PMB

Display Date 8-30-99
Publication Date 9-1-99
Certifier M. Bell

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 2

[Docket No. 97N–0023]

RIN 0910–AA99

Use of Ozone-Depleting Substances; Essential Use Determinations

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulation on the use of chlorofluorocarbon (CFC) propellants in self-pressurized containers to make it consistent with other laws. FDA is proposing to set the standard it will use to determine when the use of an ozone-depleting substance (ODS) in a product regulated by FDA is essential under the Clean Air Act. Under the Clean Air Act, FDA, in consultation with the Environmental Protection Agency (EPA), is required to determine whether the use of an ODS in an FDA-regulated product is essential. FDA is also proposing in this rule to remove current essential-use designations for products no longer marketed and for metered-dose steroid human drugs for nasal inhalation. FDA would add or remove specific essential use designations for other products by engaging in separate notice-and-comment rulemaking.

DATES: Written comments on the proposed rule should be submitted by (*insert date 90 days after date of publication in the* **Federal Register**). See section V of this document for the proposed effective date of a final rule based on this document.

NPR2

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. See section III.B.15 of this document for electronic access addresses.

FOR FURTHER INFORMATION CONTACT: Leanne Cusumano, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

The United States, as a party to an international agreement called 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)), has agreed to phase out production and importation of ODS's, including CFC's. The United States has generally banned the use of CFC's in consumer aerosols for decades and eliminated almost all manufacture and importation of CFC's as of January 1, 1996. The Montreal Protocol permits Parties to the Protocol to continue to produce or import CFC's for use in essential medical products upon approval by the Parties.

FDA, in consultation with EPA, determines whether a medical product is essential under the Clean Air Act. FDA lists essential medical products in § 2.125 (21 CFR 2.125). Most of the medical products listed as essential are metered-dose inhalers (MDI's). FDA will continue to designate ODS medical products such as MDI's as essential until non-ODS medical products adequately serve the needs of patients. The United States, through EPA, must apply annually to the Parties to the Montreal Protocol for a specific CFC production or importation allowance for CFC–MDI's that FDA has designated as essential. However, the United States has agreed to eventually phase

out all uses of CFC's. FDA is developing a strategy to ensure that the health and safety of patients in the United States are protected during the transition away from CFC use in medical products.

In the **Federal Register** of March 6, 1997 (62 FR 10242), FDA published an advanced notice of proposed rulemaking (ANPRM) that sought public comment on transition options. One approach that FDA suggested was that ODS products be considered nonessential if: (1) Alternative product(s) is (are) being marketed (a) with the same active moiety, (b) by the same route of administration, (c) for the same indication, and (d) with approximately the same level of convenience of use compared to the product containing CFC's; (2) adequate supplies and production capacity exist for the alternative products to meet the needs of the population; (3) at least 1 year of postmarketing use data for each product are available and persuasive evidence shows patient acceptance of the alternative product(s) in the United States; and (4) there is no persuasive evidence to rebut a presumption that all significant patient subpopulations are served by the alternative product(s). FDA received almost 10,000 comments on the ANPRM, and addresses those comments later in this proposed rule.

II. Description of the Proposed Rule

FDA is proposing to make the following changes to § 2.125: (1) Use the phrase ''ozone-depleting substance'' instead of the word ''chlorofluorocarbon'' in the title and text of the regulation; (2) eliminate current § 2.125(b) because it is explanatory material that has no regulatory effect; (3) in current § 2.125(c), define the products that are subject to § 2.125 as any food, drug, device, or cosmetic that is, consists in part of, or is contained in, an aerosol product or other pressurized dispenser that releases an ODS, rather than limiting the definition to those products that use CFC's as a propellant; (4) change the designation of ODS products not listed in § 2.125(e) from adulterated and misbranded to nonessential; (5) list as separate essential uses each active moiety marketed under the current essential uses for metered-dose steroid human drugs for oral inhalation and metered-dose adrenergic bronchodilator human drugs for oral inhalation; (6) eliminate the essential-use designation in current § 2.125(e) for metered-dose steroid human drugs

for nasal inhalation; (7) eliminate the essential-use designations in current § 2.125(e) for products that are no longer marketed; (8) set the standard to determine when a new essential-use designation should be added to § 2.125; (9) eliminate outdated transitional provisions in current § 2.125(g), (h), (i), (j), (k), and (l); and (10) set standards to determine whether the use of an ODS in a medical product remains essential.

A. Major Changes From the ANPRM

This proposed rule contains many changes from the ANPRM. FDA is proposing these changes in response to comments received and as the agency's thinking on the issue evolved. This document discusses in detail the changes and the reasons for the changes. FDA is highlighting the following major components here to allow for a clearer understanding of the proposed rule:

1. The agency is not proposing to use a therapeutic class approach as discussed in the ANPRM. FDA proposes to use a moiety-by-moiety approach to determine whether the use of an ODS in a medical product remains essential. An active moiety is the part of a drug that makes the drug work the way it does. Many different drug products may be marketed with the same active moiety.

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."[1]

---

[1] For purposes of this proposed rule, an essential use for an active moiety would cover all enantiomers of molecules containing the active moiety, as well as racemic and nonracemic mixtures of those enantiomers. In cases where an enantiomer has substantial clinical differences from the racemate, a petition could be submitted under proposed § 2.125(f) to list the use of the enantiomer as a new essential use.

Stereoisomers are molecules that have the same constitution (i.e., molecular formula and chemical connectivity), but differ in the spatial orientation of the atoms. When two stereoisomers are mirror images, but are not superimposable upon each other (like left and right hands), they are referred to as enantiomers. Enantiomeric

2. FDA is proposing to require more than one acceptable non-ODS alternative per an active moiety to be marketed before FDA would consider removing an essential use designation for the same active moiety if that active moiety is represented by multiple products or multiple strengths.

3. FDA had planned to publish a separate proposed rule to reorganize and update § 2.125 and to change the criteria for adding new essential use listings. FDA has decided not to publish a separate proposed rule. FDA combined the proposals into this proposed rule to prevent confusion and to present all proposed revisions to § 2.125 in the same proposed rule.

B. ''Ozone–Depleting Substance'' Versus ''Chlorofluorocarbon''

FDA is proposing to use the term ''ozone-depleting substance'' instead of the word ''chlorofluorocarbon'' in § 2.125. The use of the term ''ozone-depleting substance'' would bring § 2.125 into conformity with other Federal laws governing ODS's. The term would be defined by cross-reference to the list of substances subject to control under the Clean Air Act (40 CFR part 82, subpart A, appendices A and B). The Clean Air Act contains comprehensive lists of chemical substances considered by EPA to be ozone-depleting. CFC's are only one of the many ODS's listed by EPA. If the change from the term CFC to ODS does bring additional products within the scope of § 2.125, manufacturers of those products must seek an essential-use exemption under § 2.125 in compliance with the Clean Air Act. However, FDA believes the only ODS's released by FDA-regulated products are the CFC's released by drug products already listed in § 2.125(e). Accordingly, the agency does not believe that this change will have any substantive effect on FDA regulated products in use today.

---

molecules are identical in all physical and chemical properties, except in an environment that is also chiral (characterized by handedness). Polarized light is such an environment, and pairs of enantiomers rotate the plane of polarization by equal amounts in opposite directions. Enantiomers may be either right-handed (dextro-rotary) S(+)-isomers or left-handed (levo-rotary) R(-)-isomers. Racemates are equimolar mixtures of enantiomers of the same molecule. See 62 FR 2167, January 15, 1997, for additional explanation.

C. Elimination of Current § 2.125(b)

The agency is proposing to eliminate current § 2.125(b), which describes the effects of CFC's on the atmosphere. This explanatory material has no regulatory effect.

D. Removal of the Term "Propellant"

FDA is proposing to eliminate the definition of propellant under current § 2.125(a) because the word is not used in the proposed regulation. The agency is proposing to define the products that are subject to § 2.125 as any food, drug, device, or cosmetic that is, consists in part of, or is contained in, an aerosol product or other pressurized dispenser that releases an ODS, rather than limiting the application of § 2.125 to the use of a CFC as a propellant in a self-pressurized container. This definition is intended to encompass all products that are regulated by FDA.

E. Change to Essentiality Determinations

FDA proposes to change the adulterated and misbranded provisions of current § 2.125(c). Current § 2.125(c) states that any CFC product not found in § 2.125(e) is adulterated and/or misbranded in violation of the Federal Food, Drug, and Cosmetic Act (the act). FDA is proposing to make § 2.125 correspond with its authority under the Clean Air Act to determine whether an ODS product is essential. FDA notes that EPA is responsible for enforcing the provisions of the Clean Air Act. However, FDA is not stating by its removal of the adulterated and/or misbranded provision from § 2.125 that a nonessential ODS product is not adulterated or misbranded. Such products are still adulterated and misbranded under the act.

Current § 2.125(c) will become § 2.125(b) once current § 2.125(b) is eliminated.

F. Listing of Active Moieties

FDA is proposing to reorganize the list of essential uses for metered-dose steroid human drugs for oral inhalation (current § 2.125(e)(2))[2] and metered-dose adrenergic bronchodilator human drugs for oral inhalation (current § 2.125(e)(3)). FDA is proposing to list separately each currently marketed active moiety designated as essential in proposed § 2.125(e)(1) and (e)(2). This reorganization would not change the essential-use listings substantively. Any person wishing to market a product not listed in § 2.125 that uses an ODS would need to petition the agency under proposed § 2.125(f) to have the use of the active moiety added to § 2.125.

G. Metered–Dose Steroid Human Drugs for Nasal Inhalation

FDA is proposing to remove the essential-use designation in current § 2.125(e)(1) for metered-dose steroid human drugs for nasal inhalation. FDA bases this proposal on the following: (1) Adequate alternative non-ODS products for steroid human drugs for nasal inhalation are currently available, including metering atomizing pumps for administering nasal corticosteroids, other nonsteroidal nasal topical therapies, and systemic therapies; (2) patients use the alternative products on a widespread basis; and (3) these alternative products have been and continue to be produced and supplied at sufficient levels to meet patient needs. FDA notes that, unlike other ODS medical products currently being marketed, the diseases for which these products are indicated are not life threatening and the Parties to the Montreal Protocol no longer grant essential-use allocations for nasal steroids. FDA also notes that only the three active moieties beclomethasone, budesonide, and triamcinolone are marketed as CFC-nasal steroids. Beclomethasone and triamcinolone are also marketed in non-CFC formulations.

[2] FDA proposes to use the term corticosteroids rather than the general term steroids to describe the marketed metered-dose steroid human drugs for nasal and oral inhalation.

H. Products No Longer Marketed

FDA proposes to remove the essential-use designations listed in current § 2.125(e)(4), (e)(6), (e)(7), and (e)(9), respectively, for the following no longer marketed ODS products: (1) Contraceptive vaginal foams for human use; (2) intrarectal hydrocortisone acetate for human use; (3) polymyxin B sulfate-bacitracin zinc-neomycin sulfate soluble antibiotic powder without excipients, for use on humans; and (4) metered-dose nitroglycerin human drugs administered to the oral cavity. These drug products are either no longer being marketed or are no longer being marketed in a formulation containing CFC's (see section II.K of this document).

I. Petitions to Add New Essential Uses

FDA believes that it would be inappropriate to add new essential uses to § 2.125 in all but the most extraordinary circumstances because of the relatively near-term phaseout of the production and importation of ODS's.

FDA is proposing to require compelling evidence in support of a petition for a new essential use. For purposes of this proposed rule, compelling evidence is evidence sufficient to establish with reasonable scientific certainty the truth of the matter asserted. The evidence should be detailed and capable of scientific analysis and discussion. Unsupported, conclusory statements are not compelling evidence. Because the Clean Air Act mandates an opportunity for public comment before FDA makes a determination of essential use, a petitioner must disclose all relevant information in a petition filed under proposed § 2.125. Such information will become publicly available.

1. Commercially Marketed Drugs

FDA is proposing to limit initiation of rulemaking to establish a new essential use for those noninvestigational products for which compelling evidence shows: (1) Substantial technical barriers exist to formulating the product without ODS's; (2) the product will provide an unavailable important public health benefit; and (3) use of the product does not release cumulatively significant

amounts of ODS into the atmosphere or the release is warranted in view of the unavailable important public health benefit.

This new standard would apply to all requests for essential-use exemptions submitted after the effective date of the final rule.

2. Investigational New Drugs

FDA is proposing to amend § 2.125 to remove paragraphs (i) and (j) and to revise paragraph (f) to provide a process for adding investigational uses to § 2.125(e). FDA would permit investigational use of an ODS medical product if compelling evidence shows: (1) Substantial technical barriers exist to formulating the investigational product without ODS's; (2) a high probability that the investigational product will provide an unavailable important public health benefit; and (3) use of the investigational product does not release cumulatively significant amounts of ODS into the atmosphere or the release is warranted in view of the high probability that the investigational product will provide an unavailable important public health benefit.

Although FDA regulations at current § 2.125(j) allow an investigational drug product sponsor to collect data to demonstrate that a CFC use is essential upon a lesser showing than that required under current § 2.125(f),[3] the sponsor is not permitted by EPA regulations to obtain CFC's until

---

[3] Under current § 2.125(j), a sponsor may use a CFC product under an investigational new drug application (IND) if the sponsor explains why a CFC propellant is used in the product rather than another propellant or another dosage form, the benefit the investigational product is believed to have, and the benefit the sponsor hopes to demonstrate by the studies.

Under current § 2.125(f), a sponsor cannot market a CFC product unless the sponsor demonstrates that there are no technically feasible alternatives to the use of a CFC in the product; that the product provides a substantial health benefit, environmental benefit, or other public benefit that would not be obtainable without the use of the CFC; and that the use does not involve a significant release of CFC's into the atmosphere or that the release is warranted in view of the consequence if the use were not permitted.

the sponsor's proposed use is listed in § 2.125(e). This has prevented any investigational new drug use from being added to current § 2.125(e) as an essential use.

FDA would decide whether an investigational use should be added to § 2.125(e) in response to a citizen petition submitted under § 10.30 (21 CFR 10.30) and after notice-and-comment rulemaking. If FDA amended proposed § 2.125(e)(4) to include an investigational use, that determination would not allow commercial manufacture and marketing of an ODS product. A sponsor would need to file a separate petition under § 2.125(f)(1) to provide for a new essential-use determination for commercial marketing of the ODS product.

3. Evidence to Support New Essential Uses for Investigational and Noninvestigational Products

First, the petitioner must demonstrate through compelling evidence that substantial technical barriers exist to formulating the product without ODS's. 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 deemed to be unusable to demonstrate that substantial technical barriers exist. Alternative technologies not suitable for use by general patient populations may be suitable for use in a clinical investigation due to the increased medical supervision provided and the limited use of the investigational new drug (see FDA Response to Biovail Citizen Petition, Docket No. 95P–0045). Also, if a petitioner shows that the cost of using a non-ODS in a product is prohibitively high in comparison to the cost of using an ODS, the agency might consider cost as a technical barrier.

Second, the petitioner for a new essential use for a noninvestigational product must include in their petition compelling evidence of an unavailable important public health benefit. For investigational products, FDA proposes requiring a petitioner to provide compelling evidence that there is a high probability that the investigational product will provide an unavailable important public health benefit. ''High probability'' means that it is substantially more likely than not that the investigational product will provide an unavailable important public health benefit.

The agency intends to give the phrase ''unavailable important public health benefit'' a markedly different construction from the current phrase ''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. A petitioner should also show that patients cannot access non-ODS products and that no technology is readily available to produce and distribute non-ODS products. In unusual cases, FDA might accept a showing of nonclinical health benefit, such as the safety of the health care practitioner using the product.

Third, the proposed new criteria require a showing supported by compelling evidence that the use of the product does not release significant amounts of ODS into the atmosphere or that the release is warranted in view of the important public health benefit.[4] A petitioner should submit a well-documented statement of the number of products to be manufactured and the amount of ODS to be released by each product.

J. Elimination of Outdated Transitional Provisions

FDA is proposing to eliminate § 2.125(h). Section 2.125(h)(1) is an out-of-date transition provision requiring the submission of new drug applications (NDA's) for products without an NDA but covered under § 2.125. Section 2.125(h)(2) describes which drug products may be the subject of an abbreviated new drug application (ANDA). This provision predates passage of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) (the Hatch-Waxman Amendments). The Hatch-Waxman Amendments and regulations implementing the Hatch-Waxman Amendments govern the generic drug approval process and have rendered § 2.125(h)(2) out of date. FDA is proposing to eliminate § 2.125(g), (k), and (l) because they are also transition provisions.

---

[4] The petitioner must show only a high probability of an important public health benefit for an investigational product.

Section 2.125(d) is reserved in this proposal so that proposed § 2.125(e) will correspond to current § 2.125(e), which is cross-referenced in 40 CFR 82.66.

K. Determinations of Continued Essentiality

In § 2.125(g), FDA proposes criteria to determine whether an essential-use designation should be removed from § 2.125(e).

Under proposed § 2.125(g)(1), FDA would propose to remove an active moiety from the essential-use list (§ 2.125(e)) if it were no longer marketed in an ODS formulation. FDA believes failure to market indicates nonessentiality because the absence of a demand for the product sufficient for even one company to market it is highly indicative that the use is not essential.

Under the proposed second criterion, after January 1, 2005, FDA could find a CFC product containing a particular active moiety nonessential if the product no longer met the essential-use criteria (§ 2.125(f)). Even if all current essential-use moieties are not reformulated, sufficient alternative products may exist in the future to fully meet the needs of patients. FDA would designate any remaining CFC products as nonessential. FDA would consult with an advisory committee and provide the opportunity for public comment before making such a determination.

Under proposed § 2.125(g)(3) and (g)(4), an ODS product would remain essential until: (1) A non-ODS product(s) with the same active moiety is(are) marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use; (2) supplies and production capacity for the alternative(s) exist or would exist at levels sufficient to meet patient need; (3) at least 1 year of U.S. postmarketing data exist; and (4) patients who medically require the ODS product are adequately served by available alternatives.

In addition, under § 2.125(g)(4), an active moiety containing ODS that is marketed under more than one NDA or marketed in multiple strengths would not be removed from the essential-use list unless at least two non-ODS products with the same active moiety were marketed. FDA anticipates that ODS products of the same active moiety marketed in distinct strengths will need to be replaced by non-ODS products of the same active moiety with more than one strength.

In evaluating indications, FDA will require a non-ODS alternative to have a broader indication or (an) identical indication(s) to that of the ODS product containing the active moiety to be removed from the list of essential uses, except for minor wording changes that do not materially change the meaning of the indication.[5]

In evaluating whether an alternative has approximately the same level of convenience of use, FDA will consider whether the product has approximately the same or better portability and requires approximately the same amount of or less preparation before use as the ODS product containing the same active moiety. FDA is aware that the MDI is the most widely used delivery system for administering drugs by oral inhalation for the treatment of asthma, chronic obstructive pulmonary disease (COPD), and other respiratory diseases. Physicians and patients value the compact size and ease of use of MDI's. At present, FDA considers non-ODS MDI's and multiple-dose dry powder inhalers (DPI's) to have approximately the same level of convenience of use as MDI's.[6] FDA does not consider single-dose DPI's currently marketed in the United States to have the same level of convenience of use as CFC–MDI's because patients must carry the device and a supply of the drug and must load the device prior to each use. Manufacturers may develop additional products that FDA will evaluate on a case-by-case basis to determine whether the products have approximately the same level of convenience of use as MDI's.

In evaluating whether supplies and production capacity for the non-ODS product(s) exist or will exist at levels sufficient to meet patient need, FDA will consider whether a manufacturer of a non-ODS alternative is able to manufacture the non-ODS alternative in sufficient quantities to satisfy patient demand once the ODS product containing the same active moiety is no longer marketed. FDA expects that the non-ODS product will be manufactured at multiple manufacturing

---

[5] For example, the non-ODS product could be indicated for treatment of asthma and chronic obstructive pulmonary disease (COPD), whereas the ODS product might only be indicated for asthma.

[6] Although multiple-dose DPI's may offer a similar level of convenience of use, FDA is not at this time proposing that they meet the other criteria in § 2.125(g) necessary to qualify as acceptable alternatives.

sites if the ODS product was manufactured at multiple manufacturing sites. FDA will always work to ensure that no harm to the public health of the United States occurs because of drug product shortages during the transition to non-ODS products.

In evaluating postmarketing data, FDA will look at a composite of all available information. FDA expects to see data showing the acceptance of a non-ODS product in widespread use outside of controlled trials and in subgroups not represented adequately in the clinical trials that served as the basis for marketing approval. FDA will also look for information on device performance in uncontrolled settings, tolerability of products in widespread use, unusual adverse reactions not previously identified in premarketing studies, and effectiveness in broader patient populations.

FDA will evaluate whether patients who medically require the ODS product are adequately served by available alternatives by determining whether adequate safety, tolerability, effectiveness, and compliance exist for the indicated populations and other populations known to medically rely on the ODS product.

FDA will encourage sponsors to obtain postmarketing use data and to assess the safety, effectiveness, tolerability, and patient acceptance of possible alternatives in postmarketing clinical studies. In particular, FDA will encourage sponsors to seek data regarding patient subpopulations not fully represented in premarketing clinical trials. FDA will also evaluate data on acceptance, device performance, tolerability, adverse events, and effectiveness by using postmarketing studies and postmarketing use and surveillance data, including FDA's MEDWATCH data. Health professionals who monitor for and report serious adverse events and product problems to FDA either directly or through the manufacturer are integral to this process. MEDWATCH makes it easier for health professionals to report adverse events and product problems to FDA by operating a single system for reporting. The MEDWATCH program is supported by over 140 organizations, representing health professionals and industry, that have signed on as MEDWATCH Partners to help achieve these goals.

CDER's Office of Post-Marketing Drug Risk Assessment actively analyzes MEDWATCH data on adverse drug reaction reports from hospitals, health care providers and lay persons to identify Adverse Drug Reaction patterns that might indicate a public health problem (a ''signal''). FDA staff trained in the analysis of these data critically and individually review the reports of serious adverse events to detect serious unlabeled reactions. FDA staff epidemiologists and the relevant review division evaluate these signals for further action.

In addition, FDA will consider foreign data supportive of U.S. postmarketing use data if U.S. and foreign formulations, patient populations, and clinical practices were the same or substantially similar. FDA will monitor events related to the transition to non-ODS alternatives in other developed nations for any information relevant to the U.S. transition, including information regarding the safety, effectiveness, tolerabiltiy, performance, and patient acceptance of non-ODS alternative products.

In addition, the public will have the opportunity to comment on the acceptability of alternatives before FDA removes the essential use designation for any particular active moiety. FDA encourages health care professionals and patients to submit medically significant data based on actual use regarding the acceptability of alternatives and whether alternatives adequately serve patient subpopulations.

FDA will also consider whether a high-priced non-ODS product is effectively unavailable to a portion of the patient population because they cannot afford to buy the product.

III. Comments on the ANPRM

FDA received 9,596 comments on the ANPRM. FDA categorized the comments as general comments about the ANPRM and specific comments on the proposed criteria for phaseout. Unless otherwise noted, the comments address the criteria FDA proposed to use to determine when to eliminate the essential-use designations for metered-dose steroid human drugs for oral inhalation and metered-dose adrenergic bronchodilator human drugs for oral inhalation.

A. General Comments About the ANPRM

FDA received 8,979 general comments about the ANPRM. The general comments were submitted by 7,371 users of MDI's, 1,015 parents of MDI users, 847 relatives of MDI users, 417 health care professionals, 160 organizations, 3 industry members, 1 consultant, and 42 government entities. Many comments fell within multiple submitter categories.

1. Approximately 4,000 of these comments expressed general opposition to the phaseout of CFC–MDI's. The Clean Air Act requires the phaseout of CFC–MDI's, when they are no longer essential.

FDA is issuing this proposed rule as part of a transition process to ensure that the phaseout is safe for the users of MDI's. FDA expects CFC–MDI's to remain on the market until FDA determines under the criteria in this proposed rule that safe and effective alternatives exist.

2. More than 1,400 comments asked that the agency not remove MDI's until alternatives are available. Nearly 800 comments requested that the agency not remove any MDI's until alternatives exist for all CFC–MDI's.

The agency will not remove essential-use designations for MDI's until sufficient alternatives are available to serve the patients who require these CFC–MDI's. This was the intent of the ANPRM, and is the mandate under the Clean Air Act and the Montreal Protocol. However, the agency cannot require companies to produce a non-CFC product for every CFC–MDI currently marketed. Accordingly, the agency cannot guarantee that every CFC–MDI on the market today will be replaced by a non-CFC product containing the same active moiety. However, users of CFC–MDI's not replaced by non-CFC products with the same active moiety could use other non-CFC alternatives. Thus, there may be a time, even if all currently available CFC–MDI's are not replaced by non-CFC products with the same active moiety, that the use of CFC's in MDI's would no longer be essential. The public will have the opportunity to comment on all essential use designations and the removal of any designation.

3. Over 500 comments asked that the agency proceed cautiously.

The agency is proceeding with full caution. To obtain the largest possible number of public comments, the agency first published an ANPRM before proceeding with rulemaking. FDA is now in rulemaking, a process that includes publishing this proposed rule, receiving and incorporating further comments on the proposal, and issuing a final rule. As proposed, the final rule would not phase out any CFC–MDI for the treatment of COPD or asthma. Rather, the final rule will finalize the criteria by which FDA will determine whether to begin rulemaking to eliminate an essential use because of the existence of acceptable non-CFC alternative products. Any such rulemaking would provide to the public the opportunity for further comment.

4. Over 1,500 comments stated that there are problems switching between products, and about 600 comments requested a long transition period. About 1,000 comments stated that MDI's provide benefits unavailable with alternatives.

FDA is working to ensure that the patient's transition from CFC to non-CFC products is as easy as possible. The agency wants patients to have adequate time to find acceptable replacement products. In recognition of the fact that MDI's provide certain benefits not available with some current alternatives, the agency is proposing to require that an alternative have the same route of delivery, indication, and approximate level of convenience of use as a CFC–MDI.

5. More than 900 comments expressed concern about the cost of replacement products and the removal of generics.

As part of any subsequent proposed rule to eliminate an essential-use listing for a CFC–MDI, FDA will consider the cost of alternative products in determining whether patients are adequately served by the non-ODS products.

6. Approximately 890 comments did not discuss the ANPRM, 21 comments were indecipherable, 2 comments were abusive or insulting, and 1 comment was threatening.

FDA will not address these comments.

7. Numerous comments focused on the environmental impact of CFC use. About 1,700 comments stated that MDI's are responsible for minimal amounts of CFC's, 117 comments said

that there was no proof that CFC's harm the environment, 10 comments said they wanted MDI's to remain on the market regardless of the effect on the environment, 254 comments said FDA should focus on other sources of CFC's, 271 comments said FDA should focus on consumer aerosols, 743 comments said FDA should focus on other environmental problems, and 400 comments said that MDI's do not release CFC's into the atmosphere because they are inhaled.

Through the Clean Air Act and the Montreal Protocol, the United States has committed to eliminate the use of all CFC's, including use of CFC's in MDI's when no longer essential. The agency notes that EPA has found the release of CFC's to be harmful. MDI's do release CFC's into the atmosphere after inhalation because the vast majority of the aerosol puff released is CFC, and the CFC contained in each puff is either directly released into the atmosphere or inhaled and subsequently exhaled by the patient. The agency also notes that, for nearly two decades, no consumer aerosols other than CFC–MDI's and other products listed in § 2.125 have been allowed to use CFC's in the United States.

B. Specific Comments on the ANPRM

FDA received a number of specific comments on the phaseout criteria proposed in the ANPRM. The agency categorized the comments and responds to them in the following section of this document.

1. Number of Alternatives Proposed

In the ANPRM, FDA sought comments on phasing out CFC–MDI's using either a therapeutic class approach or a moiety-by-moiety approach. Under the therapeutic class approach, FDA would eliminate the essential-use designation for a class of CFC–MDI's once three acceptable non-CFC alternatives existed for the class. FDA would require two of the three alternatives to contain different active moieties. Under the moiety-by-moiety approach, FDA would eliminate the essential-use designation for an active moiety's CFC–MDI's once at least one acceptable non-CFC alternative existed that contained that active moiety.