DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

21 CFR Part 2

[Docket No. 2006N–0416]

RIN 0910–AF93

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Direct final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulation on the use of ozone-depleting substances (ODSs) in pressurized containers to remove the essential use designations for beclomethasone, dexamethasone, fluticasone, bitolterol, salmeterol, ergotamine tartrate, and ipratropium bromide used in oral pressurized metered-dose inhalers (MDIs). Under the Clean Air Act, FDA, in consultation with the Environmental Protection Agency (EPA), is required to determine whether an FDA-regulated product that releases an ODS is essential. None of these products is currently being marketed, which provides grounds for removing their essential use designation. We are using direct final rulemaking for this action because the agency expects that there will be no significant adverse comment on the rule. In the proposed rule section in this issue of the **Federal Register**, we are concurrently proposing and soliciting comments on this rule. If significant adverse comments are received, we will withdraw this final rule and address the comments in a subsequent final rule. FDA will not provide additional opportunity for comment.

cd03156 2006N-0416 NFR 1

DATES: The direct final rule is effective [*insert date 135 days after date of publication in the* **Federal Register**], except for § 2.125(e)(4)(v) (21 CFR 2.125(e)(4)(v)), which is effective August 1, 2007. Submit written or electronic comments on or before [*insert date 75 days after date of publication in the* **Federal Register**]. If we receive no timely significant adverse comments, we will publish a document in the **Federal Register** before [*insert date 105 days after date of publication in the* **Federal Register**], confirming the effective date of the direct final rule. If we receive any timely significant adverse comments, we will publish a document of significant adverse comment in the **Federal Register** withdrawing this direct final rule before [*insert date 135 days after date of publication in the* **Federal Register**].

ADDRESSES: You may submit comments, identified by Docket No. 2006N–0416 and RIN Number 0910–AF93, 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 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 number and Regulatory Information Number (RIN) for this rulemaking. All comments received will 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 "Request for Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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

SUPPLEMENTARY INFORMATION:

I. Background

FDA, in consultation with EPA, determines whether a medical product is essential for purposes of Title VI of the Clean Air Act (42 U.S.C. 7671 *et seq.*). If a medical product, including a drug, is determined to be essential and meets the other elements of the definition found in section 601 of the Clean

Air Act, the product will be considered a "medical device." "Medical devices" are exempt from the general prohibition on nonessential uses of chlorofluorocarbons (CFCs) (a class of ODSs) found in section 610 of the Clean Air Act. ODSs produced for use in "medical devices" may also be exempt, if other conditions are met, from the general prohibitions on production and consumption of ODSs found in sections 604 and 605 of the Clean Air Act.

In 1978, we published a rule listing several essential uses of CFCs and providing criteria for adding new essential uses (43 FR 11301 at 11316, March 17, 1978). The rule was codified as § 2.125 (21 CFR 2.125) and § 2.125 was amended at various times to add new essential uses.

Over the years, alternatives were developed to ODS products whose uses were listed in § 2.125 as being essential, while other listed ODS products were removed from the market. In light of these facts, and in furtherance of our obligations under the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer (September 16, 1987, 26 I.L.M. 1541 (1987)), we determined that it would be appropriate to revise § 2.125 to remove the essential use designations of some products and provide criteria for the removal of additional essential use designations in the future. Thus, the rule revising § 2.125 was published in the **Federal Register** of July 24, 2002 (67 FR 48370). Among other provisions, the rule removed the essential use designations of various specific products that, at the time the rule was being prepared, were no longer being marketed. The rule went into effect on January 20, 2003. That rule also revised § 2.125(g)(1) (21 CFR 2.125(g)(1)) to provide that if any product that releases an ODS is no longer being marketed, the product may have its essential use designation revoked through notice-and-comment rulemaking.

II. Citizen Petition From Glaxosmithkline

In a citizen petition dated November 15, 2005, GlaxoSmithKline (GSK) requested that MDIs containing the single active moieties beclomethasone, fluticasone, and salmeterol be removed from the essential use list of ODSs. GSK stated that because beclomethasone, fluticasone, and salmeterol are no longer being marketed in MDIs that release ODSs, all three active moieties meet the criterion under revised § 2.125(g) for being removed from the essential use list. GSK requested that the essential use designation for beclomethasone, fluticasone, and salmeterol be revoked through a direct final rule.

In addition, we have determined that dexamethasone, bitolterol, ergotamine tartrate, and ipratropium bromide are no longer being marketed in MDIs that release ODSs, which provides grounds for removing their essential use designation.

III. Direct Final Rulemaking

We have determined that the subject of this rulemaking is suitable for a direct final rule. The actions taken should be noncontroversial, and the agency does not anticipate receiving any significant adverse comments on this rule. However, in the even that significant adverse comment is received, we are also publishing a companion proposed rule to satisfy the requirement under § 2.125(g) that essential uses be removed through notice-and-comment rulemaking.

If we receive no significant adverse comment, we will publish a document in the **Federal Register**, confirming the effective date of the direct final rule. A significant adverse comment is one that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. A

comment recommending a rule change in addition to this rule will not be considered a significant adverse comment, unless the comment states why this rule would be ineffective without the additional change. If timely significant adverse comments are received, we will publish a notice of significant adverse comment in the **Federal Register** withdrawing this direct final rule within 30 days after the comment period ends.

Elsewhere in this issue of the **Federal Register**, we are publishing a companion proposed rule, identical in substance to this direct final rule, that provides a procedural framework from which to proceed with standard notice and comment rulemaking in the event the direct final rule is withdrawn because of significant adverse comment. The comment period for the direct final rule runs concurrently with that of the companion proposed rule. Any comments received under the companion proposed rule will be treated as comments regarding the direct final rule. Likewise, significant adverse comments submitted to the direct final rule will be considered as comments to the companion proposed rule, and we will consider those comments in developing a final rule. We will not provide additional opportunity for comment on the companion proposed rule.

If a significant adverse comment applies to part of this rule and that part may be severed from the remainder of the rule, we may adopt as final those parts of the rule that are not the subject of a significant adverse comment. A full description of our policy on direct final rule procedures may be found in a guidance document published in the **Federal Register** of November 21, 1997 (62 FR 62466).

IV. Beclomethasone, Dexamethasone, Fluticasone, Bitolterol, Salmeterol, Ergotamine Tartrate, and Ipratropium Bromide

The manufacturers of all approved beclomethasone, dexamethasone, fluticasone, bitolterol, salmeterol, ergotamine tartrate, and ipratropium bromide oral pressurized MDIs containing an ODS have provided information that leads us to conclude that they have removed these products from the market.[1] Accordingly, we are amending our regulation to remove beclomethasone, dexamethasone, fluticasone, bitolterol, salmeterol, ergotamine tartrate, and ipratropium bromide from the list of essential use drugs found in § 2.125(e) (21 CFR 2.125(e)). Essential uses for metered-dose corticosteroid human drugs for oral inhalation, metered-dose short-acting adrenergic bronchodilator human drugs for oral inhalation, and metered-dose salmeterol, ergotamine tartrate, and ipratropium bromide drug products for oral inhalation, are listed in § 2.125(e)(1), (e)(2), and (e)(4) by active moiety. "Active moiety" is defined in 21 CFR 314.108(a) as follows: "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."

MDIs that contain the active moieties beclomethasone, dexamethasone, fluticasone, bitolterol, salmeterol, ergotamine tartrate, and ipratropium bromide, use certain forms of these moieties. Specifically, MDIs that have beclomethasone or fluticasone as their active moieties use those moieties in

[1] The drug products discussed in this direct final rule were all approved for marketing under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355). We are unaware of any unapproved beclomethasone, dexamethasone, fluticasone, bitolterol, salmeterol, ergotamine tartrate, and ipratropium bromide oral pressurized MDIs using an ODS as a propellant that are marketed in the United States.

the forms of beclomethasone dipropionate and fluticasone propionate, respectively. Similarly, MDIs that have dexamethasone, bitolterol, or salmeterol as their active moieties use those moieties in the forms of dexamethasone sodium phosphate, bitolterol mesylate, and salmeterol xinafoate, respectively. Ergotamine tartrate is a salt of ergotamine, and it was used in oral MDIs for the treatment of migraines. Its essential use designation is for the ergotamine tartrate salt rather than the active moiety ergotamine.

A. Beclomethasone

Oral pressurized MDIs that contain beclomethasone are listed in § 2.125(e)(1)(i) as an essential use. BECLOVENT and VANCERIL are the only two oral pressurized MDIs that have been marketed and contain beclomethasone with an ODS. On January 10, 2002, GSK, the manufacturer of BECLOVENT, requested that we withdraw approval of their new drug application (NDA) for BECLOVENT ODS MDIs (NDA 18–153) and informed us that they had stopped marketing BECLOVENT ODS MDIs. On May 2, 2001, Schering-Plough Corp. (Schering), the manufacturer of VANCERIL, requested that we withdraw approval of NDA, for VANCERIL ODS MDIs, 84 micrograms per inhalation (μg/inh), and informed us that they had stopped marketing VANCERIL 84 μg/inh MDIs in November 1999. Also, on July 25, 2002, Schering informed us that they were removing VANCERIL 42 μg/inh from the market. On April 14, 2005, Schering requested withdrawal of approval of NDA 17–573 for VANCERIL 42 μg/inh.

B. Dexamethasone

Oral pressurized MDIs that contain dexamethasone are listed in § 2.125(e)(1)(ii) as an essential use. DEXACORT ORAL MDI is the only oral pressurized MDI that has been marketed and contains dexamethasone with an

ODS. On September 13, 2002, Celltech Pharmaceuticals, Inc., the manufacturer of DEXACORT ORAL MDI, requested that we withdraw approval of NDA 01–3413 for DEXACORT ORAL MDIs and informed us that they had stopped marketing DEXACORT ORAL MDIs on August 15, 1996.

C. Fluticasone

Oral pressurized MDIs that contain fluticasone are listed in § 2.125(e)(1)(iv) as an essential use. FLOVENT CFC MDI is the only oral pressurized MDI that has been marketed and contains fluticasone with an ODS. GSK, the manufacturer of FLOVENT CFC MDIs, has informed us that they stopped marketing FLOVENT CFC MDIs in November 2004.

D. Bitolterol

Oral pressurized MDIs that contain bitolterol are listed in § 2.125(e)(2)(ii) as an essential use. TORNALATE MDI is the only oral pressurized MDI that has been marketed and contains bitolterol with an ODS. On January 28, 2003, Sanofi-Synthelabo, Inc., the manufacturer of TORNALATE MDIs, informed us that they had stopped marketing TORNALATE MDIs on October 1, 2000.

E. Salmeterol

Metered-dose salmeterol drug products are listed in § 2.125(e)(4)(i) as an essential use. SEREVENT MDI is the only metered-dose salmeterol drug product with an ODS that has been marketed. GSK, the manufacturer of SEREVENT MDIs, has informed us that they stopped marketing SEREVENT MDIs in January 2003.

F. Ergotamine Tartrate

Oral pressurized MDIs that contain ergotamine tartrate are listed in § 2.125(e)(4)(ii) as an essential use. MEDIHALER ERGOTAMINE is the only

oral pressurized MDI that has been marketed and contains ergotamine tartrate with an ODS. 3M Pharmaceuticals, the manufacturer of MEDIHALER ERGOTAMINE, has informed us that they stopped marketing MEDIHALER ERGOTAMINE in November 1991.

G. Ipratropium Bromide

Oral pressurized MDIs that contain ipratropium bromide are listed in § 2.125(e)(4)(v) as an essential use. ATROVENT CFC MDI is the only oral pressurized MDI that has been marketed and contains ipratropium bromide with an ODS. Boehringer Ingelheim Pharmaceuticals, the manufacturer of ATROVENT CFC MDI, has informed us that they stopped marketing ATROVENT CFC MDIs in January 2006. This direct final rule does not affect MDIs containing ipratropium bromide and albuterol sulfate in combination, marketed as COMBIVENT, which are listed in § 2.125(e)(4)(viii) as a separate essential use.

H. Wholesale and Retail Stocks

Based on information given to us by the manufacturers, we have concluded that any beclomethasone, dexamethasone, fluticasone, bitolterol, salmeterol, and ergotamine tartrate ODS MDIs that may be in retail or wholesale stocks will have passed their expiration dates by the effective date for removal of § 2.125(e)(1)(i), (e)(1)(ii), (e)(1)(iv), (e)(2)(ii), (e)(4)(i), and (e)(4)(ii). Boehringer Ingelheim Pharmaceuticals, the manufacturer of ipratropium bromide, has informed us that any ipratropium bromide that may be in retail or wholesale stocks will have passed its expiration date by July 2007. Accordingly, we have set the effective date for removal of § 2.125(e)(4)(v) as August 1, 2007.

V. Environmental Impact

We have carefully considered, under 21 CFR part 25, the potential environmental effects of this action. We have concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. Our finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday.

VI. Analysis of Impacts

FDA has examined the impacts of the direct final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this direct final rule is not 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. Because we are removing the essential use designations for certain drug products that are either no longer being marketed or are no longer being marketed in a formulation containing ODSs, the agency certifies that the direct final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $118 million, using the most current (2004) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this direct final rule to result in any 1-year expenditure that would meet or exceed this amount.

VII. The Paperwork Reduction Act of 1995

This direct final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VIII. Federalism

FDA has analyzed this direct final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, we do not plan to prepare a federalism summary impact statement for this rulemaking procedure. We invite comments on the federalism implications of this direct final rule.

IX. Request for Comments

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

List of Subjects in 21 CFR Part 2

Administrative practice and procedure, Cosmetics, Drugs, Foods.

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

PART 2—GENERAL ADMINISTRATIVE RULINGS AND DECISIONS

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

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

§ 2.125 [Amended]

■ 2. Section 2.125 is amended by removing and reserving paragraphs (e)(1)(i), (e)(1)(ii), (e)(1)(iv), (e)(2)(ii), (e)(4)(i), (e)(4)(ii), and (e)(4)(v).

Dated: 10·13/06
October 13, 2006.

Jeffrey Shuren,
Assistant Commissioner for Policy.

[FR Doc. 06–????? Filed ??–??–06; 8:45 am]

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