



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 2

[Docket No. FDA-2015-N-1355]

RIN 0910-AH36

Use of Ozone-Depleting Substances

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to amend its regulation on uses of ozone-depleting substances (ODSs), including chlorofluorocarbons (CFCs), to remove the designation for certain products as “essential uses” under the Clean Air Act. Essential-use products are exempt from the ban by FDA on the use of CFCs and other ODS propellants in FDA-regulated products and from the ban by the Environmental Protection Agency (EPA) on the use of ODSs in pressurized dispensers. This action, if finalized, will remove the essential-use exemptions for sterile aerosol talc administered intrapleurally by thoracoscopy for human use and for metered-dose atropine sulfate aerosol human drugs administered by oral inhalation. FDA is proposing this action because alternative products that do not use ODSs are now available and because these products are no longer being marketed in versions that contain ODSs.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. If FDA receives any significant adverse comments, the Agency will publish a document withdrawing the

direct final rule before its effective date. FDA will then proceed to respond to comments under this proposed rule using the usual notice-and-comment procedures.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2015-N-1355 for “Use of Ozone-Depleting Substances.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public docket, see 80 FR 56469, September 18, 2015, or access the information at:

<http://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://www.regulations.gov> 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: Daniel Orr, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6246, Silver Spring, MD 20993, 240-402-0979, daniel.orr@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Production of ODSs has been phased out worldwide under the terms of the Montreal Protocol on Substances that Deplete the Ozone Layer (Montreal Protocol) (September 16, 1987, S. Treaty Doc. No. 10, 100th Cong., 1st sess., 26 I.L.M. 1541 (1987)). In accordance with the provisions of the Montreal Protocol, under authority of Title VI of the Clean Air Act (section 601 et seq.), the manufacture of ODSs, including CFCs, in the United States was generally banned as of January 1, 1996. To receive permission to manufacture CFCs in the United States after the phase-out date, manufacturers must obtain an exemption from the phase-out requirements from the parties to the Montreal Protocol. Procedures for securing an essential-use exemption under the Montreal Protocol are described in a request by EPA for applications for exemptions (60 FR 54349, October 23, 1995).

A drug, device, cosmetic, or food contained in an aerosol product or other pressurized dispenser that releases a CFC or other ODS propellant is generally not considered an essential

use of the ODS under the Clean Air Act except as provided in § 2.125(c) and (e) (21 CFR 2.125(c) and (e)). This prohibition is based on scientific research indicating that CFCs and other ODSs reduce the amount of ozone in the stratosphere and thereby increase the amount of ultraviolet radiation reaching the Earth. An increase in ultraviolet radiation will increase the incidence of skin cancer, and produce other adverse effects of unknown magnitude on humans, animals, and plants (80 FR 36937, June 29, 2015). Section 2.125(c) and (e) provide exemptions for essential uses of ODSs for certain products containing ODS propellants that FDA determines provide unique health benefits that would not be available without the use of an ODS.

Firms that wish to use ODSs manufactured after the phase-out date in medical devices (as defined in section 601(8) of the Clean Air Act (42 U.S.C. 7671(8)) covered under section 610 of the Clean Air Act (42 U.S.C. 7671i) must receive exemptions for essential uses under the Montreal Protocol. EPA regulations implementing the provisions of section 610 of the Clean Air Act contain a general ban on the use of ODSs in pressurized dispensers, such as metered-dose inhalers (MDIs) (40 CFR 82.64(c) and 82.66(d)). These EPA regulations exempt from the general ban “medical devices” that FDA considers essential and that are listed in § 2.125(e). Section 601(8) of the Clean Air Act defines “medical device” as any device (as defined in the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321), diagnostic product, drug (as defined in the FD&C Act), and drug delivery system, if such device, diagnostic product, drug, or drug delivery system uses a class I or class II ODS for which no safe and effective alternative has been developed (and, where necessary, has been approved by the Commissioner of Food and Drugs), and if such device, diagnostic product, drug, or drug delivery system has, after notice and opportunity for public comment, been approved and determined to be essential by the Commissioner in consultation with the Administrator of EPA. Class I substances include

CFCs, halons, carbon tetrachloride, methyl chloroform, methyl bromide, and other chemicals not relevant to this document (see 40 CFR part 82, appendix A to subpart A). Class II substances include hydrochlorofluorocarbons (see 40 CFR part 82, appendix B to subpart A).

Faced with the statutorily mandated phase-out of the production of ODSs, drug manufacturers have developed alternatives to MDIs and other self-pressurized drug dosage forms that do not contain ODSs. Examples of these alternative dosage forms are MDIs that use non-ODSs as propellants and dry-powder inhalers. The availability of alternatives to the ODSs means that certain drug products listed in § 2.125(e) are no longer essential uses of ODSs. Therefore, due to the lack of marketing of approved products containing ODSs, and the availability of alternative products that do not contain ODSs, FDA is proposing to amend its regulations to remove essential-use designations for sterile aerosol talc administered intrapleurally by thoracoscopy for human use (§ 2.125(e)(4)(ix)) and for metered-dose atropine sulfate aerosol human drugs administered by oral inhalation (§ 2.125(e)(4)(vi)).

There is currently one sterile aerosol talc product containing ODSs that is approved for administration intrapleurally by thoracoscopy for human use for the treatment of recurrent malignant pleural effusion in symptomatic patients. Section 2.125(g) sets forth standards for determining whether the use of an ODS in a medical product is no longer essential. Under § 2.125(g)(3), an essential-use designation for individual active moieties marketed as ODS products and represented by one new drug application may no longer be essential if:

- At least one non-ODS product with the same active moiety is marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the ODS product containing that active moiety;
- Supplies and production capacity for the non-ODS product(s) exist or will exist at levels

sufficient to meet patient need;

- Adequate U.S. postmarketing-use data are available for the non-ODS product(s); and
- Patients who medically require the ODS product are adequately served by the non-ODS product(s) containing that active moiety and other available products (§ 2.125(g)(3)).

On June 29, 2015, FDA published a notice and request for comment concerning its tentative conclusion that sterile aerosol talc administered intrapleurally by thoracoscopy for human use no longer constitutes an essential use under the Clean Air Act under the criteria in (§ 2.125(g)(3)). FDA requested comment on its findings that sterile aerosol talc is currently marketed for intrapleural administration in two non-ODS formulations and on its finding that the route of administration, indications, and level of convenience appear to be the same for the ODS and non-ODS formulations of sterile aerosol talc. FDA also requested comment on its finding that the non-ODS products are available in sufficient quantities to serve the current patient population. FDA received no comments on these findings or on its tentative conclusion that sterile aerosol talc administered intrapleurally by thoracoscopy for human use no longer constitutes an essential use of ODSs under the Clean Air Act.

In the same document published on June 29, 2015, FDA requested comments concerning its tentative conclusion that metered-dose atropine sulfate aerosol human drugs administered by oral inhalation no longer constitute an essential use under the Clean Air Act under the criteria in (§ 2.125(g)(1)). FDA requested comment concerning its finding that metered-dose atropine sulfate aerosol human drugs administered by oral inhalation are no longer marketed in an approved ODS formulation. Under § 2.125(g)(1), an active moiety may no longer constitute an essential use (§ 2.125(e)) if it is no longer marketed in an approved ODS formulation. The failure to market indicates nonessentiality because the absence of a demand sufficient for even

one company to market the product is highly indicative that the use is not essential. FDA received no comments concerning its finding that metered-dose atropine sulfate aerosol human drugs administered by oral inhalation are no longer marketed in an ODS formulation or concerning its tentative conclusion that these drugs no longer constitute an essential use of ODSs under the Clean Air Act.

Accordingly, FDA is proposing to amend its regulation to remove sterile aerosol talc administered intrapleurally by thoracoscopy for human use (§ 2.125(e)(4)(ix)) and to remove metered-dose atropine sulfate aerosol human drugs administered by oral inhalation (§ 2.125(e)(4)(vi)) as essential uses under the Clean Air Act.

II. Companion Rule To Direct Final Rulemaking

This proposed rule is a companion document to the direct final rule published elsewhere in this issue of the Federal Register. FDA is proposing to amend § 2.125 to remove essential-use designations for sterile aerosol talc administered intrapleurally by thoracoscopy for human use and for metered-dose atropine sulfate aerosol human drugs administered by oral inhalation. This proposed rule is intended to make noncontroversial changes to existing regulations. The Agency does not anticipate receiving any significant adverse comment on this rule.

Consistent with FDA's procedures on direct final rulemaking, we are publishing elsewhere in this issue of the Federal Register a companion direct final rule. The direct final rule and this companion proposed rule are substantively identical. This companion proposed rule provides the procedural framework within which the proposed rule may be finalized in the event the direct final rule is withdrawn because of any significant adverse comment. The comment period for this proposed rule runs concurrently with the comment period of the companion direct final rule. Any comments received in response to the companion direct final rule will also be

considered as comments regarding this proposed rule.

FDA is providing a comment period for the proposed rule of 60 days after the date of publication in the Federal Register. If we receive a significant adverse comment, we intend to withdraw the direct final rule before its effective date by publishing a notice in the Federal Register within 30 days after the comment period ends. A significant adverse comment explains why the rule either would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. In determining whether an adverse comment is significant and warrants withdrawing a direct final rule, the Agency will consider whether the comment raises an issue serious enough to warrant a substantive response in a notice-and-comment process in accordance with section 553 of the Administrative Procedure Act (5 U.S.C. 553).

Comments that are frivolous, insubstantial, or outside the scope of the proposed rule will not be considered significant or adverse under this procedure. For example, a comment recommending a regulation change in addition to the changes in the proposed rule would not be considered a significant adverse comment unless the comment states why the proposed rule would be ineffective without the additional change. In addition, if a significant adverse comment applies to an amendment, paragraph, or section of this proposed rule and that provision can be severed from the remainder of the rule, FDA may adopt as final the provisions of the proposed rule that are not the subject of a significant adverse comment.

If FDA does not receive any significant adverse comment in response to the proposed rule, the Agency will publish a document in the Federal Register confirming the effective date of the direct final rule. The Agency intends to make the direct final rule effective 30 days after publication of the confirmation document in the Federal Register.

A full description of FDA's policy on direct final rule procedures may be found in a guidance for FDA and industry entitled "Direct Final Rule Procedures" (available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125166.htm>) that was announced in the Federal Register on November 21, 1997 (62 FR 62466).

III. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. We propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to 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 \$146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Need for the Regulation

This rule is necessary to comply with the Montreal Protocol under authority of Title VI of the Clean Air Act (section 601 et seq.), which banned the manufacture of ODSs, including CFCs, to reduce the depletion of the ozone layer in the United States as of January 1, 1996. EPA regulations exempted from the ban medical devices, diagnostic products, drugs, and drug delivery systems that FDA considered essential and that are listed in § 2.125(e) when they use a class I or class II ODS for which no safe and effective alternative has been developed. The proposed rule would remove the exemptions for sterile aerosol talc products and for metered-dose atropine sulfate aerosol human drugs containing ODSs.

There is currently at least one sterile aerosol talc product not containing ODSs approved for administration intrapleurally by thoracoscopy for human use that is a safe and effective alternative, and which meets the criteria outlined in § 2.125(g)(3). Accordingly, the sterile aerosol talc product containing ODSs no longer meets the requirements for essential use and should no longer be exempted from the ban.

Metered-dose atropine sulfate aerosol human drugs administered by oral inhalation are no longer available in the product market in an approved ODS formulation. The current absence of the product in the market indicates both a lack of demand for the product and that the product is nonessential, under § 2.125(g)(1). With the adoption of this rule, the manufacturer of the sterile aerosol talc with ODSs and any potential future manufacturers of metered-dose atropine sulfate

aerosols will have notice of the requirement to comply with the ban of products from containing ODSs.

C. Costs and Benefits

1. Number of Affected Entities

The affected entities covered by this rule are the manufacturing facilities of the products that would have exemptions from the ban removed. Only one manufacturer, the Bryan Corporation that manufactures the sterile aerosol talc product containing ODSs at a single facility, would be affected. Currently, there are no manufacturers of metered-dose atropine sulfate aerosols.

2. Costs

The potential social costs from removing the exemptions are (1) the costs to patient consumers or to their insurers for paying a higher price for alternative non-ODS formulations of sterile aerosol talc products and (2) the costs for disposing of and destroying any remaining product inventory that remains after the effective date of the final rule. We lack data about the stocks of product inventory that are likely to remain after the effective date of the final rule and the relative price that consumers or their insurers would pay. Because significant notice has been given to the manufacturer about the impending removal of the exemptions, we do not believe a significant stock of inventory will remain for the sterile aerosol talc product. The most recent publicly available information shows that the annual revenues for Bryan Corporation are about \$10 million (Ref. 1). Public information about this company shows that it manufactures three different surgical and medical instruments including the talc. If total profits for the exempt talc product are 10 percent of the total annual revenues, and if total revenues are exclusively from the exempt talc, then \$1 million represents an upper bound for the total social cost of removing the

sterile aerosol talc product from the market. Because it is unlikely that the company's total profits are exclusively from the sterile aerosol talc, it is more likely that the foregone profits are at most one-third of the \$1 million; in fact, the true social cost could be significantly less than the total foregone profit of this product.

Metered-dose atropine sulfate aerosol human drugs that would be affected by this rule are no longer marketed; consequently, removal of the exemption for these products would not present the public, consumers, insurers, or producers with any costs.

3. Health Benefits

The proposed rule would implement the requirements of the Clean Air Act that ban the use of products containing ODSs that no longer meet the requirements for essential use. The social benefits of the proposed rule derive from greater compliance with the Clean Air Act. The ODSs that either would have been emitted by sterile aerosol talcs that contain them, or from potential market entrants that would have manufactured metered-dose atropine sulfate aerosols that contain ODSs will no longer be emitting them, which will help reduce the depletion of the ozone layer and the ultraviolet radiation reaching the Earth. We lack the ability to quantify the health benefits from the reduced exposure to and from the reduced risk associated with ultraviolet light that result from removing the exemptions to the ban. Because the change in exposure and resulting risk from the proposed rule is likely to be small, the incremental health impact is likely to be too small to measure.

D. Economic Summary

The proposed rule, if finalized, will remove the exemptions for sterile aerosol talc products and for metered-dose atropine sulfate aerosol human drugs containing ODSs. The primary public health benefit from adoption of the proposed rule is to reduce the depletion of the

ozone layer to decrease human exposure to ultraviolet radiation. The reduction in exposure to ultraviolet radiation because of the rule is likely to be too small to measure. The potential social costs of the proposed rule would occur if patient consumers or their health care insurers would have to pay more for otherwise comparable products and if the product manufacturers would have to safely destroy any remaining product inventories after the effective date of the rule. We estimate that the social cost of the proposed rule is likely to be significantly less than \$1 million but no more than the upper-bound estimate of the foregone annual profit of the company that manufactures the sterile aerosol talc or \$1 million. Because the metered-dose atropine sulfate aerosol is not currently in the market, there would be no social cost for removing its exemption from the ban.

Imposing no new federal requirement is the baseline for a regulatory analysis. With no new regulation, there are no compliance costs or benefits to the proposed rule. However, because sterile aerosol talc is no longer an essential use of ODSs, under the Clean Air Act, there is no longer a pathway for sterile aerosol talc products containing ODSs to remain on the market.

IV. Regulatory Flexibility Analysis

FDA has examined the economic implications of the proposed rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires Agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. We certify that the final rule will not have a significant economic impact on a substantial number of small entities. This analysis, together with other relevant sections of this document, serves as the proposed regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

V. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1995

FDA tentatively concludes 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.

VII. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed 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, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VIII. References

The following reference is on display in the Division of Dockets Management (see ADDRESSES) and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at <http://www.regulations.gov>. FDA has verified the Web site address, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. Bryan Corporation (<http://listings.findthecompany.com/1/12165972/Bryan-Corporation-in-Woburn-MA>, accessed on February 24, 2016).

List of Subjects in 21 CFR Part 2

Administrative practice and procedure, Cosmetics, Drugs, Foods.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR part 2 be amended as follows:

PART 2--GENERAL ADMINISTRATIVE RULINGS AND DECISIONS

1. The authority citation for 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 paragraphs (e)(4)(vi) and (ix)..

Dated: October 20, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016-25850 Filed: 10/25/2016 8:45 am; Publication Date: 10/26/2016]