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4164-01-P

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 exemption for anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application. FDA is proposing this action because these products are no longer being marketed in approved versions that contain ODSs and because alternative products that do not use ODSs are now available.

DATES: Submit either electronic or written comments on the proposed rule by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER)].

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 dockets, 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).

Firms that wished 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) (21 CFR 2.125(e)). Section 601(8) of the Clean Air Act defines "medical device" as any device (as defined in the Federal Food, Drug & 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).

A drug, device, cosmetic, or food contained in an aerosol product or other pressurized dispenser that releases a CFC or other ODS propellant generally is not considered an essential use of the ODS under the Clean Air Act except as provided in § 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.) Sections 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.

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 ODSs means that certain drug products listed in § 2.125(e) are no longer essential uses of ODSs. Therefore, due to lack of marketing of an approved product containing an ODS, and the availability of alternative products that do not contain an ODS, FDA is proposing to amend its regulations to remove the essential-use designation for anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application (§ 2.125(e)(4)(iii)).

On June 29, 2015, FDA published a notice and request for comment concerning its tentative conclusion that anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application no longer constitute an essential use under the Clean Air Act (June 2015 notice). FDA requested comment concerning its tentative finding that anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application are no longer being sold 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.

II. Comment on the June 2015 Notice and FDA Response

FDA received one comment concerning its tentative finding that anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application are no longer marketed in an approved ODS formulation and, therefore, no longer constitute an essential use (see June 2015 notice). On August 21, 2015, Cetylite Industries, Inc. (Cetylite) submitted a comment stating that "FDA's belief that no products are marketed under this exemption is incorrect" (Comment 1). According to the comment, Cetylite manufactures Cetacaine Spray (CETACAINE), a topical anesthetic spray with an active ingredient combination of benzocaine, tetracaine HCl, and butamben that uses a blend of CFCs as the propellant under the essential-use exemption found in § 2.125(e)(4)(iii). However, CETACAINE is not an approved drug product and does not qualify as an essential use under § 2.125(e)(4)(iii). As described in § 2.125(c), an aerosol drug product or other pressurized dispenser that releases an ODS is an essential use of the ODS under the Clean Air Act only if it is listed in § 2.125(e) and if an investigational application or an approved marketing application is in effect.

Cetylite states that CETACAINE has been marketed continuously since the mid-1950s under a request for a Drug Efficacy Study Implementation (DESI) review that was submitted in 1976. FDA published a DESI notice (DESI 8076 (Docket No. 75N-0203) in the Federal Register of December 9, 1975 (40 FR 57379)) in which the Agency offered an opportunity for a hearing on a proposal to withdraw approval of a combination drug product containing two of the three ingredients contained in CETACAINE. In response to this DESI notice, Cetylite requested a hearing regarding the effectiveness of CETACAINE. While FDA's review of the product's effectiveness has been pending, Cetylite has been marketing CETACAINE without an approved new drug application.

In 1979, based on a citizen petition submitted by Cetylite regarding its CETACAINE product, FDA proposed that anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application were essential uses of ODSs (44 FR 33114, June 8, 1979) (1979 Proposed Rule). In the preamble to the 1979 Proposed Rule, FDA noted that its tentative finding as to CETACAINE's essentiality under § 2.125 was "conditional" on the product being found effective. Similarly, in the preamble to the Final Rule amending § 2.125, FDA stated that "the determination in this document that CETACAINE Aerosol is an essential use of a chlorofluorocarbon is also conditional" on a finding that CETACAINE is effective for the use described in § 2.125(e)(4)(iii) (45 FR 22902, April 4, 1980).

To date, FDA has not made a finding that CETACAINE is effective for the use described in § 2.125(e)(4)(iii). There is no investigational new drug application or approved marketing application in effect for the ODS formulation of CETACAINE, as required for a finding of essentiality under § 2.125(c). Accordingly, CETACAINE does not meet the conditions to qualify as an essential use of ODSs under § 2.125(e)(4)(iii), and FDA believes that its proposed finding that anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application are no longer marketed in an approved ODS formulation remains correct. Moreover, alternative products for the same use that do not use ODSs, such as lidocaine, are now available, further suggesting that anesthetic drugs for topical use are no longer an essential use of ODSs. In addition, a recently completed laboratory study demonstrated that lidocaine may be a safer alternative to benzocaine (Ref. 1). The study found that benzocaine was substantially more likely than lidocaine to form methemoglobin, the cause of the serious blood disorder called methemoglobinemia.

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 Agencies 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.

Anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application are not available in the product market in an approved ODS formulation. Because the product is not marketed under an investigational new drug (IND), new drug application (NDA), or abbreviated new drug application (ANDA) and alternative products for the same use that do not use ODSs, such as lidocaine, are now available, the product is nonessential under § 2.125(g)(1). With the adoption of this rule, any potential manufacturers of these anesthetic drugs will have notice about their requirements to comply with the ban of products from containing ODSs.

C. Costs and Benefits

1. Number of Affected Entities

There are no affected entities covered by this rule because there are no current manufacturers of approved products that would qualify as "essential" products under the current regulation.

2. Costs

ODS-containing anesthetic products for topical use on accessible mucous membranes of humans where a cannula is used for application are not marketed under an IND, NDA, or ANDA and would not qualify as "essential" products under the current regulation; consequently,

removal of the exemption for such drugs 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 benefits stem from preventing the ODSs that would have been emitted by potential market entrants. The social benefits of the proposed rule derive from greater compliance with the Clean Air Act. Because there will not be any change in exposure and any resulting risk from the proposed rule, there will not be any direct public health benefits.

D. Economic Summary

The proposed rule, if finalized, will remove the essential-use exemption for anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application. 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. Because anesthetic drugs for topical use are not currently sold in the market in an approved form, there would be no health benefit or social cost for removing the exemption for such products from the ban.

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 propose to certify that this proposed 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.

V. Analysis of Environmental Impacts

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. Reference

The following reference is on display in the Division of Dockets Management (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it are also available electronically at http://www.regulations.gov.

1. Hartman, N. R., J. J. Mao, H. Zhou, et al., "More Methemoglobin is Produced by Benzocaine Treatment Than Lidocaine Treatment in Human In Vitro Systems." Regulatory Toxicology and Pharmacology, 70:182-188, 2014.

List of Subjects

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 paragraph (e)(4)(iii).

Dated: October 20, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016-25852 Filed: 10/25/2016 8:45 am; Publication Date: 10/26/2016]