeth slide 31). Statistics from NCHS (Ref. 10) indicate that slightly less than 14.1 percent of the general population does not have health insurance. While the difference between 14.1 percent and 22 percent is not significant for purposes of this document,[22] it may be true that the percentage of people with asthma who are uninsured is higher than that of the general population. Wyeth also presented data indicating that 27 percent of people with asthma do not have health insurance that provides prescription drug benefits (Wyeth slide 31). However, lack of insurance does not necessarily equate to poverty and financial barriers to adequate health care. Approximately 18 percent of uninsured Americans have household incomes of $75,000 or more, and another 17 percent have household incomes of $50,000 to $74,999 (Ref. 11).

Other barriers to health care exist, such as lack of sick leave, transportation, and child care. However, we do not have any data that would be useful in determining how these barriers affect people with asthma and their use of OTC epinephrine MDIs.

There is very little data about how barriers to health care affect use of OTC epinephrine MDIs. According to data provided by Wyeth, roughly two-thirds of OTC epinephrine MDI users use the MDIs in addition to prescription drugs, while one-third solely use OTC epinephrine MDIs (Wyeth slide 32). As discussed in section V.B.2.b of

[22]The reason we say that the difference is not significant for purposes of this document is that so many of the numbers discussed represent such broad estimates that the difference between 14 percent and 22 percent would not affect any conclusion. We are acutely aware that for the individuals and families involved, absence of health insurance is very significant.

this document, a majority of the two-thirds of OTC epinephrine MDI users who also use prescription drugs do so for reasons of convenience. However, because the two-thirds of OTC epinephrine MDI users who also use prescription drugs apparently have adequate access to health care, we will focus, for this part of the document, on the one-third of OTC epinephrine MDI users who solely use OTC epinephrine MDIs. We have very little data on why patients use OTC epinephrine MDIs instead of prescribed drugs. At the NDAC/PADAC meeting Wyeth presented data from their 2005 Internet survey of people with asthma (Wyeth slide 35). The data are summarized in table 1 as follows:

Table 1.--Most Frequent Reasons Cited by Sole OTC Epinephrine MDI Users

"Easier and quicker to obtain"	55 percent
"More reasonably priced"	41 percent
"I don't have health insurance"	25 percent
"I don't want to go to a doctor"	25 percent
"I don't have a doctor"	21 percent
"OTC drugs work better for me"	11 percent

The basis for the "more reasonably priced" response in the survey is unclear. While the perception of a percentage of the survey participants may have been that OTC epinephrine was less costly, an accurate determination of the relative price of the OTC product compared to the prescription substitutes would require a complex analysis which could not be embodied in an informal Internet opinion survey. For example, it is not clear how respondents calculated the retail price of the prescription drug products that they compared to OTC epinephrine, if they were comparing comparable drug products, or

the degree to which they factored health insurance co-payments or the availability of patient assistance programs into their price comparison. It is also unclear if the respondents viewed the cost of a visit to a physician to obtain a prescription as a part of the price of a prescription drug. Because it is not clear what this response actually means, it contributes little to our analysis of the possible public health benefits of epinephrine.

As discussed at length at the NDAC/PADAC meeting, the response in the survey that "OTC drugs work better for my asthma" is not supported by adequate and well-controlled studies.

The responses that may best inform an attempt to reach a low-end estimate of the percentage of people who solely use OTC epinephrine MDIs who do so because of barriers to health care are "I don't have health insurance" (25 percent), "I don't want to go to a doctor" (25 percent), and "I don't have a doctor" (21 percent). Those stating absence of health insurance are describing a potential barrier to health care. The other two statements are more ambiguous. "I don't want to go to a doctor" may be an expression of a general aversion to going to doctors, it may be a manifestation of a desire not to confront a potentially serious illness, or it also may reflect that an asthmatic may not wish to go to a doctor because of lack of insurance or other barriers to health care. "I don't have a doctor," may be similar to "I don't want to go to a doctor," or it may reflect a person who has not yet chosen a doctor, because of a recent arrival in a locality or because the person has stopped seeing a previous doctor.

The survey participants were permitted to select more than one reason for solely using an OTC epinephrine MDI. While we know that participants gave more than one answer (the sum of the answers is 178 percent), we do not know how the responses

overlapped with each other. We will assume, for now, that the 25 percent responding "I don't have health insurance" represents users of OTC epinephrine who do so because of barriers to health care. We realize that this may underrepresent those people with asthma whose responses of "I don't want to go to a doctor," and "I don't have a doctor" also reflected a barrier to health care. However, any underestimation may be counterbalanced by other factors, such as:

- Approximately 18 percent of uninsured Americans have household incomes of $75,000 or more, and another 17 percent have household incomes of $50,000 to $74,999 (Ref. 11). While uninsured, these people would not necessarily face barriers to health care.
- According to Wyeth's 2005 Internet survey, 28 percent of people with asthma who solely use OTC epinephrine MDIs have visited a doctor in the previous year for treatment of asthma; these patients presumably have access to health care.

We do not know how these two points relate to the numbers from Wyeth's 2005 Internet survey giving the reasons that people with asthma purchase OTC epinephrine MDIs. As was frequently noted at the NDAC/PADAC meeting, the debate over the essential-use status of epinephrine is hobbled by a paucity of data. The fact that this is an Internet survey, and that we know little about how the survey was conducted, raises questions about its reliability. However, in the absence of better data, we estimate that 25 percent of people with asthma who solely use OTC epinephrine MDIs for treatment of asthma do so because of barriers to health care. Since two-thirds of people who use OTC epinephrine MDIs also use prescription drugs to treat their asthma, somewhat less than 9

percent of all people with asthma using OTC epinephrine MDIs do so because of barriers to health care. These figures appear to be the best low-end estimate we can derive from the limited data we have before us. Referring to their 2005 Internet survey, Wyeth stated that 60 percent of people with asthma solely using OTC epinephrine MDIs replied that they had a "prescription medication coverage plan" (Wyeth slide 33). This figure is lower than the 66 percent who replied that they had insurance covering physicians visits. This means that approximately 40 percent of OTC epinephrine MDI users who solely use the product did not have prescription drug coverage. This seems a reasonable high-end estimate of the percentage of people with asthma solely using OTC epinephrine MDIs who do so because of barriers to health care. This estimate is over-inclusive because it includes people with asthma whose income would mean that absence of insurance does not present a barrier to health care and patients with asthma that have access to free or low-priced drugs through doctor's samples or free and low-priced drug programs. The fact that lack of insurance coverage for prescription drugs does not perfectly reflect barriers to health care is shown by the fact, according to Wyeth's 2005 survey, that 19 percent of asthma patients who solely use prescription drugs do not have insurance coverage for prescription drugs. While it is over-inclusive for some groups, the higher figure may do a better job of capturing people who face other poorly quantified barriers to health care, such as lack of sick leave, transportation, or child care.

We have arrived at an estimate that between 25 percent and 40 percent of people with asthma who solely use OTC epinephrine MDIs, and therefore between 9 percent and 14 percent of all people with asthma that use OTC epinephrine MDIs, do so because of barriers to health care. We have also estimated that 1.7 to 2.3 million people with asthma

use OTC epinephrine MDIs. This estimate is based on data provided by Wyeth at the NDAC/PADAC meeting, although Wyeth reached a different conclusion based on the same numbers.[23] Applying our estimate that between 9 percent and 14 percent of all people with asthma who use OTC epinephrine MDIs do so because of barriers to health care to our estimate that 1.7 to 2.3 million people with asthma use OTC epinephrine MDIs, we arrive at an estimate that between 150,000 and 320,000 people with asthma who use OTC epinephrine MDIs do so because of barriers to health care. At the NDAC/PADAC meeting, a representative for several Hispanic-American health policy organizations presented information about the high incidence of asthma among Hispanic-Americans and African-Americans (meeting transcript, pp. 162 to 169). The representative opposed removing epinephrine's essential-use designation, stating that that it would have a serious adverse impact on people with asthma who face barriers to health care, and that this impact would be disproportionately felt by Hispanic-Americans.

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According to the 2002 NHIS (Ref. 12), 7.2 percent of Non-Hispanic Whites in the United States had asthma, while the prevalence of asthma in Non-Hispanic Blacks was 9.5 percent and the corresponding figure for Non-Hispanic American Indians was 9.9 percent. The incidence of asthma among all Hispanics in the United States (4.9 percent) was lower than the incidence for the general population (7.2 percent), but the rate for

[23] At the NDAC/PADAC meeting Wyeth presented estimates that 15 to 20 percent of adults with asthma use OTC epinephrine (Wyeth slide 32). Applying these percentages to the number of adults who have asthma, they estimated that 2 to 3 million people use OTC epinephrine MDIs at any given time. Wyeth appears to have made a mistake. If we look at the 1993 ACNielsen study (Wyeth slide 29) where the study population was adults, it appears that Wyeth compared the number of respondents who reported using an OTC asthma drug (557) to the number of respondents who reported having an asthma incident in the previous 12 months (2,713). If we divide 557 by 2,713, we get 0.205 or 20 percent. The number of adults who have asthma is substantially higher than the number who have had an asthma incident in the previous 12 months; for 2004 the numbers are 14.4 million and 7.7 million respectively (ref. 35). Applying 15 to 20 percent to the number of adults with asthma would result in a significant inflation of the number of OTC epinephrine MDI users. Applying 15 to 20 percent to the number of adults who have had an asthma incident in the previous 12 months gives us an estimate of 1.7 to 2.3 million people using OTC epinephrine MDIs. We believe that this estimate is more accurate than the 2 to 3 million estimate.

Puerto Ricans was markedly higher at 13.1 percent.

The National Health Care Disparities Report (Ref. 13) (2005 NHCDR) (which was mentioned by the speaker), indicates that Hispanic-Americans have significantly worse access to health care in terms of numbers of uninsured persons (Ref. 13, p. 92) having a usual source of care (a facility where one regularly receives care) (Ref. 13, p. 94), and having a usual primary care provider (a doctor or nurse from whom one regularly receives care) (Ref. 13, p. 95). Other portions of the 2005 NHCDR provide information about asthma counseling in community health centers (Ref. 13, p. 135) and hospital admissions for pediatric asthma (Ref. 13, p. 150). None of the data in the 2005 NHDCR refer directly to the use of OTC epinephrine MDIs, so drawing specific conclusions from the 2005 NHCDR is difficult and subjective.

Results from the National Cooperative Inner City Asthma Study (NCICAS) were referred to at the NDAC/PADAC meeting. NCICAS was sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). NCICAS studied a treatment strategy for children with asthma living in inner-city census tracts where at least 20 percent of the population was below federal poverty guidelines. The study was conducted in eight study units located in seven cities across the United States. Wyeth presented information from a report from NCICAS, showing that 53 percent of the participants in the study reported difficulties in obtaining short term care for their children's asthma (Ref. 14). Ninety-three percent of the families studied in NCICAS were insured, largely by Medicaid, and while 50 percent of the families studied had to pay for health care (presumably a co-payment for most of the families), only 8 percent reported "care costs too much" as a barrier to health care. The intervention studied in the

NCICAS was described as effective by one of the lead investigators (Ref. 15). Failure to refill prescriptions for asthma drugs was mentioned by Wyeth at the NDAC/PADAC meeting (meeting transcript, p. 113). Another report from NCICAS shows that 16 percent of caregivers reported not having a prescription filled for the child with asthma for whom they were caring (Ref. 16). This number compares favorably with compliance rates found in the general population.[24] People do not always have prescriptions filled or take their medicine, regardless of income or health insurance.

Dr. Carolyn Kercsmar, who participated in the NCICAS and is a member of PADAC, responded to Wyeth's description of the data from the NCICAS by saying,

"[the children with asthma and the caregiver's] access were problems and didn't prevent them, it just hindered their care, and it was not just for acute care. It was for problems in accessing chronic care. Also, in that study, the vast majority of the patients had medication prescribed including albuterol as part of that study. . . ." (meeting transcript, p. 141).

The NCICAS data do not show that the availability of OTC epinephrine is needed for adequate treatment of asthma in poor inner-city areas. While recognizing that the patient population studied was largely insured, we believe that comparable health care access options for low-income, non-insured patients are widely available. Programs that offer free or low-cost drugs, such as Schering's "SP Cares program" (see www.schering-plough.com/schering_plough/corp/sp_cares.jsp), and organizations that provide more comprehensive health care free or at low-cost, such as Communicare in South Carolina or the Puget Sound Neighborhood Health Centers in Washington, should be able to help

[24]See Refs. 17 and 18. The various studies used different methods of measuring non-compliance, so direct numeric comparisons are not possible.

lower economic barriers to access for people with asthma who use OTC epinephrine MDIs. Although we do not believe that all of the people currently using OTC epinephrine MDIs due to economic barriers to health care can or will avail themselves of these programs, we do believe that these programs are widely available, and that they can provide adequate alternatives to OTC epinephrine MDIs for many people with asthma. This should minimize any adverse impacts that may result from the absence of OTC epinephrine MDIs.

In looking at the issue of OTC epinephrine MDIs as an alternative for people with asthma who face barriers to health care, it should be kept in mind that the retail price of OTC epinephrine MDIs is also a barrier to health care. In comparing the price of OTC epinephrine to that of its alternatives, we must keep in mind that OTC epinephrine MDIs, which cost approximately $13 per inhaler (meeting transcript, p. 127), are not available through any low-cost drug plans. Prescription drugs obtained through these programs can be substantially less expensive than OTC epinephrine MDIs. To give one example, an eligible person obtaining VENTOLIN HFA (albuterol MDI) through GSK's "Bridges to Access" program would make a $10 co-payment for a 60-day supply of the drug; after 60 days no further co-payment is required (see http://bridgestoaccess.gsk.com/index.html). OTC epinephrine MDIs are more expensive than prescription drugs for people who can and do avail themselves of low-cost drug programs such as "SP Cares" and "Bridges to Access."

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A public speaker representing an asthma education and advocacy organization before the NDAC/PADAC meeting said that the longer duration of effect of albuterol and levalbuterol (and other newer prescription drugs that do not release ODSs) means that,

while these drug are more expensive per MDI and per dose, they may be cheaper than OTC epinephrine MDIs when the price is calculated for each hour of relief (meeting transcript, pp. 159-160). While a drug's duration of action can affect the cost to a patient (or other payor) for therapy with the drug, we do not have the comparative clinical data to confirm the assertion made by the speaker.

We believe that a small population of people with asthma who face barriers to health care may derive some benefit from having epinephrine MDIs available OTC. We also believe that utilization of programs providing low-cost or free prescription drugs may significantly reduce, but not eliminate, the number of people with asthma facing barriers to health care who depend on OTC epinephrine MDIs. We are keenly interested in, and request comments on, the public the public health effect and costs that may result from the removal of OTC epinephrine MDIs from the market and how these programs may reduce any adverse impact on the public health. In assessing the public health benefits of OTC epinephrine MDIs, the benefits of having the drug available OTC must be balanced against the potential risks, if any.

c. Do risks of self-treatment of asthma outweigh the public health benefits that OTC epinephrine MDIs may provide? Much of the discussion at the NDAC/PADAC meeting focused on the issue of whether the risks of self-treatment of asthma outweigh the public health benefits that OTC epinephrine MDIs may provide. This issue could affect any decision we make on the essential-use status of OTC epinephrine MDIs. We have tentatively determined on other grounds that epinephrine is not an essential use, so we do not currently believe we need to reach a determination on the risks and benefits of having epinephrine MDIs available OTC. We currently believe that the issue of the

suitability of asthma as an indication for OTC drugs may be better discussed in another forum, such as a proposed revision to the OTC monograph covering drugs for asthma (21 CFR, part 341). It should be kept in mind that our determination is merely a tentative decision, and we do not wish to preclude comment on this issue, to the degree it applies to OTC epinephrine MDIs as an essential use of ODSs. Accordingly, we will discuss some of the points raised at the NDAC/PADAC meeting and other information we feel may be relevant.

i. Misdiagnosis of asthma. OTC epinephrine MDIs are only indicated for mild intermittent asthma. The approved labeling for OTC epinephrine MDIs states that the drug should only be used after a doctor has diagnosed asthma. This is because asthma can be a difficult disease to diagnose, even for physicians (Ref. 19). COPD, vocal chord dysfunction, heart disease, and many other illnesses can be misdiagnosed as asthma (see Ref. 5, p. 22).

The results of a study presented by Wyeth at the NDAC/PADAC meeting indicated that 92 percent of those surveyed who solely use OTC epinephrine MDI stated that they had been diagnosed with asthma by a doctor (Wyeth slide 23, citing Ref. 20). We do not have data on how recently the diagnoses were made or on the current accuracy of the diagnoses. The study did state that only 47 percent of those who solely use OTC epinephrine MDIs currently had a primary caregiver for management of asthma (Ref. 20, p. 989), which would seem to indicate that at least some of the diagnoses were not particularly recent. The Internet survey presented by Wyeth at the NDAC/PADAC meeting indicates that 8 percent of purchasers of OTC epinephrine MDIs have not been diagnosed with asthma by a physician, and 28 percent of those who solely use OTC

epinephrine MDI reported that they visited a doctor's office in the past year for treatment of their asthma (Wyeth slide 33). This would imply that 72 percent of people who solely use OTC epinephrine MDI had not seen a doctor in the past year for diagnosis and treatment of their asthma.

Asthma is a variable disease that can either lessen or worsen in severity over time. A person previously diagnosed with asthma may be asymptomatic for long periods of time. A diagnosis of asthma and, more important, an evaluation of its severity made at some point in the past may no longer be accurate. Currently, follow-up visits are recommended at 1- to 6-month intervals after an initial diagnosis of asthma (EPR-2, Ref. 5, p. 87). A previous diagnosis of asthma does not necessarily mean that an individual's current asthma-like symptoms are caused by asthma, or that the individual's asthma is of the same severity as originally diagnosed. The likelihood of the previous diagnosis accurately reflecting the patient's current status would seemingly have to decrease the older the diagnosis and evaluation is. A study referred to by Wyeth at the NDAC/PADAC meeting said that "self assessment of asthma severity may not be 'on target,' especially among individuals who self-medicate their illness with nonprescription bronchodilators" (Ref. 20, p. 992). It should be kept in mind that this was said about a group in which 92 percent had reported having been diagnosed by a physician as having asthma. This study was relatively small and, while potentially informative, it cannot be viewed as conclusive at this time.

There are some additional data available on the potential misdiagnosis of the severity of asthma by purchasers of OTC epinephrine MDIs. Wyeth presented data at the NDAC/PADAC meeting that 76 percent of OTC epinephrine MDI purchasers bought one

or two OTC epinephrine MDIs a year. This indicates that 24 percent of purchasers bought three or more OTC epinephrine MDIs each year. A Wyeth web page (http://www.primatene.com/faq/answers.asp#puffs) says that each 15 milliliters (mL) vial should deliver 270 puffs and the 22.5 mL of PRIMATENE MIST vial should deliver 405 puffs. The 15 ml vial is the most popular size of PRIMATENE MIST (meeting transcript, p. 127). The 15 mL size is also the size manufactured for sale as house brands by Armstrong. If we look at three 15 mL MDIs used over a year-long period, we see that they would provide 16 puffs a week, a level of use that would indicate asthma incidents that are so frequent or severe that it no longer should be characterized mild intermittent asthma. We realize that some of the 24 percent of people who solely use OTC epinephrine MDIs and purchase three or more MDIs in a year may not be using all of the contents of the OTC epinephrine MDIs they purchase. They may be replacing lost MDIs or purchasing extra MDIs to keep at work or in a gym bag. It also should be noted that the use of two 22.5 mL vials a year also provides 16 puffs a week, again indicating a level of use that would not be associated with mild intermittent asthma.

There is other evidence that purchasers of OTC bronchodilators were unable to correctly diagnose the severity of their asthma. A study was conducted in Australia of purchasers of albuterol (or salbutamol, as it is known in Australia and most of the rest of the world), a bronchodilator that was available both with and without a prescription in the State of New South Wales (Ref. 21). In that study, 95 percent of the surveyed purchasers who usually or always purchased albuterol without a prescription were undertreated for their asthma according to a relevant standard of care. We have not formed an opinion on the applicability of the study to the questions involved in this rulemaking. We realize

that the study involved a different drug (albuterol), in a different country (Australia), and that the study is over 13 years old. However, we also recognize that the study may represent some of the better data currently available on the question of self-diagnosis of asthma by the purchasers of OTC bronchodilators.

The evidence seems to suggest that many OTC epinephrine MDI purchasers are buying the drug based either on self-diagnosis or on an out-of-date physician's diagnosis.

The issue of the accuracy of the diagnosis of asthma upon which a purchase of an OTC epinephrine MDI is made is very important in reaching a determination on the public health benefits of having the drug available OTC. While some evidence suggests that many purchasers of OTC epinephrine MDIs are doing so based on an inaccurate diagnosis of the severity of their asthma, we have not reached a conclusion on that evidence's weight and significance.

ii. Undertreatment of asthma. Undertreatment of asthma can cause more frequent symptoms and attacks, missed work and school, activity limitations, a decline in lung health and function and, possibly, death (Ref. 9).

As mentioned earlier, in the United States, the generally recognized standard of care for asthma is set forth in the EPR-2 (Ref. 5). In the 2002 update to EPR-2 (Ref. 6) we find the latest updates to the standard. Asthma is divided into four classes of severity, which correspond to treatment "steps." More severe classes of asthma are defined by greater frequency of symptoms during the day and night, lower peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV_1) (both are measurements of how well a patient can exhale using the greatest effort), and higher variability in PEF measurements over the course of a day.

As the severity of a patient's asthma increases, treatment becomes more aggressive: for mild persistent asthma, daily use of an inhaled corticosteroid (available only by prescription) is recommended; if the patient has moderate persistent asthma, higher doses of inhaled corticosteroids and/or inhaled corticosteroids with a long-acting beta-agonist are recommended; and for severe persistent asthma, still higher doses of inhaled corticosteroids are recommended in conjunction with a long-acting bronchodilator (available only by prescription).

If a patient's asthma becomes more severe, treatment should become more aggressive, and if the asthma is well controlled, a physician should generally try to reduce the quantity of drugs being taken in order to provide good control with the minimum quantity of drugs. This approach is characterized as a "stepwise approach for managing asthma" (EPR 2002 Update, Ref. 6, Appendix A-1).

No daily medication is recommended for mild intermittent asthma, but the EPR-2 recommends the use of a short-acting inhaled $beta_2$-agonist bronchodilator, as needed to treat the occasional bronchospasm. Albuterol is a short-acting inhaled $beta_2$-agonist bronchodilator and albuterol MDIs are the most widely prescribed "rescue inhalers" in the United States. The EPR-2 does not recommend nonselective short-acting beta-agonist bronchodilators as rescue inhalers, but rather they recommend use of an inhaled short-acting $beta_2$ selective agonist. Beta-receptors are adrenergic sites in the autonomic nervous system in which physiological responses occur when agents, in this case beta-agonists, are bound to the receptor. Activation of beta-receptors causes various reactions, including relaxation of the bronchial muscles and an increase in the rate and force of cardiac contraction. The beta-receptors are subdivided into $beta_1$, located primarily in the

heart and intestinal smooth muscle, and $beta_2$, more localized to bronchial, vascular, and uterine smooth muscles. Epinephrine is a non-selective beta-agonist which affects both the $beta_1$ and $beta_2$-receptors so that it affects both heart and bronchial smooth muscles (as well as the intestinal, vascular, and uterine smooth muscles). $Beta_2$ selective agonists, such as albuterol, have less of an effect on the heart than $beta_1$ and non-selective beta-agonists have. Epinephrine's lack of selectivity has caused concerns about its effect on the heart, but the limited data we have before us do not indicate that use of OTC epinephrine MDIs is associated with a greater risk of significant adverse cardiovascular events.

The question of undertreatment of asthma for purchasers of OTC epinephrine MDIs is not confined to people with asthma who solely or primarily use OTC epinephrine MDIs. The level of usage of short-acting $beta_2$-agonists is a factor that should be monitored by physicians treating asthma patients (EPR-2, Ref. 6, p. 35). Increased usage may often indicate the need for treatment being stepped up, while decreased usage may indicate that treatment could be stepped down. The availability of OTC epinephrine MDIs allows patients to purchase a short-acting beta-agonist without a prescription. It seems possible that this may deny important information to the health care provider as to the accurate assessment of a patient's use of rescue inhalers. We are unaware of any data that directly address this issue.

iii. Patient education. Patient education is generally regarded as a key component to successful asthma treatment. The EPR-2 says, "[E]ducation for an active partnership with patients remains the cornerstone of asthma management and should be carried out by health care providers delivering asthma care. Education should start at the time of

asthma diagnosis and be integrated into every step of clinical asthma care" (Ref. 5, p. 5).

Elements of patient education can include providing information about how asthma affects the lungs, the difference between short-acting rescue medications and control medications, the importance of using control medication as prescribed, important environmental control measures that may need to be considered, such as removing asthma triggers from the patient's home, the tracking of severity of the patient's asthma, and proper use of an MDI.

The proper use of an MDI is an important factor in proper treatment of asthma. This issue was mentioned but not discussed at the NDAC/PADAC meeting (meeting transcript, p. 139). Improper use of an MDI can result in a reduction of the dose delivery by 50 percent or more (Ref. 22). A study in children and adolescents showed less than 25 percent used their MDIs correctly (Ref. 23), and a study in adults showed similar results (Ref. 24). Further, the last study showed that inadequate English language literacy is associated with poor use of MDIs.

The importance of patient education may be a significant issue in any discussion of the risks and benefits of self-treatment of asthma.

iv. Effects of undertreatment. While the cost of treatment for poor and medically underserved populations was frequently mentioned at the NDAC/PADAC meeting, much less was said about the effects and costs of undertreatment. A recent study of urban pediatric patients, who were predominantly from poor and minority households, showed that an increased use of corticosteroids in pediatric patients (in accordance with the guidelines in EPR-2) resulted in fewer hospitalizations, emergency department visits, and outpatient visits (Ref. 25).

The importance of prompt appropriate treatment of asthma is reinforced by studies suggesting that delaying treatment with inhaled corticosteroids decreases the effectiveness of the inhaled corticosteroids once treatment begins (Refs. 26 and 27).

Studies also indicate that regular use of beta-agonist bronchodilators may reduce the person with asthma's response to subsequent beta-agonist administration (Ref. 28). This tolerance could mean that patients who regularly use OTC epinephrine MDIs may be placed in a position where their occasional use of a $beta_2$-agonist, as part of a course of treatment using inhaled corticosteroids as a control medication, may not be as effective for these patients as might otherwise be possible. The effects of undertreatment of asthma may be a key issue in any discussion of the risks and benefits of self-treatment of asthma.

One public speaker did say that "a delay in the early introduction of prescription anti-inflammatory asthma therapy could lead to the development of irreversible lung damage" (meeting transcript, p. 171). We do not find his statement to be persuasive. The use of inhaled steroids was not shown to prevent damage to the lungs in several studies (Refs. 29, 30, and 31), and the evidence supporting the speaker's statement about "irreversible lung damage" is limited and not conclusive (Ref. 32). Any disagreement on the issue of permanent lung damage should not be allowed to obscure the fact that proper use of inhaled steroids significantly reduces asthma morbidity.

3. Conclusions on the Public Health Benefits of OTC Epinephrine MDIs

We believe that epinephrine does not have any clinical advantages over albuterol HFA MDIs and that patient convenience for patients that have not kept their asthma drugs prescriptions current or do not have the prescribed drug product with them is not an

Deleted: Because we have reached a tentative conclusion that there are no technical barriers to formulating epinephrine into a non-ODS product, we do not believe it is necessary to reach, at this time, a conclusion on the public health benefits of continuing to have epinephrine available OTC. If, as a result of public comments received in response to this proposed rule, FDA reconsiders its tentative conclusion regarding substantial technical barriers to reformulation, we would need to fully evaluate the public health benefits of OTC epinephrine at that time. While w

important public health benefit. We have not reached a conclusion on the risks and benefits of continuing to have epinephrine available OTC for people with asthma who face barriers to obtaining appropriate health care, and therefore we cannot reach a conclusion on whether the use of OTC epinephrine MDIs provides an important health benefit. We specifically request comments on the expected costs and public health effects to individuals with asthma if OTC epinephrine MDIs were removed from the market without a similar product being available OTC. While our tentative conclusion that epinephrine is no longer an essential use is based primarily on the conclusion we have drawn regarding technical barriers to producing the epinephrine in a non-ODS formulation, we will evaluate the public-health effects of removal of OTC epinephrine from the market, and any final conclusions we reach on the essential-use designation of epinephrine may be significantly influenced by data received in comments on the public-health issues raised by this proposal.

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Deleted: As we noted in part V.B of this notice, we currently believe that the issue of the health benefits of asthma being an indication for OTC drugs may be better discussed in another forum, such as a proposed revision to the OTC monograph covering drugs for asthma (21 CFR part 341).

C. Does Use of OTC Epinephrine MDIs Release Cumulatively Significant Amounts of ODSs into the Atmosphere or is the Release Warranted in View Of The Otherwise Unavailable Important Public Health Benefit?

The use of CFCs in MDIs for the treatment of asthma and COPD is the only legal use in the United States of newly manufactured CFCs. The quantity of CFCs used in OTC epinephrine MDIs is a significant portion of the total quantity of newly manufactured CFCs used, and therefore eventually released, in the United States. The size of the portion will increase as other MDIs containing CFCs are removed from the

Deleted: We did not follow the approach taken by the committee members at the NDAC/PADAC meeting, balancing the public health benefit of the availability of the drug OTC to the population that cannot obtain adequate therapeutic alternatives against the public health risks that arise from self-treatment of asthma.[25] We did, however, examine all of the issues, facts, and opinions presented at the NDAC/PADAC meeting. If information presented to us later in this rulemaking indicates that it is necessary and/or appropriate to address whether OTC epinephrine MDIs provide an otherwise unavailable important public health benefit or whether the release of CFCs associated with such products is warranted in view of the otherwise unavailable public health benefits, we will use an analysis similar to that used by the committee members at the NDAC/PADAC meeting. ¶ Many NDAC/PADAC members complained about the lack of existing data to inform their recommendation on the essential-use status of epinephrine. Indeed, several gave the lack of data as a reason for voting to retain the essential-use designation for epinephrine (meeting transcript, pp. 198, 201, and 205). We share the concerns raised by the members, and request that more data on the essential use of epinephrine be submitted in response to this rulemaking.

market. As we discussed in part II of this notice, the release of CFCs from MDIs is cumulatively significant. Because we have not reached a conclusion on the public health benefits of OTC epinephrine MDIs, we cannot reach a conclusion on whether the release of CFC ODSs is warranted in view of the public health benefits.

D. Conclusions

We have tentatively concluded the following:

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

We have not reached a conclusion on whether the use of OTC epinephrine MDIs provides an unavailable important public health benefit or whether the release of ODSs from OTC epinephrine MDIs is warranted in view of the otherwise unavailable public health benefit. However, as we discussed in part II of this notice, if a use fails to meet any one of the three criteria in § 2.125(f), it is no longer an essential use of ODSs.

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

VI. Environmental Impact

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

VII. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law No. 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is a significant regulatory action as defined by the Executive order.

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

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $122 million, using the most current (2005) Implicit Price Deflator for the Gross Domestic Product. This proposed rule may result in a 1-year expenditure that would meet or exceed this amount.

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

This proposed rule would prohibit sales of OTC epinephrine CFC MDIs in interstate commerce after December 31, 2010, forcing users to either self-medicate with less effective therapies (see section VII.D.3.a), or to visit a physician and get a prescription for an alternative drug product such as albuterol. Because OTC epinephrine CFC MDIs are widely regarded by physicians and people with asthma as the most effective relief medication for asthma available OTC, if users of these MDIs choose to self-medicate, they will be more likely to require hospitalization or an emergency department visit. Alternatively, if they choose to see a physician to obtain a prescription for albuterol, the OTC epinephrine CFC MDI users, or their insurers, will have to pay more, not only for visits to the physician, but also for more expensive drugs. More physician visits, however, may lead current OTC epinephrine MDI users to increase their use of prescription control medication, such as inhaled corticosteroids, which should

decrease their likelihood of both asthma attacks and hospital visits. We have no data suggesting whether current OTC epinephrine MDI users are more likely to self-medicate or to visit a physician and get an albuterol MDI prescription once OTC epinephrine MDIs are no longer available. We therefore focus on scenarios where, if OTC epinephrine MDIs are no longer available, all current OTC epinephrine MDI users either self-medicate with other products such as herbal supplements, caffeine, and OTC ephedrine or visit a physician to obtain, and fill, prescriptions for albuterol MDIs. These extreme scenarios offer plausible bounds for estimating the costs and benefits resulting from this proposed rule and regulatory alternatives.

We expect that CFCs available for production of OTC epinephrine MDIs are likely to be exhausted prior to the effective date of this proposed rule because it is likely the United States will be unable to obtain an essential-use allocation for CFCs under the Montreal Protocol for use in OTC epinephrine MDIs for 2010 (see Ref. 33, p. 59). If so, this proposed rule will have no impacts. To the extent that CFCs for production of OTC epinephrine MDIs remain available, we estimate this proposed rule will have the impacts summarized below.

Table 2.--Summary of Annual Quantifiable Effects of the Proposed Rule, Assuming CFCs for Production of OTC Epinephrine MDIs Remain Available

	Increased Health care Expenditure, in 2006 Dollars	Increased Emergency Department Visits for Asthma	Increased Hospitali-zations for Asthma	Reduced CFC Emissions from Phase-Out (tonnes)
If current OTC				

epinephrine MDI users self-medicate	$360 million to $1.0 billion	0 to 440,000	40,000 to 120,000	70
If current OTC epinephrine MDI users visit their physician for prescription albuterol (excluding controller medication)	$170 million to $340 million			70

We are unable to estimate quantitatively the reductions in skin cancers, cataracts, and environmental harm that may result from the reduction in CFC emissions by roughly 70 tonnes during these years. Although we cannot estimate quantitatively the public health effects of the phase-out, based on a qualitative assessment, the agency concludes that the benefits of this regulation justify its costs.

We state the need for the regulation and its objective in section VII.B of this document. Section VII.C of this document provides background on CFC depletion of stratospheric ozone, the Montreal Protocol, the OTC epinephrine MDI market, and the health conditions that epinephrine is used to treat. We analyze the benefits and costs of the rule, including effects on government outlays, in section VII.D of this document. We

assess alternative dates in section VII.E of this document, and discuss sensitivity analysis in section VII.F of this document. We present an analysis of the effects on small business in a regulatory flexibility analysis in section VIII of this document. We discuss our conclusions in section VII.H of this document.

B. Need for Regulation and the Objective of This Rule

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

One of the objectives of this proposed rule is to respond to the obligations under the Montreal Protocol requiring the United States to reduce atmospheric emissions of ODSs, specifically CFCs. CFCs and other ODSs deplete the stratospheric ozone that protects the Earth from ultraviolet solar radiation. We are proposing to end the essential-

use designation for ODSs used in MDIs containing epinephrine because we have tentatively concluded that no substantial technical barriers exist to formulating epinephrine in a product that does not release ODSs (see section V.A of this document). Removing this essential-use designation will comply with U.S. obligations under the Montreal Protocol and the Clean Air Act, thereby reducing emissions that deplete stratospheric ozone.

C. Background

1. CFCs and Stratospheric Ozone

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

2. The Montreal Protocol

The international effort to craft a coordinated response to the global environmental problem of stratospheric ozone depletion culminated in the Montreal Protocol, an international agreement to regulate and reduce production of ODSs. The Montreal Protocol is described in section I.B.2 of this document. One hundred and

ninety-one countries have now ratified the Montreal Protocol, and the overall usage of CFCs has been dramatically reduced. In 1986, global consumption of CFCs totaled about 1.1 million tonnes, and by 2004, total annual production had been reduced to 70,000 tonnes (Ref. 34). This decline amounts to more than a 90-percent decrease in production and is a key measure of the success of the Montreal Protocol. Within the United States, use of ODSs, and CFCs in particular, has fallen sharply—production and importation of CFCs is less than 1 percent of 1989 production and importation (Ref. 34).

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

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

3. Benefits of the Montreal Protocol

EPA has generated a series of estimates of the environmental and public health benefits of the Montreal Protocol (Ref. 35). The benefits include reductions of hundreds of millions of nonfatal skin cancers, 6 million fewer fatalities due to skin cancer, and 27.5 million cataracts avoided between 1990 and 2165 if the Montreal Protocol were fully implemented. EPA estimates the value of these and related benefits to equal $4.3 trillion in present value when discounted at 2 percent over the period of 175 years. This amount is equivalent to about $6 trillion after adjusting for inflation between 1990 and 2004.

This estimate includes all benefits of total global ODS emission reductions expected from the Montreal Protocol and is based on reductions from a baseline scenario in which ODS emissions would continue to grow for decades but for the Montreal Protocol.

4. Characteristics of Asthma

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

Early release data from the first 6 months of the 2006 NHIS indicate that 8.0 percent of people in the United States have asthma (Ref. 36, fig. 15.5). The prevalence of asthma decreases with age, with the prevalence being 9.5 percent for children ages 0 to 14, compared to 7.8 percent for persons ages 15 to 34, and 7.4 percent for adults ages 35 and over (Ref. 36, fig. 15.5).

The early release data from the first 6 months of the 2006 NHIS also indicate 4.2 percent of Americans had an asthma episode in the previous 12 months, with 5.5 percent of children under age 14, 3.6 percent of persons ages 15 to 34, and 4.0 percent of adults over age 35 reporting episodes (Ref. 36, fig. 15.2).

According to data from the National Ambulatory Medical Care Survey, in 2004 there were about 15 million outpatient asthma visits to physician offices and hospital clinics and 1.8 million emergency department visits (Ref. 37, table 19). According to data from the National Center for Health Statistics: National Hospital Discharge Survey, there were 497,000 hospital admissions for asthma in 2004 (Ref. 37, table 12) and 4,099

mortalities in 2003 (Ref. 37, table 1). The estimated direct medical cost of asthma (hospital services, physician care, and medications) was $11.5 billion in 2004 (Ref. 37, table 20).

We estimate that OTC epinephrine MDI users make roughly 280,000 to 370,000 visits to emergency departments and require roughly 75,000 to 100,000 hospitalizations annually. We know of no data or study suggesting OTC epinephrine MDI users differ from other people with asthma in their risk of requiring emergency department visits or hospitalizations. In a published study of 601 people with asthma (Ref. 38), the authors did not find any evidence that epinephrine users are more likely to visit emergency departments or to require hospitalization than people with asthma who do not use epinephrine. On the other hand, we know of no data suggesting that OTC epinephrine MDI users are less likely to visit emergency departments or require hospitalization. As described in section V.B.2.b of this document, we estimate that 1.7 to 2.3 million people with asthma use OTC epinephrine MDIs. Assuming 1.7 to 2.3 million people with asthma are OTC epinephrine MDI users, and that they require emergency department visits and hospitalization in proportion to their share of the population, OTC epinephrine MDI users account for roughly 280,000 to 370,000 emergency department visits annually [15 percent of 1.8 million = 280,000; 20 percent of 1.8 million = 370,000] and 75,000 to 100,000 hospitalizations annually [15 percent of 497,000 = 75,000; 20 percent of 497,000 = 100,000].[26]

While the prevalence of asthma (the percent of the population diagnosed with asthma) has been increasing in recent years, CDC reports that the incidence of asthma

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

(the rate of new diagnoses) has remained fairly constant since 1997 (Ref. 39). Non-Hispanic Blacks, children under 17 years old, and females have higher incidence rates than the general population and also are more likely to have had an attack of asthma in the previous 12 months. The CDC notes that although increases have occurred in the numbers and rates of physician office visits, hospital outpatient visits, and emergency department visits, these increases are accounted for by the increase in prevalence. The CDC also notes that asthma mortality and asthma hospitalization rates were declining and stated that these downward trends might indicate early successes by asthma intervention programs.

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

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

Based on data from ACNielsen for the 52 weeks ending September 9, 2006 (Ref. 40), we estimate 3.5 million OTC epinephrine MDIs are sold in the United States annually, excluding sales through Wal-Mart Stores, Inc. (Wal-Mart).[27] Wyeth estimates roughly 25 percent of OTC medications such as PRIMATENE MIST, a branded OTC epinephrine MDI product, are sold through Wal-Mart annually (Wyeth slide 32), implying a total market of roughly 4.5 million OTC epinephrine MDIs sold annually. This is equivalent to 1.3 billion inhalations per year, or 146 million days of therapy (at 9 inhalations per day, the highest recommended long-term dose).

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

Based on ACNielsen data (Ref. 40) for the 52 weeks ending September 9, 2006, adjusted for sales through Wal-Mart, we estimate OTC epinephrine MDI sales amount to roughly $60 million in the United States annually and the average U.S. retail price of OTC epinephrine MDIs is $13.29, equivalent to roughly $0.41 per day of therapy.

According to American Lung Association reports derived from the National Center for Health Statistics' 2004 NHIS (Ref. 37, table 10), 11.6 million individuals reported having had an asthma attack in the last 12 months. According to Wyeth Pharmaceuticals (Wyeth slide 32), 15 to 20 percent of adults with asthma that have had an asthma attack in the previous 12 months use OTC epinephrine MDIs. As we discussed in section V.B.2.b of this document, we estimate that 1.7 to 2.3 million people with asthma use OTC epinephrine MDIs. Each of these users, on average, purchases roughly 1.9 to 2.6 OTC epinephrine MDIs each year [4.5 million MDIs ÷ 1.7 million users = 2.6 MDIs per user per year; 4.5 million MDIs ÷ 2.3 million users = 1.9 MDIs per user per year].

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

D. Benefits and Costs of the Proposed Rule

We estimate the benefits and costs of government action relative to a baseline scenario that, in this case, is a description of the production, use, and access to OTC

epinephrine MDIs in the absence of a final rule based on this proposed rule. In this section we first describe such a baseline, and then present our analysis of the benefits of the rulemaking. We also present an analysis of the most plausible regulatory alternatives, given the Montreal Protocol. Next, we turn to the costs of the rulemaking and to an analysis of the effects on the Medicare and Medicaid programs.

1. Baseline Conditions

We developed baseline estimates of future conditions to assess the economic effects of prohibiting marketing of OTC epinephrine MDIs after December 31, 2010. It is standard practice to use, as a baseline, the state of the world without the rulemaking in question, or where the rulemaking implements a legislative requirement, the world without the statute. For this proposed rule, we make the baseline assumption that it is questionable if the United States would be able to obtain an essential-use allocation for CFCs for the manufacture of OTC epinephrine MDIs under the Montreal Protocol for 2010.[28] To the extent that new CFCs for production of OTC epinephrine MDIs remain available past that date, we estimate this rulemaking will have quantifiable impacts as summarized in table 2. If CFCs for the production of OTC epinephrine MDIs are no longer available by the end of 2010, this rule will have no impact.

2. Benefits of the Proposed Rule

The benefits of a final rule based on this proposed rule include environmental and public health improvements from protecting stratospheric ozone by reducing CFC emissions by roughly 70 tonnes annually. Benefits also include expectations of increased returns on investments in environmentally friendly technology, reduced risk of

[28] Even if there is no essential-use allocation under the Montreal Protocol for the year 2010, production of epinephrine CFC MDIs would likely continue well into the year with manufacturers using preexisting stocks of CFCs.

unexpected disruption of supply of OTC epinephrine MDIs, and continued international cooperation to comply with the spirit of the Montreal Protocol, thereby potentially reducing future emissions of ODSs throughout the world.

Failure to finalize this proposed rule would likely lead the Parties to the Montreal Protocol to consider restrictions on access to the CFCs required to manufacture these OTC epinephrine MDIs products, which would create the risk of removal of these products from the market.

a. Reduced CFC emissions. Withdrawal of OTC epinephrine MDIs from the market will reduce CFC emissions by approximately 70 tonnes per year. Current CFC inventories are substantial. Nominations for new CFC production are generally approved by the Parties to the Montreal Protocol 2 years in advance. The proposed rule would ban marketing of OTC epinephrine CFC MDIs after December 31, 2010. There is some uncertainty with respect to the amount of inventory that will be available in the future, but the United States' ability to obtain an essential-use allocation for CFCs for the manufacture of OTC epinephrine MDIs in 2010 is questionable.

In an evaluation of its program to administer the Clean Air Act, EPA has estimated that the benefits of controlling ODSs under the Montreal Protocol are the equivalent of $6 trillion in 2004 dollars. However, EPA's report provides no information on the total quantities of reduced emissions or the incremental value per tonne of reduced emissions. EPA derived its benefits estimates from a baseline that included continued increases in emissions in the absence of the Montreal Protocol. We have searched for authoritative scientific research that quantifies the marginal economic benefit of incremental emission reductions under the Montreal Protocol, but have found none

conducted during the last 10 years. As a result, we are unable to quantify the environmental and human health benefits of reduced emissions from this regulation. Such benefits, in any event, were included in EPA's earlier estimate of benefits.

The reduction of CFC emissions associated with removing OTC epinephrine CFC MDIs from the U.S. market represents only a fraction of 1 percent of total global CFC emissions. Current allocations of CFCs for OTC epinephrine MDIs account for less than 0.1 percent of the total 1986 global production of CFCs (Ref. 41). Furthermore, current U.S. CFC emissions from MDIs represent a much smaller, but unknown share of the total emissions reduction associated with EPA's estimate of $6 trillion in benefits, because that estimate reflects future emissions growth that has not occurred.

If a final rule removing the essential-use designation of OTC epinephrine MDIs takes effect before CFCs cease to be available, the proposed rule may account for some small part of the benefits estimated by EPA. However, we are unable to assess or quantify specific reductions in future skin cancers and cataracts associated with the reduced emissions that might be associated with this proposed rule or the regulatory alternatives.

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

Newly developed technologies to avoid ODS emissions have resulted in more environmentally "friendly" air conditioners, refrigerants, solvents, and propellants, but

only after significant investments. Several manufacturers have claimed development costs that total between $250 million and $400 million to develop HFA MDIs and new propellant-free devices for the global market (Ref. 42).

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

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

3. Costs of the Proposed Rule and Alternatives

The costs of removing OTC epinephrine MDIs from the market include the costs of increased physician visits, increased use of more expensive reliever MDIs, and potential increases in the use of controller medications, visits to emergency departments, and hospitalizations. Because we cannot predict whether OTC epinephrine MDI users will self-medicate or go to a physician for a prescription reliever once OTC epinephrine MDIs are removed from the market, we quantify the costs for two extreme cases. In the

first case, OTC epinephrine MDI users not already seeing a physician self-medicate, while those who already see a physician switch from OTC epinephrine MDIs to albuterol HFA MDIs. In the second case, all OTC epinephrine MDI users visit their physician and switch to albuterol HFA MDIs. We propose these two cases as reasonable bounds for the expected cost of removing OTC epinephrine MDIs from the market.

a. Self-medication. If all OTC epinephrine MDI users who do not already see a physician for asthma were to self-medicate once OTC epinephrine MDIs were no longer available, and those who do see a physician were to increase their albuterol use, we estimate this rulemaking would result in $360 million to $1.0 billion in increased spending annually. This spending includes $280 million to $1.0 billion resulting from increased hospitalizations and emergency department visits, and roughly $30 million to $80 million in increased spending on more expensive medicines. Under the assumption of self-medication, we estimate that removing OTC epinephrine MDIs from the market would result in 40,000 to 120,000 more hospitalizations for asthma annually, and up to 440,000 more asthma-related emergency department visits each year. These estimates, based on calculations throughout this section, do not capture the decreased quality of life of OTC epinephrine MDI users, lost productivity, or the cost of alternative therapies, such as herbal remedies, caffeine and OTC ephedrine.

The authors of a published study found that people with asthma who self-medicate with herbal products and caffeine, the most common forms of self medication, are at increased risk of requiring an emergency department visit or hospitalization (Ref. 38). They found that those using herbal treatments are 2.5 times as likely to require hospitalization, and that those who use caffeine to treat asthma are 3.1 times as likely as

other people with asthma to require both an emergency department visit and hospitalization.

We estimate that OTC epinephrine MDI users who do not use prescription medicine for their asthma make roughly 100,000 to 200,000 emergency department visits and require roughly 25,000 to 50,000 hospitalizations. We estimate OTC epinephrine MDI users make roughly 280,000 to 370,000 emergency department visits and require about 75,000 to 100,000 hospitalizations annually, as described in section VII.C.4 of this document. We estimate somewhere between 43 percent and two-thirds of OTC epinephrine MDI users do not use prescription medicine for their asthma, as discussed in section 6. Assuming that OTC epinephrine MDI users who do not use prescription medicine for asthma do not differ in their rates of hospitalization and emergency department visits from those who do use prescription medicine for asthma, we estimate that OTC epinephrine MDI users who do not use prescription medicine for asthma make 100,000 to 200,000 emergency department visits and require 25,000 to 55,000 hospitalizations annually [275,700 emergency department visits x 1/3 = 91,900 emergency department visits; 367,600 emergency department visits x (1-.43) = 209,532 emergency department visits; 74,550 hospitalizations x 1/3 = 24,850 hospitalizations; 99,400 hospitalizations x (1-.43) = 56,658 hospitalizations].

If current OTC epinephrine MDI users who do not use prescription medicine for asthma were to self-medicate with herbal treatments, and those self-medicating with herbal treatments face 2.5 times the risk of a hospitalization, this would imply a lower bound increase of roughly 40,000 hospitalizations [24,850 hospitalizations x (2.5 – 1) = 37,275]. As an upper bound, if all OTC epinephrine MDI users were to self-medicate

with caffeine, emergency department visits would increase by roughly 440,000 [209,532 emergency department visits x (3.1 - 1) = 440,017] and hospitalizations would increase by roughly 120,000 [56,658 hospitalizations x (3.1 – 1) = 118,983]. We do not have data that will allow us to estimate increases in hospitalizations and emergency department visits for patients using other forms of self-medication, such as OTC ephedrine. We request comments that would provide information allowing us to address this issue.

We estimate the 2006 cost of an emergency department visit for asthma at roughly $300 and the cost of hospitalization for asthma at roughly $7500. Based on data from the 2004 National Hospital Discharge Survey, the American Lung Association estimates the 497,000 hospitalizations for asthma cost roughly $3.6 billion in inpatient care and physician services, equivalent to roughly $7,300 per hospitalization (Ref. 37). The 1.8 million emergency department visits for asthma cost about $518 million, equivalent to roughly $280 per visit. Adjusting these figures for inflation according to the CPI for medical care, we estimate that the average hospitalization for asthma would cost roughly $7,500 and the average emergency department visit for asthma would cost roughly $300 in 2006.

Based on these estimates, if current OTC epinephrine MDI users who do not currently use prescription medicine were to self-medicate, the result would be costs of roughly $280 million [37,275 hospitalizations x $7,565.84 = $282,016,770] to $1.0 billion annually [(118,982 hospitalizations x $7,565.84) + (440,017 emergency department visits x $294.17) = $1,029,639,003].

Assuming current OTC epinephrine MDI users who do use prescription medicine for asthma increase their use of albuterol HFA MDIs without requiring more

frequent physician visits, we estimate that they will pay roughly $30 million to $80 million more for medicine each year. As discussed in section 6, somewhere between 43 percent and two-thirds of OTC epinephrine MDI users also use prescription medicine for their asthma. Assuming current OTC epinephrine MDI users who also use prescription medicines for their asthma use roughly the same number of OTC epinephrine MDIs per year as those who do not, we estimate dual users use roughly 2 million to 3 million OTC epinephrine MDIs annually [4,486,104 MDIs x 0.43 = 1,929,025; 4,486,104 MDIs x 2/3 = 2,990,736 MDIs]. As discussed in the following section, we estimate an albuterol HFA MDI will cost between $16 and $25 more than an OTC epinephrine MDI, and that one albuterol MDI is roughly equivalent to one OTC epinephrine MDI. The lower priced albuterol MDIs are currently being withdrawn from the market, and will not be available at the time of the proposed effective date of this rule (see 70 FR 71685). The higher price for albuterol HFA MDIs implies that if OTC epinephrine MDI users who also use prescription medicine for their asthma were to increase their use of albuterol HFA MDIs when OTC epinephrine MDIs are no longer available, they and their insurers would spend roughly $30 million to $80 million more per year for medicine [1,929,025 MDIs x $16.08 per MDI = $31,022,023; 2,990,736 MDIs x $25.15 per MDI = $76,418,426].

In total, self-medication by OTC epinephrine-only MDI users and increased albuterol use by those already using prescription medicine would result in increased spending of $360 million to $1.0 billion annually [$282,016,770 + $76,418,426 = $358,435,196; $1,029,639,003 + $31,022,023 = $1,060,661,026].

b. Increased physician visits and albuterol use. If, as a result of the removal of OTC epinephrine MDIs from the market, all current OTC epinephrine MDI users were to

seek out prescription albuterol HFA MDIs through increasing the frequency of physician visits, we estimate that this scenario would result in roughly $170 million to $340 million in increased health care spending, including $100 million to $225 million in economic costs through an increase in visits to physicians and $72 million to $114 million in increased spending on prescription albuterol.

We estimate that if current epinephrine users who do not use prescription medicine for their asthma make one additional physician visit per year to enable them to switch from OTC epinephrine MDIs to albuterol MDIs, the result would be roughly 600,000 to 1.3 million additional physician visits annually. This estimate stems directly from the estimate presented in section 6 that there are roughly 600,000 to 1.3 million epinephrine users who do not use prescription medicine for their asthma. These estimates assume that OTC epinephrine MDI users who do use prescription medicine for their asthma, and therefore already make regular physician visits, are able to increase their albuterol use without increasing the frequency of those visits.

We estimate the 2006 cost of a physician visit for asthma to be roughly $170. Based on 2004 data from the National Ambulatory Medical Care Survey, the American Lung Association estimates that 1.5 million physician visits and non-emergency outpatient hospital visits for asthma cost roughly $2.4 billion, equivalent to roughly $160 per physician visit. Adjusting these figures for inflation according to the CPI for medical care, we estimate that a physician visit for asthma would cost roughly $170 per visit in 2006. An increase of 600,000 to 1.3 million physician visits each year would therefore cost roughly $100 million to $225 million annually [584,217.75 visits x $168.966 per visit = $98,712,936; 1,332,016.47 visits x $168.966 per visit = $225,065,495]. These

estimates do not take into account the value of the time patients spend visiting their physicians.

If all current OTC epinephrine MDI users were to switch to prescription albuterol HFA MDIs, we estimate the result to be roughly $70 million to $115 million in increased spending on medicine. We estimate that it will take roughly one albuterol HFA MDI to replace each OTC epinephrine MDI removed from the market. OTC epinephrine MDIs contain roughly 270, 405, or 540 inhalations, depending on the size of the MDI. Based on ACNielsen data for the 52 weeks ending September 9, 2006 (Ref. 40), we estimate that the average OTC epinephrine MDI contained 293 inhalations, equivalent to 32.6 days of therapy, assuming OTC epinephrine MDI users use, but do not exceed, the long term maximum recommended dose of 9 inhalations per day. The usual dosage of albuterol HFA MDIs is 8 to 12 inhalations per day, and albuterol HFA MDIs contain 200 inhalations, implying that each MDI contains 17 to 25 days of therapy per MDI. Allowing for the greater therapeutic effectiveness of albuterol compared to epinephrine, we estimate it will take roughly one albuterol HFA MDI to replace each OTC epinephrine MDI removed from the market.

Based on ACNielsen data from the 52 weeks ending September 9, 2006 (Ref. 40), we estimate the average retail price of an OTC epinephrine MDI to be $13.29. Based on average retail sales prices across all payer types for the first half of 2004, the average albuterol HFA MDI cost $39.42 (Ref. 43). This estimate does not reflect less expensive albuterol HFA MDIs introduced to the market since that time. Some market analysts also predict that albuterol HFA MDI prices will decline up to 20 percent as the market switches away from albuterol CFC MDIs and large payers use their market power

to drive down prices (Ref. 44). Taking these factors into consideration, we estimate the average retail price of an albuterol HFA MDI is $30 or more, a price increase of roughly $16 to $25 per MDI. If current OTC epinephrine MDI users must purchase one albuterol MDI for each OTC epinephrine MDI they currently purchase, total expenditures by current OTC epinephrine MDI users and their insurers would increase roughly $70 million to $115 million [4,486,104 MDIs x $16.08 per MDI = $72,134,239; 4,486,104 MDIs x $25.55per MDI = $114,627,640].

If, instead of self-medicating, OTC epinephrine MDI users go to the physician and increase their use of albuterol HFA MDIs, we estimate increased spending of roughly $170 million to $340 million dollars annually [$98,712,936 for physician visits + $72,134,239 for medicine (albuterol) = $170,857,175; $225,065,495 in physician visits + $114,627,640 in medicines = $339,693,135].

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

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

be social costs. We are unable to estimate the fraction of those increased expenditures on drugs that constitute social costs.

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

In a study of almost 50,000 asthma patients (Ref. 45), the authors found that patients with low adherence to controller medication have significantly higher risk (odds ratio of 1.72) of emergency department visits or of hospitalization relative to patients with moderate or high adherence. The study found that patients receiving high daily doses of controller medication had the lowest risk (odds ratio of .37) of emergency department visits or of hospitalization. As discussed in section VII.D.3.a of this document, we estimate OTC epinephrine MDI users who do not use prescription medicines make roughly 100,000 to 200,000 emergency department visits and require about 25,000 to 55,000 hospitalizations annually. If they all were to visit their physicians, receive prescriptions for a controller medication, fill them, and use the medication, based on the results of the study of almost 50,000 asthma patients, we estimate 20 to 40 percent of these emergency department visits and hospitalizations could be avoided, equivalent to roughly 20,000 to 80,000 fewer emergency department visits [20 percent of 91,900 is 18,380; 40 percent of 209,532 is 83,813] and 5,000 to 10,000 fewer hospitalizations [20 percent of 24,850 is 4,970; 40 percent of 56,658 is 11,332]. Assuming the average cost for an emergency department visit for asthma is about $300 and the average cost of a hospitalization for asthma is roughly $7,500, as discussed in

section D.3.a of this document, this would reduce health care costs by roughly $40 million to $100 million annually [($294.17 per visit x 18,380) + ($7565.84 per hospitalization x 4,970) = $41,236,000; ($294.14 per visit x 83,813) + ($7565.84 per hospitalization x 11,332) = $105,837,600]. This cost is roughly $70 to $80 per current OTC epinephrine MDI user per year [$41,236,000 / 584,218 OTC epinephrine only MDI users = $70.58; $105,837,600 / 1,332,016 OTC epinephrine only MDI users = $79.46].

We looked at a range of CFC-free controller medications such as FLOVENT HFA, ASMANEX TWISTHALER, PULMICORT TURBOHALER, and QVAR, and found the wholesale price of the smallest dose of the least expensive medication to be roughly $1.00 per day of therapy,[29] equivalent to roughly $370 per patient year of therapy. On average, the cost of increasing the use of controller medication among current OTC epinephrine MDI users who do not currently use prescription medicine would exceed the benefits, in terms of decreased emergency department visits and hospitalizations, by over $280 per person per year. This number would be lower if a greater fraction of people with asthma at high risk of emergency department visits were to begin using controller medication on a regular basis, and higher if a greater fraction of low risk people with asthma were to begin using controller medication on a regular basis. These estimates do not take into account the impact of asthma attacks on individuals' quality of life and productivity.

4. Effects on Medicaid and Medicare

As a result of the removal of OTC epinephrine CFC MDIs from the market, we estimate State and Federal Medicaid spending will increase $35 million to $250 million

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

annually and that Federal Medicare spending, together with private spending by Medicare beneficiaries, will increase $20 million to $250 million annually. Some OTC epinephrine MDI users may be eligible for both Medicare and Medicaid. To the extent this population is large, these estimates overstate potential spending increases from this proposed rule by counting these individuals twice: once in Medicaid estimates and once in Medicare estimates. We are unable to estimate the size of the population of OTC epinephrine MDI users eligible for both programs.

a. Medicaid. We estimate that 20 to 25 percent of the costs of the removal of OTC epinephrine MDIs from the market will be born by State and Federal Medicaid programs, equivalent to $70 million to $250 million annually if Medicaid-eligible OTC epinephrine MDI users who do not use prescription medicine for their asthma were to self-medicate upon implementation of this proposed rule, and equivalent to $35 million to $85 million annually if Medicaid-eligible OTC epinephrine MDI users were to visit their physicians to obtain and fill prescriptions to enable them to switch to albuterol. Assuming epinephrine users with insurance, including Medicaid, are more likely to visit a doctor, and less likely to self-medicate, the costs of this proposed rule are more likely to fall in the $35 million to $85 million range.

According to proprietary surveys conducted by or for Wyeth between 1993 and 1994 (Wyeth slide 31), 27 percent to 33 percent of OTC epinephrine MDI users had incomes of less than $20,000 at the time the surveys were conducted. A 2005 Internet survey conducted by Wyeth found that 20 percent of OTC epinephrine MDI users had incomes of less than $25,000. Eligibility for Medicaid varies by State but is generally tied to the Federal poverty guidelines (Ref. 46). The 2006 Federal poverty guidelines

establish a poverty threshold of $20,000 in annual income for a family of four (Ref. 47). Accordingly, if we assume 20 percent to 25 percent of OTC epinephrine MDI users are eligible for Medicaid, if Medicaid-eligible OTC epinephrine MDI users who do not use prescription medicine were to self-medicate, and if those who do self-medicate were to switch to albuterol, Federal Medicaid spending would increase roughly $70 million to $250 million annually [20 percent of $360 million = $72 million; 25 percent of 1 billion = $250 million]. If all current epinephrine users eligible for Medicaid were to instead visit their physicians and use prescription albuterol, we estimate that Federal Medicaid spending would increase by $35 million to $85 million dollars annually [20 percent of $170,857,175 = $34,171,435; 25 percent of $339,693,135 = $84,923,284]. These estimates exclude costs that may result from increased prescribing of controller medications, and do not take into account the impact of asthma attacks on individuals' quality of life and productivity.

b. Medicare. We estimate 10 percent to 25 percent of the costs of the removal of OTC epinephrine MDIs from the market will be paid by Federal Medicare spending and by Medicare beneficiaries. If all Medicare-eligible OTC epinephrine MDI users were to self-medicate upon implementation of this proposed rule, Federal Medicare spending and spending by Medicare beneficiaries would increase roughly $40 million to $250 million dollars annually. Alternatively, if all Medicare-eligible OTC epinephrine MDI users were to visit their doctors to obtain and fill prescriptions for albuterol, Federal Medicare spending and spending by Medicare beneficiaries would increase roughly $20 to $85 million annually. Assuming epinephrine users with insurance, including

Medicare, are more likely to visit a doctor, and less likely to self-medicate, the costs of this proposed rule are more likely to fall in the $20 million to $85 million range.

According to proprietary surveys conducted by or for Wyeth between 1993 and 2005 (Wyeth slide 31), 16 percent to 33 percent of OTC epinephrine MDI users are over the age of 55, implying the percentage of epinephrine users over the age of 65, and therefore eligible for Medicare, must be lower. Accordingly, if we assume 10 percent to 25 percent of OTC epinephrine MDI users are over the age of 65, Medicare spending and private spending by Medicare beneficiaries would increase $40 million to $250 million annually if all Medicare-eligible OTC epinephrine MDI users were to self-medicate [10 percent of $360 million = $36 million; 25 percent of $1.0 billion = $250 million], and by $20 million to $85 million annually if they were all to visit their physicians for prescription albuterol [10 percent of $170,857,125 = $17 million; 25 percent of $339,693,135 = 84,923,284]. These estimates exclude costs that may result from increased prescribing of controller medications, and do not take into account the impact of asthma attacks on individuals' quality of life and productivity.

E. Alternative Phase-out Dates

Because of our obligation under the Montreal Protocol, the only feasible regulatory options are different effective dates. The alternatives we considered included the following phase-out dates:

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

Spending per year does not differ among the regulatory alternatives. The only difference among the alternatives is how long the estimated costs shown in table 2 of this document would accrue. At some time in the near future, the unavailability of CFCs--not the proposed rule or an alternative--would remove OTC epinephrine from the marketplace. Our current belief is that bulk CFCs are likely to be unavailable in 2010 (see section VII.A), so the costs for the first alternative would be the present value of the annual costs for 2 years, 2008-2009, and the cost for the second alternative would be the present value of the costs for 1 year, 2009. The third alternative, which is the proposed rule, would have no quantifiable costs or benefits. We invite comments on these projections and on the costs and benefits of any other possible alternative effective dates, such as December 31, 2011 or 2012.

F. Sensitivity Analyses

The estimated costs summarized in table 2 incorporate a range of estimates about the price increases consumers and other payers will face, the size of the affected market, and the consequences of consumers' response to the removal of OTC epinephrine MDIs from the market. This represents the full range of uncertainty for the estimated effects of this proposed rule. The full range incorporates the ranges of estimates for the individual uncertain variables in the analysis.

In each section of the document, we show the ranges associated with each major uncertain variable, taking into account the possibility that in response to the removal of OTC epinephrine MDIs from the market, OTC epinephrine MDI users who do not currently use prescription medicines will either self-medicate or visit a physician to get an albuterol prescription. The estimated increases in emergency department visits and

hospitalizations depend upon a range of estimates of the percentage of people with asthma that use OTC epinephrine MDIs (15 to 20 percent) and the fraction of OTC epinephrine MDI users that do not use prescription medicines and are therefore more likely to self-medicate (somewhere between 33 and 57 percent), as well as the rate we estimate hospitalizations and emergency department visits will increase among this population (2.5 to 3.1 times).

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

G. Conclusion

Limits in available data prevent us from quantifying the costs and benefits of the proposed rule and weighing them in comparable terms. The benefits of international cooperation to reduce ODS emissions are potentially enormous but difficult to attribute to any of the small steps, such as this rulemaking, that make such cooperation effective. As

discussed above in detail, the benefits of the removal of OTC epinephrine MDIs from the market include environmental and public health improvements from protecting stratospheric ozone by reducing CFC emissions. Benefits also include expectations of increased returns on investments in environmentally friendly technology, reduced risk of unexpected disruption of supply of CFC MDIs, and continued international cooperation to comply with the spirit of the Montreal Protocol, thereby potentially reducing future emissions of ODSs throughout the world. The removal of OTC epinephrine MDIs from the market could potentially cost public and private consumers of OTC epinephrine MDIs hundreds of millions of dollars annually, and increase hospitalizations and emergency department visits for asthma significantly. If CFCs cease to be available for OTC epinephrine MDIs before the effective date of a final rule removing the essential-use designation of OTC epinephrine MDIs, however, this proposed rule would have no benefits or costs. We specifically request comments on the costs and benefits of this proposed rule.

VIII. Regulatory Flexibility Analysis

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

IX. 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.

X. 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.

XI. Request for Comments

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

An upcoming public meeting on the essential-use status of OTC MDIs containing epinephrine will provide an additional opportunity for public comment. We will provide details on the meeting in a notice published in the FEDERAL REGISTER in the near future.

XII. References

The following references have been placed on display in the Division of Dockets

Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. FDA has verified the Web site addresses, but we are not responsible for subsequent changes to the Web site after this document publishes in the FEDERAL REGISTER.[30]

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List of Subjects in 21 CFR Part 2

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

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Clean Air Act, and under authority delegated to the Commissioner of Food and Drugs, after consultation with the Administrator of the Environmental Protection Agency, 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. In § 2.125, remove and reserve paragraph (e)(2)(v).

Dated: _____

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