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## 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 November 30, 1999. See section V of this document for the proposed effective date of a final rule based on this document.

**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.

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#### 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."<sup>1</sup>

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

<sup>1</sup> 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 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 (levorotary) R(-)-isomers. Racemates are equimolar mixtures of enantiomers of the same molecule. See 62 FR 2167, January 15, 1997, for additional explanation.

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.

### 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))<sup>2</sup> and metered-

<sup>2</sup> FDA proposes to use the term corticosteroids rather than the general term steroids to describe the

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.

#### 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).

marketed metered-dose steroid human drugs for nasal and oral inhalation.

#### 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),<sup>3</sup> the sponsor is not permitted by EPA regulations to obtain CFC's until 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

<sup>3</sup> 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.

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.<sup>4</sup> 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

<sup>4</sup> The petitioner must show only a high probability of an important public health benefit for an investigational product.

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.

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.<sup>5</sup>

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.<sup>6</sup> 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

<sup>5</sup> 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.

<sup>6</sup> 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.

longer marketed. FDA expects that the non-ODS product will be manufactured at multiple manufacturing 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, tolerability, 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.

8. Five comments requested that FDA phase out a CFC product once one non-ODS product was on the market. One comment requested that the agency allow phaseout only if there were a non-ODS product for each active moiety. One comment said it was very important that the non-ODS product contain the same active moiety.

FDA is proposing to use the moiety-by-moiety approach overall. However, FDA notes that some companies are unlikely to reformulate their CFC products into non-ODS products because of economic considerations. Some manufacturers of CFC-MDI's with small market shares have already stopped marketing their products. Therefore, in addition to using the moiety-by-moiety approach, FDA is proposing a process to remove products from the essential-use list if the products are no longer marketed or, after January 1, 2005, if available non-ODS products fully meet the needs of patients who previously required the product on the essential-use list.

9. One comment requested that FDA phase out long-acting CFC-MDI's but permit rescue inhalers to remain on the market as CFC-MDI's.

U.S. law does not permit CFC use to continue once acceptable alternatives exist. FDA is proposing this rule to protect the public health by setting criteria designed to ensure that adequate treatments exist throughout the CFC phaseout.

10. One comment asked that FDA not allow a phaseout until there are at least three or more non-CFC containing alternatives.

FDA is proposing to require that at least one acceptable alternative for each active moiety be marketed before elimination of an essential-use designation. This means that many alternatives representing many different active moieties will exist before the transition to non-ODS products is complete.

11. Four comments stated that two different active moieties within a therapeutic class were not sufficient, but did not explain why or offer an alternative number. One comment stated that the therapeutic class approach would not permit sufficient alternatives to serve all patient subgroups because it would reduce the number of products available once three non-CFC products were available. Nine comments claimed that there are medically significant differences among individual members within the therapeutic classes of drugs proposed by FDA. One comment stated that the various short-acting beta-2 agonists on the market such as albuterol, terbutaline, and pirbuterol are essentially identical. One comment asked that no CFC products be removed until 75 percent of all products had been replaced, but did not provide a justification for using an exact percentage. Six comments stated that the proposal to eliminate all CFC products within a class once two alternatives were on the market could lead to a situation in which no high-potency formulations, such as fluticasone propionate, were available. The comments noted that the high-potency formulations are more convenient to use because they require fewer puffs per dose. One comment asked that FDA require one low-, one medium-, and one high-potency inhaled steroid to maintain asthma control and compliance. One comment requested that FDA ensure that alternatives existed for not only fast-acting MDI's, but also corticosteroids. One comment requested that inhaled salmeterol not be banned without an exact replacement. One comment stated that 30 percent of patients using inhaled corticosteroid use Aerobid, yet Aerobid could be deemed nonessential if three other products reach the market first.

After careful consideration of the public comments, FDA has decided not to propose to use the therapeutic class approach. Rather, FDA is proposing to use a moiety-by-moiety approach. This means that FDA would not propose eliminating the essential use for an

active moiety unless patients had access to the same active moiety in at least one non-ODS product. FDA is proposing to require at least two different non-ODS products for an active moiety if an active moiety is marketed under multiple NDA's or exists in multiple strengths.

12. Three comments requested that more than one alternative for albuterol exist before phaseout of albuterol CFC-MDI's.

FDA is proposing to require at least two acceptable alternative non-CFC products for all active moieties manufactured under multiple NDA's from multiple sponsors, including albuterol, before it will consider eliminating the essential use designation for that active moiety.

13. Two comments stated that not all short-acting bronchodilators or inhaled steroids are therapeutically equivalent. One comment requested that the agency require well-documented bioequivalency before CFC-MDI's are removed from the market. One comment requested that FDA demonstrate that all products within a class are substitutable for all patient subpopulations. One comment suggested considering safety and efficacy, potency, delivery to target, bioavailability, and bioequivalence in evaluating replacements.

The agency will evaluate safety and efficacy, potency, product quality, and bioavailability in the course of evaluating new non-CFC products for approval, as it does in evaluating all new drugs. The agency agrees that not all drugs for the treatment of asthma and COPD are therapeutically equivalent or bioequivalent. However, drugs need not be strictly therapeutically equivalent or bioequivalent to each other to provide effective alternative treatment for a disease. It is not the agency's goal to replace CFC-MDI's with only bioequivalent non-ODS products. Rather, it is the agency's goal to ensure that adequate acceptable alternatives exist to meet the needs of patients who have relied on CFC-MDI's.

14. One comment stated that there are few scientific studies that demonstrate the equivalent doses between different inhaled corticosteroid preparations.

FDA agrees that such data are for many reasons lacking for the currently available CFC products. FDA is encouraging sponsors of alternative products to submit clinical trials with comparator arms using a currently available CFC formulation to provide data to assess comparability of clinical effects.

15. One comment stated that anti-inflammatories, also called corticosteroids, are the mainstay of

asthma control, and therefore FDA should not phase out CFC corticosteroids until there are sufficient non-CFC corticosteroids.

As explained previously, FDA is not proposing to eliminate the essential-use designation for any individual active moiety until at least one non-CFC alternative exists that contains the same active moiety or, after January 1, 2005, until adequate alternatives exist, as described in proposed § 2.125(g).

16. Five comments stated that over-the-counter (OTC) epinephrine-containing bronchodilator drugs should not be given an essential-use exemption. Of those comments, one stated that FDA's assertion that OTC medications are used only by the poor or those without access to medical care was not supported by their research. One comment stated that OTC-MDI's are relied upon by people who do not choose traditional medicine or who do not have access to medical care.

Epinephrine CFC-MDI's are manufactured under multiple NDA's. FDA will evaluate the essentiality of epinephrine the same way it will evaluate the essentiality of all active moieties manufactured under multiple NDA's. As explained previously, FDA is not proposing to eliminate the essential-use designation for any individual active moiety marketed under multiple NDA's until at least two non-CFC alternatives exist that contain the same active moiety or, after January 1, 2005, until adequate alternatives exist, as described in proposed § 2.125(g).

17. Two comments stated that the use of spacers may affect the delivery and effectiveness of new drugs. One of the comments stated that even with the same drug and dose, different delivery systems could result in different distribution of particle size with different spacers and, therefore, different patterns of deposition in the lung and different effectiveness levels. The other comment stated that in the case of albuterol, the actuator orifice with the CFC-based product is 0.022 inch while the hydrofluoroalkanes (HFA) orifice is 0.009 inch, with both canisters having the same internal pressure. The comment stated that the difference in orifice size results in significant differences in aerosol characteristics when used with an improperly sized adaptor and requested that the manufacturers of adaptors be provided adequate time to modify their products to accommodate the new, HFA-based preparations.

FDA agrees that interactions between spacers and non-ODS-MDI's and CFC-MDI's may differ, given the different pharmaceutical properties of these

products. However, spacers and holding chambers are usually approved for general use rather than for use with specific products. A patient decides with his or her health care practitioner whether to use such a device with an MDI, regardless of whether the MDI is a CFC-MDI or a non-CFC alternative.

2. Specific Comments on the Proposed Criteria for Phaseout

18. One comment requested that FDA compress the time it takes to develop a final regulation and to phase out nonessential CFC-MDI's.

FDA recognizes that it often takes an extended period of time to publish a final rule. However, this time is necessary, particularly in the context of this rule, for FDA to fully consider the comments provided and to make sound policy decisions based on strong science and responsiveness to important public concerns.

19. Two comments requested that FDA define the terms "postmarketing surveillance, subpopulations, therapeutic class, [and] convenience of use" to reduce the likelihood and viability of administrative or legal challenges.

Since FDA has chosen not to propose to use the therapeutic class approach, FDA is not defining the term "therapeutic class." FDA has provided explanations regarding its proposed application of the other terms in section II of this document.

20. One comment requested that FDA require the same delivery system rather than the same route of delivery for replacements.

FDA believes advances in technology may bring even more convenient delivery systems to market, and therefore it is not requiring the same delivery system.

21. One comment stated that FDA's requirement of "same indication" should include all current indications and patient populations covered by CFC products containing the same active moiety. One comment asked FDA to require replacements for all currently approved indications, including indications for exercise-induced asthma and for children age 4 and older.

FDA agrees generally that non-CFC products with the same active moiety should be approved for the same indications as their CFC counterparts prior to being considered as alternatives. For example, if a CFC-MDI is approved for use in the pediatric population down to age 6 but non-ODS products are only labeled down to age 12, a significant patient subpopulation would exist that would not be adequately served by non-ODS products. Absent other data, the agency would not eliminate the

essential-use designation for the CFC-MDI based on this factor alone.

22. One comment stated that evaluation of the level of convenience should consider dosing regimes, including number of refills per month; type, size, and shape of the product; and physical and mental ability of the patient to operate the product, taking into account patient education. One comment said it is appropriate to consider tolerability, patient compliance, or convenience only if these factors relate to safety and effectiveness.

FDA will consider such factors in determining whether replacement products are adequate replacements, even if the factors do not directly affect efficacy and safety. For instance, FDA would not consider a product that needs to be administered with an air-pressure driven nonportable nebulizer a viable replacement for a CFC-MDI because of its lack of portability and ease of use, even if it were as safe and effective as an MDI.

23. One comment stated that FDA should require convincing evidence of adequate production capacity and component supply from non-CFC product manufacturers. One comment said that a manufacturer should not be required to demonstrate supply capacity as long as there is a reasonable transition period, and that supply capacity should be considered inadequate only if due to limited capacity or manufacturing problems. One comment said that FDA needs to account for the potential risk of an out of stock situation in implementing any phaseout.

FDA already has mechanisms in place to determine whether a drug shortage exists and to manage supply (see *Manual of Policies and Procedures (MAPP) 4730.1—Drug Shortage Management, Center for Drug Evaluation and Research, FDA*). FDA will use such procedures to evaluate whether non-CFC product manufacturers have sufficient production capacity and potential capacity to manufacture non-CFC products for all patients who currently use the CFC product(s).

24. Two comments requested that the agency collect scientific evidence on the effectiveness of alternatives.

FDA will continue to require NDA's to comply with all applicable new drug laws and regulations (see, e.g., section 505 of the act (21 U.S.C. 355)). As with all new drug products, FDA is requiring clinical data from adequate and well-controlled trials to establish the safety and effectiveness of non-CFC products prior to approval. FDA is also requiring

at least 1 year of postmarketing data on the use of alternatives by the general population before it will propose removing the essential-use designation for any CFC-MDI.

25. One comment requested that the agency not base the phaseout proposal on the assumption that manufacturers are developing alternatives.

The agency is not assuming that manufacturers are developing alternatives, nor is it projecting a timetable for availability of any such products. Rather, FDA is establishing a framework to use once alternatives are available.

26. One comment asked that FDA eliminate broad exemptions from § 2.125.

The agency is proposing to narrow the exemptions in § 2.125 by listing the individual active moieties exempted rather than listing classes of drugs. For convenience, FDA proposes listing each active moiety under a heading describing its use.

27. One comment suggested that FDA follow the Australian model for phaseout. Australia has proposed reducing CFC use over time by simply eliminating a percentage of the amount of CFC's used in MDI production each year.

FDA is not proposing this approach because it is concerned that in the U.S. market such an approach would not ensure that patients' needs were met throughout the transition.

### 3. Intolerance or Allergy to Drug Products or Propellants

28. Eleven comments pointed out that many asthmatics are allergic to propellants and inactive ingredients such as alcohol, sulfate, oleic acid, trisorbitan oleate, lecithin, and lactose. Two comments stated specifically that albuterol alone was not a sufficient alternative because of patient intolerance. One comment requested that, with a doctor's written authorization, patients be permitted to continue to use CFC-MDI's until a non-CFC alternative to which they were not allergic was available. One comment noted that some patients develop a potentially fatal addiction to the aerosol component of MDI's and requested that FDA require manufacturers to put warnings on CFC-MDI labels and develop nonaerosol alternatives.

FDA acknowledges that intolerance and sometimes true allergies or addiction to drug products or components are a concern for patients any time new medications are used, regardless of whether the medication is CFC-based. To address this concern, FDA is requiring at least 1 year of postmarketing data to ensure that

subpopulations are served by the available alternatives without widespread intolerance or allergy. If subpopulations of patients cannot use a product because of intolerance or allergic reactions and no other medically suitable options exist for those patients, that product would not be considered an acceptable alternative to the CFC-MDI counterpart.

29. One comment stated that the side effects experienced from one drug within a class might not be experienced in using another drug in the same class. One comment stated that asthma patients need to change drugs over the course of the disease, since one drug does not always continue to work.

FDA agrees that patients may tolerate some drugs better than others or might need to switch therapies and therefore is proposing a transition strategy that would ensure that many acceptable alternatives exist before the transition to non-CFC products is complete.

### 4. Patient Subpopulations

#### a. Children

30. One comment stated that one of the major problems for asthma patients, particularly children, is getting the drug to the site of action.

FDA agrees that children present special concerns in terms of optimally utilizing inhalation devices. FDA intends to consider such factors when assessing the adequacy of an alternative as a replacement for a CFC-based product.

31. One comment stated that not all alternatives, including DPI's, are acceptable alternatives for children.

FDA acknowledges that devices relying on patient inspiratory efforts for the delivery of drug, such as DPI's, may not be acceptable alternatives in very young children or those with severe airflow obstruction. However, FDA anticipates that multiple-dose DPI's will serve as viable alternatives for at least some patients. In practice, FDA expects that non-ODS MDI's will most commonly serve as replacements for CFC-MDI's.

32. One comment expressed the belief that the proposed phaseout would limit access to asthma treatments and might endanger the medical stability of children with asthma.

It is not FDA's intent to limit access to therapies for any patient group. Rather, by developing a transition strategy, FDA is attempting to ensure patient access to acceptable and safe treatment throughout the mandated phaseout of CFC's.

33. One comment noted that, in the past, new products have generally been marketed without a pediatric indication



and asked how FDA would address this issue.

FDA is working on several pediatric initiatives to encourage the labeling of drugs for pediatric use. FDA recently published a final rule requiring certain sponsors to submit pediatric studies and labeling (see 63 FR 66632, December 2, 1998). In addition, the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) (Public Law 105-115) provides incentives for sponsors to perform pediatric studies. Section 505A of the act (21 U.S.C. 355a) permits certain applications to obtain an additional 6 months of exclusivity if, in accordance with the requirements of the statute, a sponsor submits information relating to the use of a drug in the pediatric population. The Modernization Act also exempts from payment of prescription drug user fees supplements to NDA's proposing to include a new indication for use in pediatric populations. FDA anticipates that these provisions will result in increased pediatric labeling. Of course, FDA will evaluate whether patients, including pediatric subpopulations, are served by acceptable alternatives before proposing to remove essential-use exemptions for CFC-MDI's.

*b. Elderly*

34. One comment stated that the elderly require special education and an extended time period to become comfortable with new medications.

FDA acknowledges this comment (though disagreeing with it as a statement of general applicability to all elders) and reiterates that the intent of the proposed rule is to allow for such considerations in all patient subgroups.

*c. Other subpopulations*

35. One comment stated that medical studies have documented that African-Americans, especially in Chicago, IL, experienced consistently higher asthma mortality than Caucasians between 1968 and 1991. Two other comments stated that a study conducted in Brooklyn, NY, found that the prevalence of asthma was significantly higher among Hispanics, African-Americans, and children from the lowest income families. Another comment stated that African-Americans represent a disproportionate share of asthma sufferers and requested that any new rule issued by FDA ensure that it does not have a disproportionate adverse impact, either perceived or real, on minority persons.

FDA is aware of epidemiological data that show minorities and inner-city residents disproportionately experience asthma morbidity and mortality compared to the general population. FDA intends to take into account the needs of the entire asthma population.

FDA plans to take into account the medical needs of demographic subgroups, including racial and ethnic groups, economic groups, or other socioeconomic or medical groups.

36. One comment stated that many patients in Hawaii, for genetic reasons, are sensitive to alcohol and therefore cannot use non-ODS products that contain alcohol. FDA would invite data in support of special sensitivities to be submitted to the agency at the time that any removal of an essential-use listing is proposed.

FDA stresses that the intent of the proposed rule is to ensure that adequate numbers of alternatives exist at all times in the transition to address such concerns.

37. One comment suggested that if a patient subpopulation is not served by non-ODS products, FDA allow the CFC product to remain on the market but: (1) Require the labeling to be changed to reflect use for that subpopulation only, and (2) reduce the manufacturer's CFC allowance.

The use of CFC's in a product is either nonessential or essential. If there is a portion of the population that cannot be medically served by the available alternatives, then such CFC use would remain essential.

38. One comment stated that only one CFC-MDI, terbutaline, is rated Pregnancy Category B, and that all others are rated Pregnancy Category C.

FDA acknowledges this comment. FDA believes that not all manufacturers will perform human pregnancy studies for alternative products. However, the moiety-by-moiety approach proposed is not intended to and should not reduce the number of MDI's available within each pregnancy category.

39. Two comments stated that acceptance in "significant" subpopulations is not a sufficient measure of the adequacy of alternatives. One comment stated that, to an asthma patient, a significant group is one. One comment asked that FDA require an affirmative showing that all patient subpopulations are served before eliminating the essential use for any product.

As the mandated phaseout of CFC's occurs, FDA intends to ensure that the U.S. market contains an acceptable number of products at all times to meet patient needs. Just as all patients are not served by one CFC-MDI, all patients will not be served by any single alternative product. FDA is proposing to make determinations of essentiality on a moiety-by-moiety approach. FDA will take into account all other available therapies, whether CFC-based or non-

CFC-based, in making a determination about the essentiality of a product.

5. Experimental Nature of Alternative MDI's

40. One comment stated that the person had seen an alternative MDI manufactured by Glaxo Pharmaceuticals in limited use and that the alternative did not receive a favorable response from most of the patients who tried it. Another comment stated that the person had participated in Glaxo Wellcome studies on the non-CFC Ventolin and found that the delivery method was not as effective. One comment stated that the person had participated in a University of Arizona study to test a new drug and had to drop out before the 12-week study was over because he did not do as well with the new drug. One comment stated that five new studies on potential asthma medications were being conducted at the University of Nebraska Medical Center and that the studies should be have been completed in late 1997.

FDA is aware that sponsors are conducting extensive research to determine which CFC-MDI replacements are safe and effective in the treatment of asthma and COPD patients. FDA expects that, as a result of reformulation efforts and extensive clinical programs, asthma and COPD patients will have adequate treatment alternatives throughout the transition. FDA also expects that not every treatment alternative will be equally effective for every patient, just as not every CFC-MDI works the same for every patient. However, in making essential-use determinations, FDA will assess whether the entire market, including specific non-ODS alternatives for a particular CFC-MDI, other non-CFC products, and remaining CFC products, is adequate to serve patient needs.

41. One comment stated that Pulmicort is a good alternative. Two comments stated that budesonide is a good alternative that does not use CFC's and asked when it would be approved in the United States.

Budesonide (Pulmicort) is approved for marketing in the United States as a multiple-dose DPI. Because budesonide is not marketed as a CFC-MDI in the United States or listed as an essential-use exemption in § 2.125(e), the factors proposed in this rule would not apply to budesonide. However, FDA will consider all available treatment options, including budesonide DPI's, in evaluating whether the use of CFC's remains essential.

42. One comment stated that the long-term effect of using other medications with CFC replacements is unknown and

that replacements may be endocrine disruptors or have other adverse effects.

All drugs, including CFC-MDI replacements, are required to meet FDA standards of safety and effectiveness before approval. After approval, FDA may require sponsors to collect and report use data that characterizes the long-term safety of the drug in humans. FDA is proposing to require at least 1 year of postmarketing data on alternatives before FDA would propose to eliminate the essential-use designation for any CFC product. Sponsors have already collected a large amount of animal and human safety data for alternative propellants used in non-CFC products. Sponsors have collected and reported pharmacology and toxicology data on alternative propellants at levels comparable to or in excess of that developed for many new drug substances and at greater levels than for most other drug product excipients.

43. One comment stated that most physicians are brand loyal and therefore will not prescribe a CFC-free product. The comment went on to state that even if a physician does prescribe the CFC-free product, a pharmacist may substitute a cheaper generic CFC product to comply with third-party payer rules.

FDA plans to continue to work with other government and nongovernment bodies to further a campaign of physician, pharmacist, and patient education to address these issues and to ensure that patients are allowed the opportunity to try non-CFC products. FDA anticipates that the non-CFC products will not be rated as bioequivalent to the CFC-MDI's. Therefore, pharmacists will not be able to substitute a CFC-MDI for a prescription written specifically for a non-CFC product.

#### 6. Choice of Technically Feasible Alternatives

44. Numerous comments discussed DPI's. One comment said that DPI's are not an alternative to MDI's. Another comment said that powders are not the answer because one is not certain if the dosage has been inhaled or how much powder remains. Three comments said powders did not work for them. Two comments said that powders cannot be used in certain areas of the country because of high humidity. Two comments said that powders aggravate or cause dry mouth. Three comments said that many patients, most notably elderly and children, are not capable of properly using DPI's. One comment said that DPI's require patients to breathe at an inspiratory flow rate  $\leq 60$  l/minute, which may not be possible for all

patients. One comment said that DPI's should not be considered a substitute because not all drugs are available as powders. One comment said that DPI's cannot be used with spacers to reduce systemic side effects and oral candidiasis and dysphonia. One comment said that Swedish experience shows that DPI's can be used by 80 to 90 percent of asthma patients. One comment said that DPI's are better than CFC-MDI's and their use should be expedited.

Manufacturers began marketing the first multiple-dose DPI's in the United States very recently. At present, FDA cannot predict whether any multiple-dose DPI will be an acceptable alternative to a CFC-MDI. FDA will use the factors determined by this rulemaking and through public comment to determine whether any particular multiple-dose DPI is an acceptable alternative.

45. One comment said that atomizers do not deliver consistent doses. Two comments said that spinhalers, because they use dry powder, can irritate the lungs. Two comments said that sometimes, when using spinhalers, the whole top of a capsule will break off, causing the user to inhale the top of the capsule and choke. One comment said that spinhalers do not deliver even dosages. One comment said that spinhalers could be used as an alternative. One comment said that breath activated inhalers are useless during a full-blown attack because there is minimal breath available to actuate the inhaler. One comment said that turbuhaler dispensers do not force the medication into the lungs and therefore are not a good alternative for fast-acting MDI's. One comment said that rotohalers are not a good replacement because it is difficult to insert the pill into the rotohaler while having an asthma attack. Three comments said that nebulizers should not be considered an alternative because they are large and not portable, require a source of electricity, and take about 15 minutes to deliver treatment. One comment said that MDI's have advantages over all alternatives.

FDA cannot predict which products will be acceptable alternatives to CFC-MDI's. FDA anticipates that non-CFC MDI's will be the primary replacements for CFC-MDI's. However, advances in technology may mean that manufacturers develop new alternatives that are even better than CFC-MDI's. In addition, non-MDI products can serve at least a portion of the patient population, even if they cannot serve the entire population. Accordingly, FDA is not limiting the rule to require that all CFC-

MDI's be replaced by non-CFC MDI's. FDA will consider such products as part of an overall determination regarding whether the patient population is adequately served by available alternatives.

FDA notes that MDI's do not force medication into the lungs. MDI's deliver the medication to the mouth, but the patient must breathe in the medicine at the time they use the MDI or no medicine will reach their lungs. DPI's can be used more effectively by some patients because patients do not need to go through a two-step process to get the medicine to their lungs. Patients deliver the medication to their lungs as they inhale from the DPI.

46. Three comments said that the new inhalers should be able to use the same old Aerochambers. Two comments said that use of steroid inhalers without an Aerochamber leads to tooth decay and oral candidiasis and dysphonia. One comment suggested that manufacturers use a carbon dioxide cartridge to propel the medicine from disposable inhalers. One comment said that the specifications for a replacement inhaler should include: (1) Pocket size, (2) lightweight, (3) easy to clean, and (4) separate medicine from propellant. Five comments recommended that manufacturers put MDI's into another form, like spinhalers, injections, pumps, glass atomizers, or hand-pumped dispensers.

FDA does not control the design of new drug products. FDA is attempting to ensure that new alternatives are adequate by requiring these alternatives to meet the criteria in this proposed rule before FDA will propose the elimination of an essential use of CFC's for any active moiety.

#### 7. Proventil HFA

47. Numerous patients commented on whether Proventil HFA, the first non-CFC MDI approved in the United States, which contains the active moiety albuterol, should replace all albuterol CFC-MDI's.

Because FDA is not proposing to eliminate the essential-use designation for albuterol in this proposed rule or in the resulting final rule, these comments will not be addressed here.

#### 8. Postmarketing Data and Suggested Duration

48. Many comments suggested varying lengths of time to collect postmarketing data. One comment suggested that CFC-MDI's should be banned immediately. One comment stated that patient acceptance should be judged in a shorter time than 1 year. One comment suggested collecting data during the first 6 to 12 months of marketing. One comment suggested 12

months for phaseout of individual products and 6 months for phaseout of classes. One comment said that FDA should require at least 1 year of postmarketing data on alternatives before removing any comparable inhalers. One comment said FDA should wait to ban any CFC-MDI's until 1 year after all the replacements are in place. Two comments said that a postmarketing evaluation cannot be completed in less than 1 year. One comment said that inhalers should be phased out within 18 months of availability of an alternative. Two comments said FDA should require 2 to 3 years of postmarketing data. One comment recommended at least 5 years notice before banning CFC-MDI's. One comment requested that the phaseout not be completed until 2005. Three comments said FDA should allow a 10- to 15-year phaseout period. Two comments said that 1 year of postmarketing data is insufficient because most asthmatics must try a number of medications and different seasons affect the efficacy of medications. Four comments said that 1 year of postmarketing data is insufficient because it will not reveal the side effects of long-term usage.

Under this proposed rule, FDA will not begin to assess the acceptability of an alternative product as a replacement for any CFC-MDI until at least 1 year of postmarketing data is available for the non-ODS product. FDA stresses that even after it does issue a proposed rule to amend § 2.125(e) to remove an essential-use listing for a particular active moiety, the public will have time to comment on the proposal before it is finalized. FDA also anticipates that any final rule to remove an essential-use listing will permit some time for patient use of already manufactured CFC-MDI's.

49. One comment recommended that FDA implement the use of non-CFC products as rapidly as possible, provided that all patient protection and physician education elements and safeguards explained in the ANPRM are in fact carried out.

FDA does not dictate medical practice. FDA is proposing this rule to ensure that patients have medically acceptable treatments. FDA agrees that patient and health care practitioner education is an important part of the transition and is therefore actively participating in education efforts.

50. One comment said that MDI's should not be phased out until manufacturers produce a full range of MDI products with highly effective delivery, at practical prices, and a sound degree of availability. One comment

requested that phaseout not occur until patients have sufficient experience with alternatives. One comment said that phaseout should not occur until replacements: (1) Are as effective as the present products, (2) are tested by FDA, and (3) cost the same as the products they replace.

FDA believes that the criteria proposed in this rule (see section II of this document) will ensure that sufficient experience exists with a full range of alternative products with highly effective delivery, at practical prices, and with a sound degree of availability before any CFC-MDI's are phased out. FDA expects that the price of replacement products will be equivalent. However, FDA does intend to consider relative costs in considering whether alternatives adequately serve patients.

51. One comment requested that FDA set a specific timeframe for the elimination of the essential-use exemption once alternatives are available but did not recommend a particular timeframe. One comment said that it is difficult to set an arbitrary time period for determining patient acceptance, because the length of time a product is on the market does not necessarily measure usage.

FDA believes it is premature to set a specific timeframe for the elimination of all essential-use exemptions because too many variables exist as to when applications for new products will be submitted to the agency, when they will gain approval, and when the products might be considered clinically acceptable alternatives to CFC-MDI's.

52. Another comment suggested that FDA should not designate a CFC-MDI as nonessential if the sponsor is exercising due diligence in developing, testing, and evaluating an alternative.

FDA expects that under the moiety-by-moiety approach in this proposal companies will not lose essential-use exemptions prior to approval of an alternative product if they are exercising due diligence in reformulating their products. However, FDA cannot guarantee that a company's CFC-MDI will remain essential merely because a company is exercising due diligence.

53. One comment stated that FDA should leave it to physicians, patients, and the market to establish when the switch to non-CFC products should be completed. Another comment said that FDA should let patients choose which product meets their needs.

Patients and their health care providers can now and will continue to be able to choose any product available on the market. However, the Clean Air Act will not allow CFC products to

remain on the market if the products are not essential. FDA is required by U.S. law and regulations to determine, in conjunction with EPA, whether a medical product remains an essential use of CFC's. FDA wants to ensure through development of a planned transition strategy that the transition occurs in a manner that protects the safety of patients.

54. Another comment stated that the phaseout should not occur before 5 years of marketing because at least 5 years on the market in combination with widespread exposure in all patient subgroups is necessary to detect serious or important adverse events (citing 61 FR 51625 at 51629, October 3, 1996).

FDA notes that the alternative products will contain the same active moieties as the CFC products. Therefore, FDA has more than 5 years of exposure information from U.S. marketing for the large majority of these moieties. FDA does not believe it is necessary to have 5 years of marketing data before proposing the elimination of an essential-use designation because the active moieties in the non-ODS products will not be newly marketed.

55. One comment said that postmarketing data should address not only market penetration but also physician education; patient education; patient acceptance, particularly in the subpopulations of children and the elderly; and patient compliance. One comment said that FDA should contact patients through their doctors and have them complete a survey to determine what kind of asthmatic they are, what substitute medications have already been tried, and the result. Another comment suggested that FDA survey a representative sample of all allergists, including private practitioners, rather than relying on drug companies or selected clinics in assessing the adequacy of replacements. Another comment said that FDA should let pharmacists, not MDI manufacturers, determine the adequacy of supplies, effectiveness, and other criteria through customer surveys. One comment said that new products should contain an insert that makes comment possible or that consists of a brief "satisfaction survey" to be filled out. Another comment said that FDA should require objective postmarketing studies that include a sample of at least 20 percent of diagnosed asthmatics. One comment said that any postmarketing study should be limited to showing that adverse events related to a new CFC-free formulation, but not found in the CFC product's labeling: (1) Occur at very low rates; (2) do not develop in patient populations not generally included in

premarketing trials; or (3) expose drug-drug or drug-disease interactions not seen in the pivotal clinical trials, as determined by the equivalent of 100,000 patient years of exposure or a more formal postmarketing surveillance study, at the manufacturer's discretion.

One comment said that postmarketing evaluation should include FDA's factors and an analysis of the first year's postmarketing experience with regard to adverse event reports, consumer and health care professional comments, and extent of market uptake; an assessment of the ability of the manufacturer to meet the market demand for the CFC-MDI with the replacement product; and an assessment of the need for revised patient and health care professional education efforts to facilitate conversion to the replacement. Another comment said that patient acceptance should be measured through postmarketing reports that evaluate: Efficacy of the product compared to the previously used CFC product (this can include quality of life); whether the replacement product is compatible with other CFC products that the patient is also using (i.e., the new combination of inhalers); confusion regarding changes in daily dose regimens; product taste, feel, and device dimensions; mechanical performance of inhalation device; and confidence that the new product is a dependable replacement. One comment simply said that FDA should disclose the types of studies that it believes are necessary to demonstrate product comparability for phaseout purposes.

FDA's intent in requesting at least 1 year of postmarketing use data and in suggesting a postmarketing study is to gain data that demonstrate the acceptance of the product in widespread use outside of controlled clinical trial settings and in subgroups not represented in clinical trials. Although FDA will have found newly marketed products to be safe and effective through its approval process, FDA cannot assess the ability of a new non-CFC product to adequately replace in widespread use an existing CFC product without additional postmarketing data. FDA believes issues such as device performance in uncontrolled settings and tolerability of the product in widespread use are important. FDA believes that properly designed postmarketing studies would characterize the acceptability of these products better than standard postmarketing data that rely on anecdotal self-reporting.

56. One comment said that FDA should not consider the absence of a postmarketing study the basis for extending an exemption.

FDA will not require a postmarketing study if available data, including more traditional postmarketing surveillance data, are sufficient to support a finding that the CFC product is no longer essential.

57. One comment said that European postmarketing data are just as valid as United States data and should be accepted by FDA.

FDA may accept European postmarketing data and find the information useful. However, dramatic differences exist between U.S. and European health care practices and drug pricing systems. For example, products available in Europe are not necessarily pharmaceutically equivalent to those marketed in the United States. Although FDA would consider European data in making essential-use determinations, FDA would not propose to eliminate an essential-use designation unless it had additional data from U.S. populations.

58. One comment noted that medications may be accepted in different ways by patients, different medicines may not compare on a microgram ( $\mu\text{g}$ ) per  $\mu\text{g}$  basis, and taste may affect patient acceptance. Another comment stated that propellants can have a significant effect on the distribution of the medication into the airways and, therefore, the effectiveness of the treatment.

FDA will evaluate these issues through premarketing comparability testing and postmarketing data before proposing the elimination of an essential-use designation from § 2.125(e).

59. One comment said that FDA may not be able to enforce current good manufacturing practice (CGMP) regulations at companies making one of three alternatives if the United States is dependent on the companies to supply the patient population.

FDA is committed to ensuring that CGMP standards are met by all manufacturers, including those producing CFC products and new alternatives. FDA does not believe that CGMP violations are any more likely to occur with alternatives than with currently available products.

#### 9. Timing of Phaseout

60. Four comments suggested that FDA should allow the sale of CFC-MDI's in conjunction with alternatives.

Under the proposed rule, CFC-MDI's and alternatives will necessarily be sold at the same time for a period.

61. Two comments suggested that FDA require the use of non-CFC products at home and work, and CFC-MDI use only as necessary.

FDA is proposing this rule to fulfill its obligation under the Clean Air Act to

make essential-use determinations that will lead to the eventual phaseout of CFC-MDI's. Once FDA has determined that a product is essential, a consumer can use the product for the essential use as needed and prescribed.

62. One comment asked why FDA is preparing this proposal now.

The Parties to the Montreal Protocol, through the Technical and Economic Assessment Panels, have asked that all Parties develop transition strategies. Parties were required to present a draft transition strategy no later than January 31, 1999, and were encouraged to present a strategy before January 31, 1998. In publishing the ANPRM, FDA provided a draft proposal for public comment and consideration domestically and internationally. FDA recognizes that rulemaking can take many months or years to complete. FDA published the ANPRM early to give the public time to comment and to give FDA time to develop a final rule that would be most protective of public health.

63. One comment asked why one is able to obtain CFC's for a car air conditioner but not for MDI's.

A consumer can obtain recycled CFC's to use in a car air conditioner but cannot obtain new CFC's. Since 1996, no new CFC's have been manufactured or imported into the United States for any use other than those uses designated as essential under the Clean Air Act. Recycled CFC's can contain impurities that would prohibit use in MDI's inhaled directly into human lungs on a chronic, recurrent basis. Manufacturers must use pharmaceutical grade CFC's in CFC-MDI's to ensure that they are safe to use.

64. One comment said that patient safety should take precedence over all other factors. One comment said that FDA should allow the phaseout to occur according to the Montreal Protocol timeframe and should not take any steps to phase out CFC-MDI's. One comment said that once patients understand the FDA proposal, they agree that it makes more sense to set up guidelines now, rather than waiting until no CFC-MDI's remain on the market and insufficient non-CFC products exist to meet patient needs.

FDA's priority is to protect and promote the public health. FDA is proposing this rule to develop a transition strategy as required under the Montreal Protocol. Through this rule, FDA seeks to ensure that public and patient health and safety are determining factors in deciding whether alternatives can replace CFC-MDI's.

65. One comment said that as more people use non-ODS products, CFC use

will decrease and the problem of CFC use will solve itself.

Although it is possible that the phaseout would occur without intervention, Title VI of the Clean Air Act mandates FDA involvement in the process. Accordingly, FDA is issuing this proposal to develop a phaseout process that will ensure that patients have adequate alternatives.

#### 10. Nasal Steroids

66. One comment stated that nasal pumps cause postnasal drip, which can aggravate an asthmatic cough. Another comment stated that nasal pumps cause liquid to drain down the throat, so they cannot be used by people with gastroesophageal reflux disease and ulcers. Another comment claimed that nasal pumps make symptoms worse and are not appropriate for all patients. Two comments said that for noses that are very swollen and inflamed, wet sprays do not work. Another comment said that there are still substantial numbers of patients who cannot stand the sensation/taste/smell of the aqueous solutions and much prefer the aerosols.

One comment said that alternative propellants should be developed for nasal steroids, and these should be considered alternatives. Another comment suggested FDA first limit nasal steroid inhalers, which are available as both aqueous preparations and CFC-propellant preparations. Another comment stated that nasal steroid inhalers need not be exempted because there are sufficient alternatives.

For the reasons set forth previously, 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 notes that the Parties to the Montreal Protocol have not granted essential-use exemptions for manufacture of nasal steroid CFC-MDI's since the general ban on CFC production went into effect in industrialized nations on January 1, 1996. The Parties do not consider CFC-based nasal steroids to be medically essential products because of the available alternatives. Any CFC-based nasal steroids currently being manufactured are presumably being manufactured with CFC's manufactured prior to 1996. In addition, the indications for which these products are approved and used are not life threatening.

67. One comment claimed that topical nasal dexamethasone is more effective than any other product in treating nasal polyps and sinusitis. Another comment claimed that nasal steroids are superior for treatment of nasal polyps because they permit effective penetration of the nose.

FDA is unaware of any substantiating data to support the clinical superiority of any one MDI over all aqueous formulations for these or any other indications, and these comments did not themselves include any data substantiating these assertions.

68. One comment asked that FDA grant an exception for Dexacort Turbinaire because clinical trials are being done to show it has unique potential in the treatment of chronic sinusitis.

An applicant should apply for an essential-use exemption if data shows a unique use for a particular CFC product.

69. One comment said that Vancenase AQ does not dispense properly and therefore is not an adequate replacement for the old Vancenase.

FDA approved both Vancenase AQ formulations (42 µg and 84 µg) as safe and effective and, therefore, concluded that the product was of sufficient quality. FDA has no basis to believe this determination to be in error. A CFC-based nasal corticosteroid could, in theory, meet the proposed standards to become an essential use of CFC's, and the manufacturer could successfully petition the agency for a new listing under § 2.125(e). However, at this time, FDA does not believe that the current nasal corticosteroid CFC-MDI's meet the standards of essential use.

#### 11. Miscellaneous Comments

70. One comment stated that FDA is intruding on the practice of medicine.

FDA is not intruding on the practice of medicine. FDA is fulfilling its statutorily mandated obligation to determine whether a medical product remains essential under the Clean Air Act.

71. One comment asked whether FR-12 is a replacement for CFC's in MDI's.

FR-12 is another term for CFC-12, a chlorofluorocarbon that cannot be used as a replacement.

72. One comment said that the United States was really phasing out CFC's because they can be used to make bombs.

FDA is unaware of any such motivation on the part of the United States. The Parties to the Montreal Protocol, including the United States, have agreed to phase out the use of CFC's to protect the ozone layer and the public health.

73. One comment stated that people with asthma should be on the deciding committee.

Thousands of patients provided their input through the public comment process. FDA will seek further input from patients when individual drug moieties are proposed for removal from the list of essential uses of CFC's.

74. One comment suggested that instead of removing CFC-MDI's, FDA should remove sulfites from the U.S. food supply, and that doing so would lead to a decrease in CFC-MDI use.

These issues are independent. FDA is required to make essential-use determinations under the Clean Air Act and the Montreal Protocol, regardless of the amount of sulfites in the food supply.

75. One comment said that FDA should only allow CFC-MDI use in minimally acceptable dosages for physician-certified, life threatening risks.

If the use of a CFC-MDI remains medically necessary to treat life-threatening conditions and no satisfactory alternatives exist, then the CFC use would remain essential.

76. Two comments said that FDA should publicize the proposal more, define terms for laymen, and allow adequate time for response to encourage more comments. One comment argued against granting any extension of the comment period.

FDA received approximately 9,600 comments on the ANPRM, more than on almost any other proposal in the history of the agency. The public will have further opportunities for comment as FDA finalizes the transition process and proposes to remove individual moieties from the essential-use listing. FDA plans to publicize these additional opportunities for comment in its educational programs, through its Internet site, and through press releases.

77. One comment said that if benefit outweighs risk, FDA should allow drugs to stay on the market.

FDA intends to use the criteria proposed to ensure public and patient health and safety before elimination of an essential use for an active moiety.

78. One comment said that FDA must reveal the amount of CFC's companies have stockpiled for interested parties to evaluate whether a rational basis exists for the proposed rule.

FDA does not have these data. If FDA did have the data, FDA could not disclose the data because the information is confidential and exempt from disclosure. FDA notes that the Technology and Economic Assessment Panel (TEAP) recently recommended to the Parties to the Montreal Protocol that members be permitted to maintain a maximum of 1 year of stockpiled CFC's (April 1998 TEAP Report at p. 16, section 1.2.4).

#### 12. Incentives for Development of Alternatives

79. Fourteen comments stated that FDA should accelerate approval of CFC replacement products.

The agency is committed to the timely review of all drug applications. FDA does not believe that NDA's with CFC replacement products meet the criteria for priority review at the current time.

80. Eight comments stated that FDA should halt approval of new CFC-MDI's. One comment stated that FDA should not approve any CFC-MDI's for an active moiety for which there is an approved non-ODS product, even if it has not yet determined that the non-ODS product is an alternative.

FDA will not withhold approval for a drug product that contains a moiety listed as an essential use under § 2.125(e). FDA will not approve ODS-products not currently listed in § 2.215(e) unless FDA has determined they are essential.

81. Four comments stated that FDA should impose fines on companies who do not produce alternatives within a reasonable time or institute a tax advantage for introducing an approved replacement.

FDA does not have the authority to take either of these actions.

82. Five comments requested that FDA require MDI manufacturers to pursue the development and marketing of alternative propellants with due diligence. Two comments stated that FDA should set standards for evaluating industry's pursuit of alternatives. One comment stated that elimination of an essential use because of a lack of due diligence on the part of the manufacturer unfairly penalizes patients.

The Parties to the Montreal Protocol, including the United States, request MDI manufacturers that receive CFC allowances to demonstrate that they are pursuing alternatives with due diligence.

83. Ten comments requested that FDA support research and development of safe and effective alternatives. One comment stated that FDA should organize research using pooled resources to develop new, unpatented delivery systems.

FDA is working with industry to facilitate the development of safe and effective alternatives.

84. One comment stated that FDA should seek money from the tobacco industry for research to develop safe and effective MDI's that do not contain CFC's.

FDA does not have the statutory authority to require funding of a particular research project.

85. One comment stated that inventors of non-CFC products should be rewarded with the same patent protections as all other inventors. One comment stated that non-CFC

formulations of CFC-MDI's should not be patented.

The Patent and Trademark Office of the United States awards patents in compliance with laws enacted by the U.S. Congress. FDA has no authority to award patents to new drug products.

86. One comment requested that FDA ease the rules for generic availability by allowing a non-CFC generic to become immediately available for each MDI class which has a CFC generic.

FDA does not have the authority to permit this. The act, as enacted by Congress, governs when FDA may approve a generic. FDA does not have the authority to change the act.

87. One comment stated that FDA should demand more effective delivery systems.

FDA believes that the modern MDI is an effective delivery system. Although FDA encourages advances in delivery systems, the Montreal Protocol does not mandate changes to delivery systems.

88. One comment stated that FDA should reward those who develop CFC-free products by phasing out CFC products.

FDA plans to eliminate essential uses according to the standards it develops through this rulemaking process. FDA is not considering whether any particular standard rewards non-CFC product developers. FDA is simply promoting and protecting the public and patient health and safety as it complies with the terms of the Clean Air Act and the Montreal Protocol.

89. One comment stated that FDA should allow non-CFC product manufacturers to advertise performance improvements without conducting clinical trials to prove those benefits.

FDA requires all claims to be supported by adequate evidence. FDA does not permit manufacturers to make claims of superior performance without supporting comparative evidence.

90. One comment stated that manufacturers should be allowed to advertise important technological attributes of the CFC-free MDI's.

Manufacturers may advertise claims supported by adequate evidence.

91. One comment stated that the Federal Government should favor the reimbursement of non-CFC products.

FDA does not have the authority to control drug costs or reimbursement.

92. One comment stated that it is not within FDA's statutory purview to offer incentives to spur market innovation to phase out CFC-MDI's. One comment said that it is not necessary for FDA to offer development incentives since incentives exist. Another comment said that FDA should focus on market-

oriented incentives rather than "command and control" techniques.

FDA does not have the authority to offer incentives. FDA is simply determining whether the use of an ODS in an FDA regulated product is essential.

93. One comment said that instead of implementing the proposal in the ANPRM, FDA should: (1) Stop production of CFC's, (2) tighten issuance of essential-use allowances, (3) reimpose an excise tax, (4) subsidize use of non-CFC propellants, (5) purchase CFC stockpiles, and (6) allow production and use of CFC-MDI's until stockpiles are exhausted.

FDA does not have the authority to take these measures. FDA can only make determinations in consultation with EPA regarding whether the use of CFC's in an MDI is essential.

94. Four comments stated that users should be required to recycle their empty inhalers.

FDA does not have the authority to require specific types of CFC-MDI disposal.

95. Two comments said that the release of CFC's at MDI manufacturing plants should be regulated.

FDA may regulate the release of CFC's at manufacturing plants if the release violates CGMP's. FDA notes that the Parties to the Montreal Protocol, including the United States, encourage manufacturers to release the lowest possible amount of CFC's during manufacturing.

96. One comment stated that no new exemptions should be granted unless there is a demonstration of special medical need and benefit (e.g., an indicated use that is not available for any other approved product with the same moiety).

FDA is proposing in this rule the standards it will use to grant and maintain essential use exemptions. FDA believes the standards require a showing of special medical need and benefit.

### 13. Cost of New Products

97. Two comments stated that FDA should consider whether lack of competition will increase costs. Another comment requested that FDA not allow phaseout unless alternative products are manufactured by at least two independent manufacturers. A third comment requested that FDA not allow phaseout until there are at least three competitors available in each of the three categories: Quick-acting, 12-hour, and cortisone-based inhalers. One comment asked that FDA not eliminate CFC-MDI's until generic competition for the non-CFC products exists. Two comments said that if CFC substitutes are produced using proprietary

technology, phaseout should not be mandated until the technology is in the public domain. Another comment asked that asthma medicine continue to be available at the lowest possible prices. One comment stated that non-CFC products would likely be higher priced than current MDI's. Five comments stated that FDA's proposal, if implemented, would have an enormous financial impact for state Medicaid drug costs, Medicare patients, and uninsured or inadequately insured individuals who could not afford the new non-CFC agent. Another comment evaluated their institution's cost of replacing generic albuterol CFC-MDI's with Proventil HFA and concluded that the annual cost for albuterol MDI's would increase from approximately \$25,000 to more than \$200,000.

FDA recognizes that cost is a concern for many patients and health care providers. However, when generic products become available is dictated by manufacturers' decisions whether to produce a generic product, by U.S. patent laws, by the exclusivity provisions of the act, and by the approvability of any particular generic drug application. The agency notes that in the current market of CFC-MDI's, only the four active moieties of epinephrine, isoetharine, albuterol, and beclomethasone are marketed by more than one sponsor. Generic products are available for only one active moiety: albuterol. In part due to considerations such as those raised in these comments, FDA has proposed requiring that multiple-source CFC-MDI products be replaced by at least two non-CFC alternative products. FDA has also proposed to consider cost in determining whether alternatives meet patient needs. In addition, FDA expects that the price for most non-CFC products will approximate the price for branded CFC products (see section VII of this document).

98. Another comment stated that any FDA action should consider the research and development costs borne by all parties who strive to replace CFC in their inhalants. One comment stated that FDA should evaluate the cost of postmarketing requirements because they could also drive up costs. One comment asked how much the transition will cost. Two comments predicted that increased costs will result in decreased compliance. One comment stated that lack of generics and additional physician visits due to medication switching will increase costs.

FDA has completed an analysis of the economic impact of its proposal that

addresses these issues (see section VII.B of this document).

99. Four comments stated that FDA should undertake a cost/benefits study comparing the benefits of removing CFC-MDI's from the market to the benefits of allowing continued marketing of CFC devices. One comment stated that FDA should determine whether to eliminate CFC products based on sound science that includes a cost/benefit study whose methodology is published in the **Federal Register**.

FDA has not completed such a study because a statute mandates the removal of nonessential CFC-MDI's from the market.

100. One comment said that large- and small-volume nebulizers and the hand-held ultrasonic nebulizers have been discontinued as covered Medicare devices. The comment asked that FDA work with the Health Care Financing Administration to reverse this policy.

At this time FDA does not consider traditional nebulizers to be alternatives to MDI's because they are not as portable. Therefore, the cost of these products is not addressed in this proposed rule.

101. One comment requested that FDA require new inhalers to be dispensed in the same number of "puffs" as the old inhalers to prevent a cost increase.

Manufacturers determine the number of puffs or the amount of medication given per puff.

102. One comment asked that new medications be available in less expensive sample sizes to allow patients to determine whether they are effective.

FDA cannot mandate the creation or distribution of physician samples. However, manufacturers generally produce such samples for new products to promote familiarity with the new product.

103. One comment requested that FDA require medicine and hospital treatments for asthma and COPD to be free to patients, or otherwise insure all asthma and COPD patients with health and life insurance.

FDA does not have the authority to require either the free distribution of medicine or the provision of health insurance.

14. Environmental Impact of CFC-MDI Use

104. One comment claimed that a continuing exemption for MDI's is permitted under the Montreal Protocol, Title VI of the Clean Air Act, and the regulatory and policy actions of EPA. The comment went on to question whether termination of the essential-use exemption for MDI's will materially

advance stratospheric ozone protection and whether this benefit outweighs the potential social and economic costs of phaseout.

Eight comments stated that the pharmaceutical use of CFC aerosols accounts for less than 1 percent of worldwide consumption. One comment stated that only 0.1 percent of the fluorocarbons in today's world are generated by MDI's used for the treatment of asthma. One comment stated that only one-half of 1 percent of CFC's are generated by MDI's. One comment stated that the environmental impact of CFC's used in MDI's is minimal; therefore, it would be an inefficient use of limited regulatory resources to eliminate CFC-MDI's. One comment stated that there is no way to quantify the effect of eliminating CFC use in MDI's. One comment asked whether the continued use of CFC's in MDI's would be fatally detrimental to the health and well-being of the people of the world.

Three comments stated that CFC's do not cause ozone depletion. Four comments questioned how CFC's could reach the ozone layer.

One comment asked whether anyone knows how thick the ozone layer is supposed to be.

One comment requested that FDA provide figures for: (1) Stockpiled amounts of CFC's; (2) a comparison of CFC amounts to be released over the next decade, particularly MDI and air conditioning use; and (3) measurable change in CFC release due to FDA policy.

One comment asked whether use of an aerochamber reduces CFC release into the atmosphere and requested that if it does, FDA mandate that MDI's be manufactured with the adapters. Another comment asked whether there is a way to use inhalers without releasing CFC's into the atmosphere.

Two comments stated that CFC replacements, including the ones approved for use in MDI's, also cause ozone depletion, but to a lesser extent, and asked why FDA is planning to replace CFC's, which have a long history of safe use in humans, with toxic chemicals that also may be phased out.

One comment stated that FDA is required to prepare an environmental impact statement under the National Environmental Protection Act.

One comment stated that stratospheric ozone is our main global protectant against ultraviolet B light (UVB), and international restrictions on CFC releases will allow the progressive destruction of stratospheric ozone to cease and begin to rebuild in the early 21st century. The comment also noted

that the current generation of children face a 1:70 risk of melanoma. In addition, the comment stated that basal and squamous cell carcinoma, cancer precursor lesions, premature skin aging (spotting, wrinkling, fragility, sallowness, sagging), photo-induced medication reactions, autoimmune disease (i.e. lupus), immune suppression, porphyria, and regular sunburn are all exacerbated by the UVB rays in sunlight, which will become more intense on an increasing basis by 2010 due to ozone depletion.

One comment asked that FDA cut the CFC allocations for companies manufacturing products with technically feasible alternatives rather than for all companies across the board.

One comment stated that FDA should not assess the potential beneficial effects of reducing CFC emissions from drug products since the United States has already assessed the effects and made the decision to eliminate CFC's.

The United States evaluated the environmental effect of eliminating the use of all CFC's in an environmental impact statement in the 1970's (see 43 FR 11301, March 17, 1978). As part of that evaluation, FDA concluded that the continued use of CFC's in medical products posed an unreasonable risk of long-term biological and climatic impacts (see Docket No. 96N-0057). Congress later enacted provisions of the Clean Air Act that codified the decision to fully phase out the use of CFC's over time (see 42 U.S.C. 7671 *et seq.* (enacted November 15, 1990)). FDA notes that the environmental impact of individual uses of nonessential CFC's must not be evaluated independently, but rather must be evaluated in the context of the overall use of CFC's. Cumulative impacts can result from individually minor but collectively significant actions taking place over a period of time (40 CFR 1508.7). Significance cannot be avoided by breaking an action down into small components (40 CFR 1508.27(b)(7)). Although it may appear to some that CFC-MDI use is only a small part of total CFC use and therefore should be exempted, the elimination of CFC use in MDI's is only one of many steps that are part of the overall phaseout of CFC use. If each small step were provided an exemption, the cumulative effect would be to prevent environmental improvements. FDA is merely fulfilling its obligation to make essential-use determinations for FDA-regulated products, in accordance with the Clean Air Act.

FDA notes that CFC-MDI's do release CFC's as part of their intended use. Tube spacers, inhalation techniques,

and other factors do not alter this release.

15. Proposed Mechanism for Phaseout  
105. One comment requested that FDA publish this proposed rule by September 1997.

FDA was not able to meet this request. The comment period for the ANPRM did not close until May 5, 1997. During the comment period, FDA received approximately 9,400 comments and has since received approximately another 200 comments. FDA required a sufficient amount of time to carefully review and analyze these numerous comments, and therefore could not publish this proposed rule by September 1997.

106. One comment said that FDA should establish target dates by which significant reductions in CFC-MDI use should be accomplished. The first date should be by the end of the year 2000.

FDA's authority under the Clean Air Act is to determine whether ODS products are essential. This proposed rule is designed to set forth the criteria FDA will use to make those determinations.

107. One comment requested that, as part of the phaseout procedure, FDA require industry to educate physicians and patients that: (1) CFC's serve no medical purpose, and (2) the transition is not about removing drugs but about getting rid of CFC's. Two comments said that FDA should require patient and physician education. One comment said that a seamless transition scheme should be developed and should include patient and health care provider educational resources and programs as well as public awareness campaigns well before projected phaseout dates. Another comment said that transition should be undertaken as a joint project by FDA, the National Asthma Education and Prevention Program (NAEPP) of the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH), industry (e.g., International Consortium of Pharmaceutical Aerosol Manufacturers (IPAC), professional organizations (e.g., American Lung Association) and patient advocacy groups (e.g., Mothers of Asthmatics) to ensure dissemination of consistent information. The comment went on to say that educational efforts should include presentations at national scientific and professional meetings and seminars, consultations with public interest groups, one-on-one instruction, and publications in professional as well as lay media (e.g., flyers, posters, newspaper articles, videos, stories, plays). One comment said that FDA should consider psychological factors that could result in slow acceptance of

new products. Ten comments said that patients, physicians, and managed care companies need education.

FDA recognizes the need to educate patients, health care providers, and interested parties about the planned phaseout of CFC-MDI's for the transition to non-CFC products to occur as smoothly as possible. Although FDA cannot require industry to undertake an educational plan, FDA has been involved in public education for the past several years. Members of the Center for Drug Evaluation and Research's (CDER's) Division of Pulmonary Drug Products have made presentations and participated in panel discussions on the phaseout of CFC's at national scientific and professional society meetings and will continue to do so.

The division has also worked in close cooperation with the NAEPP, an ongoing comprehensive national asthma education, treatment, and prevention program directed by the staff of the National Heart, Lung, and Blood Institute of NIH. NAEPP educates physicians, other health care providers, and patients about issues related to the prevention and treatment of asthma, including the phaseout of CFC's. The NAEPP Coordinating Committee formed a CFC Workgroup to educate patients and physicians about the CFC phaseout. The NAEPP CFC Workgroup, in cooperation with IPAC, recently developed a "fact sheet" for patients entitled "Your Metered-Dose Inhaler Will Be Changing \* \* \* Here Are the Facts." The fact sheet is available through the FDA web site <http://www.fda.gov/cder/mdi/>. The NAEPP CFC Workgroup is continuing to broaden its educational effort. FDA provides appropriate advice and assistance to the NAEPP CFC Workgroup.

FDA has also published articles on the phaseout of CFC's in FDA Consumer, Journal of the American Medical Association (JAMA), and the FDA Medical Bulletin to educate health care providers and patients about FDA actions, or proposed actions, related to the transition to non-ODS inhalation products.

The agency views these educational efforts as a critical component of the transition process and intends to continue these efforts as the transition to non-ODS products moves forward.

108. One comment stated that FDA must provide notice and an opportunity for hearing before withdrawing any drug.

FDA uses the procedures in 21 CFR 314.200 to withdraw approval of a drug. Under proposed § 2.125, FDA is not



proposing to withdraw approval of any drug, FDA is simply proposing a process for determining whether the use of an ODS in a particular medical device continues to be essential. To maximize public input, FDA will use notice-and-comment rulemaking to evaluate whether a moiety should remain on the list of essential uses.

109. One comment stated that, upon publication of a proposed rule, FDA must disclose in appropriate detail and specificity the data and technical information upon which the agency relied in reaching its policy decisions.

FDA has disclosed in the ANPRM and in this proposed rule the data and technical information upon which it relied in drafting this proposal. 16. International Mandate (Montreal Protocol)

110. Three comments said that FDA should take no further action until the plenary meeting of the Montreal Protocol Parties scheduled for November 1998.

Although FDA did not publish this proposed rule before the November 1998 meeting, it has continued to work to develop the proposal. The Parties to the Montreal Protocol suggested that Parties requesting essential-use allowances submit an initial transition strategy by January 31, 1998, and required these Parties to submit an initial strategy no later than January 31, 1999. FDA is acting now to ensure that patients in the United States are not put at risk by the phaseout.

111. Three comments stated that medical use of CFC's should be permitted and should be the only worldwide exception. One comment noted that although the total amount of CFC's used in MDI's represents a small portion of total use, that use is increasing and it is inconsistent with the Montreal Protocol to claim that a small use justifies delay.

The Clean Air Act requires the phaseout of nonessential CFC MDI's. 17. Legal Arguments

112. Seven comments challenged FDA's authority to withdraw an application because of failure to meet the essential-use requirements of § 2.125.

FDA is not proposing to withdraw approval of any applications in applying proposed § 2.125. Rather, FDA is determining whether the use of a CFC in a particular medical device remains essential as alternative products become available and are accepted. Even when a moiety is removed from the essential-use listing of § 2.125(e), the NDA's for the affected moiety need not necessarily be withdrawn under section 505(e) of the act. FDA notes that manufacturers

may not be eligible to receive CFC allowances under the Montreal Protocol and the Clean Air Act even if they have approved applications.

One comment stated that FDA has no legal authority to prohibit the continued use of existing inventories of CFC's used in medical devices.

This proposed rule does not necessarily prohibit the continued use of existing inventories of CFC's in medical devices. Rather, the proposal sets forth the factors FDA would use to determine whether the use of CFC's in a medical product is essential.

113. Several comments stated that FDA does not have the statutory authority under the act to declare that a drug product is adulterated or misbranded simply because the product contains an ODS.

The agency is proposing to remove the provisions of § 2.125 that state that a product in a self-pressurized container that contains an ODS is adulterated and/or misbranded. This change should not be interpreted to mean that FDA agrees with these comments. Such nonessential products are adulterated and/or misbranded under certain act provisions, including sections 402, 403, 409, 501, 502, 601, and 602 of the act (21 U.S.C. 342, 343, 348, 351, 352, 361, and 362). The basis for FDA's authority to declare such products adulterated and/or misbranded is discussed in the preambles for the current § 2.125 and related rules and proposed rules (see 43 FR 11301, March 17, 1978; 42 FR 24536, May 13, 1977; 42 FR 22018, April 29, 1977; and 41 FR 52071, November 26, 1976). However, FDA is changing the regulation to conform to the authority delegated to it under the Clean Air Act. FDA notes that EPA is responsible for enforcement of provisions of the Clean Air Act.

114. One comment stated that all CFC-MDI's with the same active moiety as an approved non-CFC alternative must be phased out upon approval of the non-CFC alternative because: (1) Section 601(8) of the Clean Air Act (42 U.S.C. 7671(8)) indicates that as soon as a non-CFC product receives FDA approval, all CFC-MDI's for which the non-CFC product is an alternative can no longer qualify as essential; and (2) non-CFC product approval by FDA constitutes a formal administrative adjudication by FDA that there is a technically feasible alternative to the use of CFC's in certain adrenergic bronchodilator MDI's.

FDA disagrees with this comment. Section 601(8) of the Clean Air Act (42 U.S.C. 7671(8)) defines which medical products may continue to use ozone-

depleting substances. The definition states:

(8) Medical device. The term "medical device" means any device (as defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321)), diagnostic product, drug (as defined in the Federal Food, Drug, and Cosmetic Act), and drug delivery system—

(A) if such device, product, drug, or drug delivery system utilizes a class I or class II substance for which no safe and effective alternative has been developed, and where necessary, approved by the Commissioner; and

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

The comment wrongly assumes that a non-CFC product with the same active moiety as a CFC product is a "safe and effective alternative" to that CFC product. A non-CFC product simply having the same active moiety as a CFC product is only one factor to be considered. Other factors, such as whether the non-CFC product has the same route of administration, the same indication, and can be used with approximately the same level of convenience, are important considerations. Additionally, FDA must consider whether patients who medically need the CFC product are adequately served by the non-CFC product. In those instances where an active moiety is marketed by two or more NDA's or marketed in multiple, distinct strengths, at least two non-CFC products that contain the same active moiety must be marketed to adequately serve the consumer.

This comment also demonstrates a misunderstanding of the meaning of an FDA-approval of a non-CFC product. FDA's approval of a non-CFC product is a determination that the product is safe and effective, but it is *not* a determination that the product is a safe and effective *alternative* to any other product. That requires a separate and distinct analysis.

The comment is correct to the extent that it indicates that once a non-CFC product that is a safe and effective alternative is approved, the CFC-product must be phased out. Those factors described previously and those incorporated into this proposed rule are factors to be considered when determining whether a non-CFC product is a safe and effective alternative to a CFC-product. FDA believes these factors are also an important part of the analysis used to determine whether a product is essential. FDA and EPA will be consulting to determine whether such medical products are essential and safe and effective alternatives.

115. One comment stated that under the Montreal Protocol, for use of an ODS in a product to be no longer essential there must be multiple alternatives and the alternatives must be: (1) Technically feasible, (2) economically feasible, (3) acceptable from an environmental standpoint, and (4) acceptable from a health standpoint. The comment stated that FDA is responsible for making determinations (1), (2), and (4), and that EPA is responsible for making the third determination.

Under this proposal, FDA is requiring the existence of feasible alternatives that are acceptable from a health standpoint before it will find any CFC-MDI no longer essential.

116. Two comments stated that there is no need for FDA to make a determination of essential use under the Clean Air Act, although it does have the authority to do so, because the determination is to be made under the Montreal Protocol.

Section 601 of the Clean Air Act explicitly directs "the Commissioner [of FDA] in consultation with the Administrator" of EPA to determine whether a device, product, drug, or drug delivery system is essential under the Clean Air Act (42 U.S.C. 7671(8)). This determination is different from the essential use determination made under the Montreal Protocol.

117. One comment stated that the Clean Air Act does not require a preferable or popular alternative but only an alternative that is FDA approved (safe and effective) and technically feasible.

As explained previously, although FDA approval does constitute a determination that a product is safe and effective on its own, this finding does not constitute a determination regarding whether one product is a medically acceptable alternative for another.

118. One comment discussed extensively products EPA has allowed to stay on the market and concluded that FDA should not ban MDI's.

First, FDA is not banning any MDI's. Rather, FDA is making a determination regarding whether the use of CFC's in particular medical products continues to be essential. Second, FDA cannot speak on behalf of EPA regarding why certain products may remain on the market. However, FDA notes that the comment's analysis relies on 42 U.S.C. 7671i(e), which states specifically that it does not apply to medical devices as defined in the Clean Air Act (42 U.S.C. 7671(8)).

119. One comment stated that FDA cannot find products nonessential if they do not have a therapeutically equivalent replacement.

Neither the Clean Air Act or the Montreal Protocol requires alternative products to be therapeutically equivalent to a CFC product before the CFC product can be considered nonessential.

120. One comment stated that the ANPRM conflicts with the Drug Price Competition and Patent Term Restoration Act of 1984 by impeding generic competition, because under section 505(c)(3)(D) of the act, products with an active ingredient that do not contain a new chemical entity will receive 3 years of market exclusivity and products with an active ingredient that is a new chemical entity will receive 5 years of market exclusivity. Further, patent protections may extend the time during which generic competition is prevented.

FDA recognizes that the phaseout of CFC-MDI's may affect the availability of generic products, depending on whether the phaseout occurs before generic versions of non-CFC products may be marketed. However, the Clean Air Act and the Montreal Protocol mandate the phaseout of non-essential uses of CFC's.

121. One comment noted that, in the case of Seldane, FDA acknowledged that not all patients are well-served when there are only two drugs available, and questioned whether the therapeutic class approach proposed in the ANPRM is consistent with this.

Although FDA disputes this interpretation of the Seldane notice of opportunity for hearing (62 FR 1889, January 14, 1997), FDA is no longer proposing to use the therapeutic class approach to remove essential uses from § 2.125(e).

122. One comment noted that FDA expressed concern about the differences between MDI's in its proposed rule to amend the OTC monograph for bronchodilator drug products (60 FR 13014, March 9, 1995).

FDA did express concern about the differences between MDI's in the OTC proposed rule. FDA noted that the differences meant that all new MDI's should be approved by FDA under an NDA supported by clinical trials designed to examine the effect of MDI differences. In recognition of the complexities of this dosage form, FDA is requiring each non-CFC MDI to be reviewed as a new NDA, rather than as a supplement to an existing CFC-MDI NDA. In addition, FDA has been encouraging sponsors to include in these clinical trials comparators representing the currently available CFC-based products. FDA believes its action regarding the development of the non-ODS products is consistent with its

concerns expressed in the OTC proposal of March 9, 1995.

123. One comment noted that de minimis exemptions from statutory requirements are permitted and therefore requested that MDI's be exempted from the Clean Air Act requirement that all uses of CFC's cease.

FDA does not have the discretion to decide how to implement the Clean Air Act because EPA is the primary agency charged with implementing these provisions. However, as a matter of general statutory construction, provision of a specific exemption for medical products makes it unlikely that de minimis exemptions for medical products would also be permitted under the Clean Air Act.

124. One comment posited that FDA is operating under a false construct whereby the agency assumes it must follow environmental recommendations made by EPA and Parties to the Montreal Protocol.

FDA is not taking this action as a result of recommendations made by EPA or the Parties to the Montreal Protocol. Rather, FDA is complying with the statutory mandate of U.S. law as embodied in the Clean Air Act, which implements the Montreal Protocol and requires the phaseout of CFC use. FDA is taking this action to ensure that patient health is protected throughout the transition.

125. Two comments stated that FDA must comply with Executive Order 12866. One of those comments also said that FDA must comply with Executive Orders 12291, 12606, 12898, and the Regulatory Flexibility Act.

Executive Order 12291 was revoked by Executive Order 12866 section 11. 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. The agency has complied with this requirement to the extent necessary (see section VII of this document).

Executive Order 12606 was revoked and replaced by Executive Order 13045 section 7-702. Executive Order 13045 applies only to regulatory actions initiated after the date of the Executive Order (Executive Order 13045 section 2-202). The ANPRM was published on March 6, 1997, before the Executive Order was signed on April 21, 1997. Accordingly, this proposed regulatory action is exempt from Executive Order 13045. In addition, Executive Order 13045 applies only to significant regulatory actions that concern an environmental health risk or safety risk that an agency has reason to believe may

disproportionately affect children. First, this proposal is not a significant regulatory action because it is not anticipated that it will have an annual net effect on the economy of \$100 million or more, nor would it adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities. Second, the phaseout of CFC-MDI's is not an environmental health risk.

Rather, the phaseout constitutes an environmental health benefit, since reduction in CFC use could decrease ongoing damage to the ozone layer and thereby decrease related health problems. In particular, children will benefit from a phaseout because they are more susceptible to skin cancers due to increased sensitivity and lifetime exposure. Therefore, Executive Order 13045 does not apply to this proposal.

Executive Order 12898 requires agencies to identify and address disproportionately high adverse human health or environmental effects on minority populations and low-income populations. The agency does not anticipate that this proposed rule, if implemented, will have any adverse effects on human health or the environment.

The Regulatory Flexibility Act (5 U.S.C. 601 *et seq.*) requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The agency has complied with this requirement (see section VII.A of this document).

126. One comment stated that FDA must assess environmental impacts under 2 U.S.C. 1532 and 1535.

The primary purpose of the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) is to end the imposition of unfunded Federal mandates on other governments without the full consideration of the Federal Government (2 U.S.C. 1501(2)).

However, the Unfunded Mandates Reform Act does also ask agencies to estimate the impact of unfunded Federal mandates on the private sector (2 U.S.C. 1501(3)). As part of that estimate, the agency is to examine the effect of the Federal mandate on health, safety, and the natural environment. FDA has complied with this requirement (see section VII of this document). In addition, FDA believes that environmental benefits are analyzed with the regulations implementing the Clean Air Act.

#### IV. Legal Authority

FDA's proposal to determine when CFC uses are essential in medical

devices is authorized by the Clean Air Act. EPA regulations implementing the provisions of section 610 of the Clean Air Act (42 U.S.C. 7671i) contain a general ban on the use of CFC's in pressurized dispensers (40 CFR 82.64(c) and 82.66(d)). The Clean Air Act and EPA regulations exempt from the general ban "medical devices" that FDA considers essential and that are listed in § 2.125(e) (42 U.S.C. 7671i(e); 40 CFR 82.66(d)(2)). Section 601(8) of the Clean Air Act defines "medical device" as any device (as defined in the act), diagnostic product, drug (as defined in the act), and drug delivery system, if such device, product, drug, or drug delivery system uses a class I or class II ozone-depleting substance for which no safe and effective alternative has been developed (and, where necessary, approved by the Commissioner of Food and Drugs (the Commissioner)); and if such device, product, drug, or drug delivery system has, after notice and opportunity for public comment, been approved and determined to be essential by the Commissioner in consultation with the Administrator of EPA (the Administrator). Class I substances include CFC's, 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 (HCFC's) (see 40 CFR part 82, appendix B to subpart A). Essential-use products are listed in § 2.125(e). Although § 2.125 includes a mechanism for adding essential-use products to the regulations, the regulations do not include a mechanism for removing products from the essential-use list. This proposed rule, if enacted, would provide a mechanism for FDA to remove products from the essential-use list in an orderly and rational fashion.

#### V. Proposed Implementation Plan

FDA proposes that any final rule that may issue based on this proposal become effective 1 year after its date of publication in the **Federal Register**. After that date, FDA would evaluate products on the essential-use list according to the criteria set forth in the rule. As the criteria for eliminating essential uses are met, FDA will publish proposals to eliminate essential uses for the appropriate individual active moieties. FDA intends that such proposals will be published and finalized in an expeditious manner.

#### VI. Request for Comments

Interested persons may, on or before November 30, 1999, submit to the

Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one 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 office above between 9 a.m. and 4 p.m., Monday through Friday.

In particular, FDA seeks comment on the following issues:

1. The criteria FDA should use to determine whether a subpopulation is significant;
2. The type of postmarketing information FDA should consider in evaluating the adequacy of alternatives; and
3. The timing of the removal of the essential-use designation for nasal steroids.

#### VII. Analysis of Impacts

##### A. Introduction

FDA has examined the impacts of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601-612), and under the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs regulatory 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). Unless the agency certifies that the rule is not expected to have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant economic impact of a rule on small entities. Section 202 of the Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation). The agency has conducted analyses of the proposed rule, and has determined that the rule is consistent with the principles set forth in the Executive Order and in these statutes. FDA finds that this proposed rule will not result in costs in excess of \$100 million, and therefore no further analysis is required under the Unfunded Mandates Reform Act. In addition, FDA certifies that this

proposed regulation would not result in a significant economic impact on a substantial number of small entities. Thus, the agency need not prepare an interim Regulatory Flexibility Analysis.

This proposed rule would amend the regulation that permits the use of ODS's in particular circumstances by setting the standards that FDA will use to determine when the use of ODS's in FDA-regulated products is essential under the Clean Air Act. In 1987, the United States became a party to an international agreement known as the Montreal Protocol. The Parties to the Protocol have agreed to eventually eliminate all uses of ODS's. However, the Parties currently permit the use of ODS's in essential medical products. FDA, in consultation with EPA, must determine whether the uses of ODS's in medical products are essential. Currently, the United States has secured essential-use designations for the use of CFC's (which are ODS's) in MDI's through the year 2000 and will continue to seek such designations until acceptable alternatives make CFC-MDI's nonessential.

CFC's are presently used as propellants in MDI's. FDA has approved 17 active moieties that use CFC's in MDI's, although only 16 are marketed as either prescription or OTC products (see Table 1 of this document). These CFC-MDI's are approved for the treatment of asthma and other COPD's. Several manufacturers are in the process of reformulating their CFC-MDI's to use non-ODS propellants in the United States. In some foreign markets, reformulated products are already in the process of displacing or have already displaced products containing ODS's.

FDA is also proposing to remove the essential-use designation for metered-dose steroid human drugs for nasal inhalation. Four manufacturers market five CFC-nasal inhalation drug products, which constitute less than 20 percent of the nasal inhalation product market. The drug products contain either beclomethasone, budesonide, or triamcinolone. Beclomethasone and triamcinolone are also marketed in non-CFC formulations. The manufacturer of budesonide has represented publicly that it intends to market a non-CFC formulation.

### *B. Economic Impacts*

The proposed regulation articulates the standards used by FDA to determine whether the use of CFC-MDI's is essential. This proposal would not have any economic impact, since it simply establishes the criteria FDA would use to make essential-use determinations. However, application of the rule in

future rulemakings would generate both regulatory benefits and costs. FDA discusses some of those possible benefits and costs here, but notes that it would conduct additional analyses as part of its notice-and-comment rulemaking for essential-use designations for particular products.

#### 1. Regulatory Benefits

The potential benefits of the rule are the environmental gains associated with the diminished use of ODS's in medical products. FDA has not attempted to quantify the value of these environmental improvements, which would constitute only a small fraction of the overall benefits of compliance with the Clean Air Act and Montreal Protocol. Nevertheless, even a relatively small percentage would represent a significant value. EPA has estimated in prior regulatory impact analyses that the aggregate public health benefit of the phaseout of ODS's due to reduced cases of skin cancer, cataracts, and other health effects ranges between \$8 and \$32 trillion (Ref. 1).

Currently, about 14.6 million patients are being treated for asthma and COPD (Ref. 2). FDA believes that these patients are treated with MDI's. Over 120 million prescriptions for the affected drug substances are dispensed each year. Although the Clean Air Act and the Montreal Protocol require the eventual elimination of essential-use designations for these products, the agency has carefully structured its rule to avoid negative impacts on the nation's public health. Most importantly, the proposed regulation would ensure that adequate supplies of reformulated products with comparable therapeutic roles are available prior to rescission of an essential-use designation. An alternative product that could not demonstrate comparable therapeutic outcomes would not be considered a medically acceptable alternative and the essential-use designation for the CFC-MDI would remain in place. Thus, the rule would ensure that treatment outcomes would not be threatened as products are reformulated with acceptable, non-ODS propellants.

FDA notes that upon approval, new non-ODS products could be eligible for market protections under the Hatch-Waxman Amendments. Thus, existing lower-priced generic CFC-MDI's could disappear from the market if their active moiety were no longer designated as essential. However, FDA finds that the total number of pharmaceutical prescriptions purchased has not typically increased following the introduction of generic competition (Ref. 3). Consequently, FDA does not

anticipate a significant decrease in the total number of prescriptions purchased due to curtailment of generic competition. However, these impacts may vary for particular products or markets and FDA asks for public comment on this issue, with particular attention to evaluating effects on patient affordability.

FDA also notes that removal of the essential-use designation for nasal steroids would not have a negative impact on the nation's public health. Adequate supplies of reformulated products with comparable therapeutic roles exist and are used widely by patients for the treatment of seasonal and perennial allergic rhinitis. FDA also notes that the price of the alternative nasal inhalation drugs are approximately the same as for the CFC-products on a dose per dose basis.

#### 2. Regulatory Costs

Sponsors who elect to reformulate their products will incur significant costs to collect the detailed clinical data necessary for approval of reformulated products. One sponsor that has developed alternative formulations has stated that the total development costs of reformulated MDI's have approached \$250 million (Ref. 4). FDA has no empirical data to confirm these costs, but notes that these outlays imply global expenses for replacing propellants, as required by various environmental agreements, such as the Montreal Protocol. Product manufacturers are well aware of the mandate to eliminate the marketing of ODS's and are already engaged in the development of reformulated products. Because these international development activities will continue regardless of FDA's precise standards for rescinding essential-use determinations, FDA considers these reformulation costs a direct consequence of the statutory requirements of the Clean Air Act, rather than of FDA's forthcoming regulation. Postmarketing studies of reformulated products would be part of these development costs. Thus, FDA finds that the aggregate costs of the rule are directly attributable to the enactment of the Clean Air Act.

For nasal steroids, FDA does not anticipate any regulatory costs as a result of this proposal, since the manufacturers that market the CFC-products are the same manufacturers that market non-CFC alternatives or have filed an application to do so.

#### 3. Distributive Impacts

The future establishment of specific rules for the elimination of essential-use designations could have significant

distributional impacts on various economic sectors. In particular, FDA's essential-use designation decisions would determine when individual generic CFC-MDI's would no longer be considered essential. Such decisions could force generic consumers to switch to higher-priced reformulated, branded products until non-ODS generic products became available. These consumers could face significant cost increases, of which third-party payers, including the nation's Medicaid system, might bear roughly 70 percent. Alternatively, patients that use brand name products should experience little change in either costs or outcomes due to this rule. Experience from the United Kingdom (Ref. 4) and comments from potential manufacturers indicate that the reformulated brand name products would likely be priced comparably to current brand name products. Diminished generic alternatives are not expected to alter this expectation, as several studies have shown that the availability of generic substitutes has had little impact on the price of branded products (Refs. 3, 5, 6, 7, and 8).

Distribution systems (warehouses, distribution centers, and retail pharmacies) for pharmaceutical products are reported to generate higher profit rates per prescription for generic products than for branded products (Refs. 9 and 10).<sup>7</sup> Accordingly, each branded prescription substituted for a generic prescription could result in lost revenue for distributors and retailers. Generic manufacturers could also lose sales revenues following the rescission of an essential-use designation, although these firms might mitigate these losses by shifting production resources to other generic products. In total, therefore, patients, third-party payers, distributors, and generic manufacturers could experience overall sector losses due to the removal of a product from the essential-use list in § 2.125.

On the other hand, manufacturers of reformulated branded products would receive increased revenues, because sales of branded products would increase by capturing the current demand for generic prescriptions.

These distributional impacts will not be triggered, however, until the completion of a future rulemaking on each ODS-containing product. FDA plans to conduct specific market analyses to determine the approximate magnitude of these economic effects prior to determining the essentiality of these ODS products.

FDA does not anticipate any distributive impacts due to the removal of the essential-use designations for nasal inhalation products because the alternative products are marketed by the same manufacturers.

### C. Small Business Impact

#### 1. Initial Analysis

The proposed standards provide a framework for FDA's future decisions regarding essential-use designations for particular CFC-MDI's and would remove the essential-use designations for metered-dose steroid human drugs for nasal inhalation. FDA certifies that this rule would not have a significant impact on a substantial number of small entities. Nevertheless, FDA has prepared the elements of an Initial Regulatory Flexibility Analysis to alert any potentially affected small entities of the opportunity to submit comments to the agency. FDA notes that the direct regulatory costs are attributable to the Clean Air Act and Montreal Protocol mandate to phase out the use of ODS's and are not dependent upon the enactment of this proposed rule.

#### 2. Description of Impact

The objective of the proposed regulation is to provide the basis for essential-use designations for ODS's in FDA-regulated products, without jeopardizing the public health. The proposed regulation would accomplish this objective by articulating the standards to be used for revising essential-use designations for approved drug products. The statutory authority for the proposed rulemaking is discussed in section IV of this document.

The industry primarily affected by the rescission of essential-use designations would be manufacturers of pharmaceutical preparations (Ref. 11, SIC 2834). Census data indicate that more than 92 percent of the approximately 700 manufacturing establishments and 87 percent of the 650 firms in this industry have fewer than 500 employees. The Small Business Administration (SBA) considers firms with fewer than 750 employees in this sector to be small, but census size categories do not correspond to the SBA designation. Nevertheless, when the procedures of this proposed regulation are implemented, the major impact would likely be incurred by fewer than five small manufacturers of generic products and even fewer small manufacturers of branded products.

Table 1 of this document shows that seven drug substances will be eligible for generic competition in the next

several years. However, even in the absence of any FDA decision, many of these drug substances are unlikely to attract generic competition because of their relatively small market share and the knowledge that ODS's are to be removed from the market. In fact, several drug substances that have lost market exclusivity have not been subject to generic competition.

FDA notes that metered-dose steroid human drugs for nasal inhalation are manufactured by four manufacturers, none of whom are small. Therefore, FDA does not expect its proposal to remove the essential-use designation for metered-dose steroid human drugs for nasal inhalation to have a significant impact on a substantial number of small entities.

FDA does not expect significant impacts on wholesalers of pharmaceutical products (Ref. 11, SIC 5122) or retail pharmacies (Ref. 11, SIC 5912) because only a few of the thousands of pharmaceutical products sold by these firms is likely to be affected.

#### 3. Analysis of Alternatives

FDA examined several alternatives to the proposed rule. First, FDA considered denying new essential-use designations but allowing currently exempted drug products to continue to use ODS's. This alternative would continue the availability of current therapies at no additional transfer of costs. However, there would be no incentive to reformulate products. Thus, this alternative would not meet the environmental requirement to eliminate the use of ODS's.

Next, FDA considered allowing essential-use designations for all CFC-MDI's to remain in place until a specific time. However, this alternative imposes a risk of significant market disruption when products are removed. FDA preliminarily estimated that disruption of therapies and additional costs of shortages could cost almost \$1 billion. In addition, allocations of ODS's are not guaranteed. The United States must seek and be granted allocations through procedures established by the Montreal Protocol. As part of those procedures, the United States has committed to a yearly examination of essential-uses.

FDA also considered removing essential-use designations for all drug products within a therapeutic class as soon as any two active moieties within the class were available in non-ODS formulations. Defining alternative therapies to include all active moieties within a therapeutic class would hasten the removal of ODS's from the environment. However, FDA rejected

<sup>7</sup>Data indicate this to be true in both absolute and proportional terms.

this alternative because of concerns about the ability of a few products to replace all products within a therapeutic class.

Another option would have been for the United States to remove essential-use designations for products on a regular basis or by reduction in CFC allocations. FDA is not encouraging selection of this option because there would be inadequate consideration of the public health impact of essential-use designations.

**D. Conclusion**

This analysis examined the impact of FDA's proposed rule to set the conditions and standards for determining the essentiality of using ODS's in MDI's and to remove the essential-use designations for metered-dose steroid human drugs for nasal inhalation. FDA believes that this rule would ensure adequate product availability without jeopardizing the desired therapeutic outcomes associated with the affected products. Also, the

agency finds that its rule would impose nominal net societal costs, although FDA recognizes that removing essential-use designations for products for the treatment of asthma and COPD could generate substantial losses and gains for particular sectors of the economy. As each essential-use removal for such products would be made through notice-and-comment rulemaking, FDA would examine the particular impact of each essential-use designation at the time of the specific proposal.

TABLE 1.—DESCRIPTION OF THE AFFECTED DRUG SUBSTANCE (AS OF SEPTEMBER 1998)<sup>1</sup>

Drug Substance in MDI	Generic Available?	Number Distributed Annually (millions)	Approximate Market Share (percent)	Off Patent Date
Albuterol	Yes	48.80 <sup>2</sup>	40.5	Off
Beclomethasone	No	21.31	17.7	December 1999
Ipratropium	No	13.47	11.2	Off
Triamcinolone	No	9.26	7.7	October 1999
Salmeterol	No	6.84	5.7	January 2012
Flunisolide	No	4.45	3.7	June 2007
Fluticasone	No	3.37	2.8	November 2003
Albuterol/Ipratropium	No	2.15	1.8	June 2015
Pirbuterol	No	2.07	1.7	May 2004
Metaproterenol	No	1.52	1.3	Off
Cromolyn	No	1.47	1.2	September 2000
Nedocromil	No	0.87	0.7	October 2006
Bitolerol	No	0.12	0.1	Off
Isoetharine	No	0.07	0.1	Off
Terbutaline	No	0.02	0.0	Off
Total		115.79	96.2 <sup>3</sup>	

<sup>1</sup> Source: FDA CDER data and *Approved Therapeutic Drug Products*, 19th ed.

<sup>2</sup> Including 34.96 million generic and relabeled prescriptions.

<sup>3</sup> Percentages do not add to 100 percent because data are not available for epinephrine and isoproterenol.

**VIII. The Paperwork Reduction Act of 1995**

The proposed rule does not require information collections subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Section 2.125(f) provides that a person may seek to add or remove an essential use listed under § 2.125(e) by filing a petition under part 10 (21 CFR part 10). Section 10.30(b) requires that a petitioner submit to the agency a statement of grounds, including the factual and legal grounds on which the petitioner relies. Section 2.125(f) describes the factual grounds necessary to document a petition to add or remove an essential use, as required by § 10.30(b). The burden hours required to provide the factual grounds for a petition have been calculated under § 10.30 and have been approved under OMB control No. 0910–0183, which expires on June 30, 2000.

**IX. References**

The following references have been placed on display in the Dockets Management Branch (address above)

and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. ICF Inc., *Regulatory Impact Analysis: Compliance with Section 604 of the Clean Air Act for the Phaseout of Ozone Depleting Chemicals*, ch. 6, July 1, 1992.

2. U.S. National Center for Health Statistics, *Vital and Health Statistics*, Series 10, No. 193, 1996.

3. Caves, R. E. et al., "Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry," in "Brookings Papers on Economic Activity: Microeconomics," edited by M. N. Brady, pp. 1–66, 1991.

4. "Glaxo Ventolin Evohaler U.K. Launch Stresses Consistency With Predecessor," *Pink Sheet*, vol. 60:37, 1998.

5. Grabowski, H. G., and J. M. Vernon, "Brand Loyalty, Entry, and Price Competition in Pharmaceuticals After the 1984 Drug Act," *Journal of Law and Economics*, 35:10(331–350), 1992.

6. Wiggins, S., and R. Maness, "Price Competition in Pharmaceutical Markets," PERC Working Paper No. 9409, Texas A&M University, Economics Department, 1993.

7. Ellison, S. F. et al., "Characteristics of Demand for Pharmaceutical Products: An Examination of Four Cephalosporins," *RAND Journal of Economics*, 28:3(426–446), 1997.

8. Frank, R. G., and D. S. Salkever, "Generic Entry and the Pricing of

Pharmaceuticals," *Journal of Economics and Management Strategy*, 6:1(75–90), 1997.

9. Grabowski, H. G., and J. M. Vernon, "Longer Patents for Increased Generic Competition in the United States: The Waxman-Hatch Act After One Decade," *PharmacoEconomics*, 10 (Suppl. 2):110–123; 1996.

10. U.S. Congressional Budget Office, *How Increased Competition From Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry*, 1998.

11. U.S. Small Business Administration, *Table of Size Standards*, 1996.

**List of Subjects in 21 CFR Part 2**

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Clean Air Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 2 be amended as follows:

**PART 2—GENERAL ADMINISTRATIVE RULINGS AND DECISIONS**

1. The authority citation for 21 CFR part 2 is revised 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. Section 2.125 is revised to read as follows:

**§ 2.125 Use of ozone-depleting substances in foods, drugs, devices, or cosmetics.**

(a) As used in this section, *ozone-depleting substance* (ODS) means any class I substance as defined in 40 CFR part 82, appendix A to subpart A, or class II substance as defined in 40 CFR part 82, appendix B to subpart A.

(b) Except as provided in paragraph (c) of this section, 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 is not an essential use of the ODS under the Clean Air Act.

(c) A 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 is an essential use of the ODS under the Clean Air Act if paragraph (e) of this section specifies the use of that product as essential. For drugs, including biologics and animal drugs, and for devices, an investigational application or an approved marketing application must be in effect, as applicable.

(d) [Reserved]

(e) The use of ODS's in the following products is essential:

(1) *Metered-dose corticosteroid human drugs for oral inhalation.* Oral pressurized metered-dose inhalers containing the following active moieties:

- (i) Beclomethasone.
- (ii) Dexamethasone.
- (iii) Flunisolide.
- (iv) Fluticasone.
- (v) Triamcinolone.

(2) *Metered-dose short-acting adrenergic bronchodilator human drugs for oral inhalation.* Oral pressurized metered-dose inhalers containing the following active moieties:

- (i) Albuterol.
- (ii) Bitolterol.
- (iii) Metaproterenol.
- (iv) Pirbuterol.
- (v) Terbutaline.
- (vi) Epinephrine.

(3) [Reserved]

(4) *Other essential uses.* (i) Metered-dose salmeterol drug products administered by oral inhalation for use in humans.

(ii) Metered-dose ergotamine tartrate drug products administered by oral inhalation for use in humans.

(iii) Anesthetic drugs for topical use on accessible mucous membranes of

humans where a cannula is used for application.

(iv) Metered-dose cromolyn sodium human drugs administered by oral inhalation.

(v) Metered-dose ipratropium bromide for oral inhalation.

(vi) Metered-dose atropine sulfate aerosol human drugs administered by oral inhalation.

(vii) Metered-dose nedocromil sodium human drugs administered by oral inhalation.

(viii) Metered-dose ipratropium bromide and albuterol sulfate, in combination, administered by oral inhalation for human use.

(ix) Sterile aerosol talc administered intrapleurally by thoracoscopy for human use.

(f) Any person may file a petition under part 10 of this chapter to amend paragraph (e) of this section to add or remove an essential use.

(1) If the petition is to add use of a noninvestigational product, the petitioner must submit compelling evidence that:

(i) Substantial technical barriers exist to formulating the product without ODS's;

(ii) The product will provide an unavailable important public health benefit; and

(iii) Use of the product does not release cumulatively significant amounts of ODS's into the atmosphere or the release is warranted in view of the unavailable important public health benefit.

(2) If the petition is to add use of an investigational product, the petitioner must submit compelling evidence that:

(i) Substantial technical barriers exist to formulating the investigational product without ODS's;

(ii) A high probability exists that the investigational product will provide an unavailable important public health benefit; and

(iii) Use of the investigational product does not release cumulatively significant amounts of ODS's into the atmosphere or the release is warranted in view of the high probability of an unavailable important public health benefit.

(g) FDA will use notice-and-comment rulemaking to remove the essential-use listing of a product in paragraph (e) of this section if the product meets any one of the following criteria:

(1) The product using an ODS is no longer being marketed; or

(2) After January 1, 2005, the product is not available without an ODS and FDA determines that the product no longer meets the criteria in paragraph (f) of this section after consultation with a

relevant advisory committee(s) and after an open public meeting; or

(3) For individual active moieties marketed as ODS products and represented by one new drug application (NDA) and one strength:

(i) 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;

(ii) Supplies and production capacity for the non-ODS product(s) exist or will exist at levels sufficient to meet patient need;

(iii) At least 1 year of U.S. postmarketing use data is available for the non-ODS product(s); and

(iv) Patients who medically required the ODS product are adequately served by the non-ODS product(s) containing that active moiety and other available products; or

(4) For individual active moieties marketed as ODS products and represented by two or more NDA's or marketed in multiple distinct strengths;

(i) At least two non-ODS products that contain the same active moiety are being marketed with the same route of delivery, for the same indication, and with approximately the same level of convenience of use as the ODS products; and

(ii) The requirements of paragraphs (g)(3)(ii), (g)(3)(iii), and (g)(3)(iv) of this section are met.

Dated: August 19, 1999.

**Jane E. Henney,**

*Commissioner of Food and Drugs.*

**Donna E. Shalala,**

*Secretary of Health and Human Services.*

[FR Doc. 99-22887 Filed 8-30-99; 12:40 pm]

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**DEPARTMENT OF TRANSPORTATION**

**Federal Highway Administration**

**23 CFR Chapter I**

[FHWA Docket No. FHWA-99-4970]

RIN 2125-AE54

**Federal Lands Highway Program; Transportation Planning Procedures and Management Systems Pertaining to the Fish and Wildlife Service and the Refuge Roads Program**

**AGENCY:** Federal Highway Administration (FHWA), DOT.

**ACTION:** Advance notice of proposed rulemaking (ANPRM); request for comments.

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