Executive Order 12866

This document does not meet the criteria for a ''significant regulatory action'' as specified in Executive Order 12866.

Regulatory Flexibility Act

Because no notice of proposed rulemaking is required for this rule, the provisions of the Regulatory Flexibility Act (5 U.S.C. 601 *et seq.*) do not apply.

Drafting Information

The principal author of this document was Suzanne Kingsbury, Regulations Branch, Office of Regulations and Rulings, U.S. Customs Service. However, personnel from other offices participated in its development.

List of Subjects in 19 CFR Part 191

Claims, Commerce, Customs duties and inspection, Drawback.

Amendment to the Regulations

For the reason stated above, part 191 of the Customs Regulations (19 CFR part 191), is amended as set forth below.

PART 191—DRAWBACK

1. The general authority citation for part 191 continues to read as follows:

Authority: 5 U.S.C. 301; 19 U.S.C. 66, 1202 (General Note 23, Harmonized Tariff Schedule of the United States), 1313, 1624.

* * * * *

1. Section 191.26 is amended:

a. In paragraph (b)(2) by removing the word ''and'' after the semi-colon;

b. At the end of paragraph (b)(3) by removing the period and adding ''; and''; and

c. By adding a new paragraph (b)(4) to read as follows:

§ 191.26 Recordkeeping for manufacturing drawback.

* * * * *

(b) *Substitution manufacturing.* * * *

(4) If the designated merchandise is a chemical element that was contained in imported material that was subject to an *ad valorem* rate of duty, and a substitution drawback claim is made based on that chemical element:

(i) The duty paid on the imported material must be apportioned among its constituent components. The claim on the chemical element that is the designated merchandise must be limited to the duty apportioned to that element on a unit-for-unit attribution using the unit of measure set forth in the Harmonized Tariff Schedule of the United States (HTSUS) that is applicable to the imported material. If the material is a compound with other constituents, including impurities, and the purity of the compound in the imported material is shown by satisfactory analysis, that purity, converted to a decimal equivalent of the percentage, is multiplied against the entered amount of the material to establish the amount of pure compound. The amount of the element in the pure compound is to be determined by use of the atomic weights of the constituent elements and converting to the decimal equivalent of their respective percentages and multiplying that decimal equivalent against the above-determined amount of pure compound.

(ii) The amount claimed as drawback based on the chemical element must be deducted from the duty paid on the imported material that may be claimed on any other drawback claim.

Example to paragraph (b)(4)

Synthetic rutile that is shown by appropriate analysis in the entry papers to be 91.7% pure titanium dioxide is imported and dutiable at a 5% *ad valorem* duty rate. The amount of imported synthetic rutile is 30,000 pounds with an entered value of $12,000. The total duty paid is $600. Titanium in the synthetic rutile is designated as the basis for a drawback claim under 19 U.S.C. 1313(b). The amount of titanium dioxide in the synthetic rutile is determined by converting the percentage (91.7%) to its decimal equivalent (.917) and multiplying the entered amount of synthetic rutile (30,000 pounds) by that decimal equivalent (.917 × 30,000 = 27,510 pounds of titanium dioxide). The titanium, based on atomic weight, represents 59.93% of the constituents in titanium dioxide. Multiplying that percentage, converted to its decimal equivalent, by the amount of titanium dioxide determines the titanium content of the imported synthetic rutile (.5993 × 27,510 pounds = 16,486.7 pounds). Therefore, up to 16,486.7 pounds of titanium is available to be designated as the basis for drawback. The ratio between the amount of titanium and the total amount of imported synthetic rutile is determined by dividing the weight of the titanium by the weight of the synthetic rutile (16,486.7 ÷ 30,000 = .550) or 55%. Accordingly, 55% of the duty is apportioned to the titanium content which is the designated merchandise of the imported synthetic rutile. As the per-unit duty paid on the synthetic rutile is calculated by dividing the duty ($600) by the amount of the imported synthetic rutile (30,000), the per-unit duty is two cents of duty per pound ($600 ÷ 30,000 = $0.02). The per pound duty on the titanium is calculated by multiplying the factor of 55% (.55 × $0.02 = $0.011 per pound). If an exported titanium alloy ingot weighs 17,000 pounds, in which 16,000 pounds of titanium was used to make the ingot, drawback is determined by multiplying the duty per pound factor ($0.011 per pound) by the weight of the titanium contained in the ingot (16,000 pounds) to calculate the duty available for drawback ($0.011 × 16,000 = $176). Because only 99% of the duty can be claimed, drawback is determined by multiplying the available duty amount by 99% (.99 × $176 = $174.24). As the oxygen content of the titanium dioxide is 45% of the synthetic rutile, if oxygen is the designated merchandise on another drawback claim, that factor would be used to determine the duty available for drawback based on the substitution of oxygen.

Robert C. Bonner,

Commissioner of Customs.

Approved: July 18, 2002.

Timothy E. Skud,

Deputy Assistant Secretary of the Treasury.

[FR Doc. 02–18609 Filed 7–23–02; 8:45 am]

BILLING CODE 4820–02–P

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:

SUMMARY: The Food and Drug Administration (FDA) is amending its regulation on the use of chlorofluorocarbon (CFC) propellants in self-pressurized containers to make it consistent with other laws. FDA is setting the standard it will use to determine which FDA-regulated products that utilize an ozone-depleting substance (ODS) are 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 an FDA-regulated product that utilizes an ODS is essential. FDA is also removing current essential-use designations for products no longer marketed and for metered-dose steroid human drugs for nasal inhalation. FDA will add or remove specific essential-use designations for other products by

engaging in separate notice-and-comment rulemaking.

DATES: *Effective Date*: This rule is effective January 20, 2003.

Applicability Date: The removal of the essential-use exemption for metered-dose steroid human drugs for nasal inhalation applies as of August 25, 2003.

ADDRESSES: This document and related information are available on the Internet at http://www.fda.gov/cder/mdi.

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

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

FDA, in consultation with EPA, determines whether a medical product is essential for purposes of Title VI of the Clean Air Act (42 U.S.C. 7671, *et seq.*) (Title VI). If a medical product is determined to be essential, and meets the other elements of the definition found in section 601 of the Clean Air Act, it will be considered a ''medical device.'' ''Medical devices'' are exempt from the general prohibition on nonessential uses of CFCs found in section 610 of the Clean Air Act. If certain conditions are met, EPA may authorize production of ODS for use in ''medical devices'' under an exemption from the general prohibitions on production and consumption of ODS found in sections 604 and 605 of 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 (MDIs). FDA will maintain the designation of ODS medical products such as MDIs as essential until non-ODS medical products adequately meet the needs of patients.

In the **Federal Register** of September 1, 1999 (64 FR 47719), FDA published a proposed rule that sought public comment on the process FDA would use to make essential-use determinations.[1] FDA received 22 comments on the proposed rule and addresses those comments in section IV of this document.

The United States, as a party to the 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 ODSs, including CFCs. The United States has generally banned the use of CFCs in consumer aerosols for decades and eliminated almost all manufacture and importation of CFCs as of January 1, 1996. However, the Montreal Protocol permits parties to the Protocol to continue to produce or import CFCs for use in essential medical products if such production or importation is approved by the parties, and the United States continues to do so at this time.

The twelfth meeting of the parties to the Montreal Protocol took place in Ouagadougou, Burkina Faso. The parties issued Decision XII/2—''Measures to facilitate the transition to chlorofluorocarbon-free metered-dose inhalers.'' Decision XII/2 is contained in the Report of the Twelfth Meeting of the Parties to the Montreal Protocol on Substances that Deplete the Ozone Layer. The report can be found on the United Nations Environment Programme Web site at http://www.unep.org/ozone/mop/12mop/12mop-9.e.shtml. Decision XII/2 states the following:

> [A]ny chlorofluorocarbon metered-dose inhaler product approved after 31 December 2000 for treatment of asthma and/or chronic obstructive pulmonary disease in a non-Article 5(1) Party is not an essential use [under the Montreal Protocol] unless the product meets the criteria set out in paragraph 1(a) of decision IV/25.

The United States is a non-Article 5(1) Party under the Montreal Protocol. Paragraph 1(a) of Decision IV/25 provides that:

> a use of a controlled substance should qualify as 'essential' [under the Montreal Protocol] only if:
>
> (i) It is necessary for the health, safety or is critical for the functioning of society (encompassing cultural and intellectual aspects); and
>
> (ii) There are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health.

Decision IV/25 is contained in the Report of the Fourth Meeting of the Parties to the Montreal Protocol on Substances that Deplete the Ozone Layer. The report can be found on the United Nations Environment Programme Web site at http://www.unep.org/ozone/mop/04mop/4mop-15.e.shtml.

FDA believes that this rule is consistent with Decision XII/2. This rule is also a key step in fulfilling the United States' obligation under paragraph 5 of Decision XII/2 to develop a national transition strategy that ''includes effective criteria and measures for determining when chlorofluorocarbon metered-dose inhaler product(s) is/are no longer essential.''

Title VI and the Montreal Protocol work in independent but complementary ways. The Montreal Protocol deals primarily with restrictions on the production and importation of new ODSs. Title VI deals with the use of ODSs, as well as their production and importation. The following hypothetical example may be helpful in illustrating the interaction of Title VI and the Montreal Protocol. A United States company makes CFC-propelled plastic party streamers using recycled and stockpiled CFCs. This use of ODSs would not be impacted by the Montreal Protocol because no newly manufactured or imported ODSs were used. However, this use of ODSs would be prohibited by Title VI, because CFC-propelled plastic party streamers are specifically banned by section 610(b)(1) of the Clean Air Act.

[1] FDA included in the proposed rule a summary of the comments the agency received on the advanced notice of proposed rulemaking (ANPRM) published in the **Federal Register** of March 6, 1997 (62 FR 10242).

The purpose of this rule is to implement Title VI. A determination that a product that contains ODSs is essential under Title VI does not guarantee that the manufacturer of that product will be allocated ODSs for use in the product. As the example above illustrates, the ability to manufacture and market an ODS-containing product requires compliance with both the Clean Air Act and the Montreal Protocol.

II. Highlights of the Final Rule

FDA is making the following changes to § 2.125:

- Using the phrase ''ozone-depleting substance'' instead of the word ''chlorofluorocarbon'' in the title and text of the regulation;
- Revising § 2.125(b) to remove explanatory material that has no regulatory effect;
- In revised § 2.125(b), defining a product that is 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 CFCs as a propellant;
- Changing the designation of ODS products not listed in § 2.125(e) from adulterated and misbranded to nonessential;
- Listing as a separate essential use 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;
- Eliminating the essential-use designation in § 2.125(e) for metered-dose steroid human drugs for nasal inhalation;
- Eliminating the essential-use designations in § 2.125(e) for products that are no longer marketed;
- Setting the standard to determine when a new essential-use designation should be added to § 2.125;
- Eliminating outdated transitional provisions in current § 2.125(g), (h), (i), (j), (k), and (l); and
- Setting standards to determine whether the use of an ODS in a medical product remains essential.

We are highlighting the most important portions of the final rule here.

A. Removal of the Term ''Propellant''

The agency is defining 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 products that use a CFC as a propellant in a self-pressurized container. This brings within the scope of the regulation medical products that use ODSs for purposes other than as a propellant. This provision is intended to encompass all products that are regulated by FDA.

B. Change to Essentiality Determinations

Former § 2.125(c) stated that any CFC product not found in § 2.125(e) was adulterated and/or misbranded in violation of the Federal Food, Drug, and Cosmetic Act (the act). FDA is changing this paragraph to reflect the agency's 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 may still be considered adulterated and misbranded under the act.

C. Metered-Dose Steroid Human Drugs for Nasal Inhalation

FDA is removing the essential-use designation for metered-dose steroid human drugs for nasal inhalation for the following reasons:

- Adequate alternative non-ODS products for steroid human drugs for nasal inhalation are currently available, including metering atomizing pumps for administering nasal corticosteroids, other nonsteroid nasal topical therapies, and systemic therapies;
- Patients use the alternative products on a widespread basis; and
- These alternative products have been and continue to be produced and supplied at sufficient levels to meet patient needs.

While it was not a factor in the agency's decision, FDA notes that, unlike other ODS medical products currently being marketed, the diseases for which these products are indicated are not life threatening. FDA also notes that only the three active moieties beclomethasone, budesonide, and triamcinolone are marketed as CFC-nasal steroids and that these three moieties are also marketed in non-ODS formulations.

D. Products No Longer Marketed

FDA is removing the essential-use designations for the following ODS products that are no longer marketed:

- Contraceptive vaginal foams for human use;
- Intrarectal hydrocortisone acetate for human use;
- Polymyxin B sulfate-bacitracin zinc-neomycin sulfate soluble antibiotic powder without excipients, for use on humans; and
- 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 CFCs. Additionally, in instituting a list in § 2.125 of each marketed active moiety for metered-dose adrenergic bronchodilator human drugs for oral inhalation, the following moieties will not be listed as essential uses of ODS, as they are no longer being marketed in a formulation containing CFCs: Isoetharine, isoproterenol, terbutaline.

E. Petitions To Add New Essential Uses

By this final rule, FDA is amending § 2.125 to provide a process for adding investigational uses to § 2.125(e) and amending the existing process for adding noninvestigational uses to § 2.125(e). 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 ODSs and because of the United States' commitment to reducing its consumption of ODSs. Therefore, FDA is requiring compelling evidence in support of a petition for a new essential use. For purposes of this 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 to add a new essential use to § 2.125(e). Such information will become publicly available. FDA will use this information in issuing a proposed rule to add the essential use if it finds that the petitioner has submitted compelling evidence.

This new standard applies to all requests for essential-use exemptions submitted after the effective date of this rule.

1. Noninvestigational Uses

Noninvestigational products are products that are not intended to be used in preclinical or clinical

investigations of a medical product. Noninvestigational uses include the use of ODSs in medical products that are commercially distributed under an approved marketing application. FDA does not intend to consider proposing a new essential use for a noninvestigational product unless a petitioner submits:

- Compelling evidence that substantial technical barriers exist to formulating the product without ODSs;
- Compelling evidence that the product will provide an unavailable important public health benefit;
- Information describing the cumulative release of ODS into the atmosphere and a discussion of the significance of the release; and
- The basis for why the release is warranted in view of the unavailable important public health benefit.

2. Investigational Uses

FDA does not intend to consider proposing a new essential use for an investigational use of an ODS medical product unless a petitioner submits:

- Compelling evidence that substantial technical barriers exist to formulating the investigational product without ODSs;
- Compelling evidence that a high probability exists that the investigational product will provide an unavailable important public health benefit;
- Information describing the cumulative release of ODS into the atmosphere and a discussion of the significance of the release; and
- The basis for why the release is warranted in view of the unavailable important public health benefit.

FDA notes that inclusion of an investigational use in § 2.125(e)(4) will not allow commercial manufacture and marketing of an ODS product. A sponsor will need to file a separate petition under § 2.125(f)(1) for a new essential-use determination for commercial marketing of the ODS product.

3. Requesting Addition of a New Essential Use

A party seeking a new essential use will need to file a citizen petition under § 10.30 (21 CFR 10.30) requesting that FDA initiate rulemaking to add a new essential use. The petitioner will need to include compelling evidence justifying addition of the new essential use, as provided for in § 2.125(e). FDA will deny the petition if the petitioner has not submitted compelling evidence. If the petitioner has submitted compelling evidence, FDA will grant the petition and initiate notice-and-comment rulemaking to add the new essential use.

First, the petitioner must demonstrate through compelling evidence that substantial technical barriers exist to formulating the product without ODSs. Generally, FDA intends the term ''technical barriers'' to refer to difficulties encountered in chemistry and manufacturing. To demonstrate that substantial technical barriers exist, the petitioner will 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. FDA notes that 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). The agency might consider cost as a technical barrier if the petitioner shows that the cost of using a non-ODS in a product is prohibitively high in comparison to the cost of using an ODS.

Second, the petitioner for a new essential use for a noninvestigational product must include compelling evidence of an unavailable important public health benefit. For investigational products, FDA is requiring the 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 will give the phrase ''unavailable important public health benefit'' a markedly different construction from the previous phrase ''substantial health benefit.'' For example, the 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. The 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 petitioner must submit compelling evidence showing that the use of the product does not release significant amounts of ODS into the atmosphere. Alternatively, the petitioner may show that the release is warranted in view of the important public health benefit or, for an investigational product, in view of a high probability of an important public health benefit. The petitioner must submit a well-documented statement of the number of products to be manufactured and the amount of ODS to be released by each product.

F. Determinations of Continued Essentiality

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

1. Products No Longer Marketed

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

2. Products Marketed After January 1, 2005

Section 2.125(g)(2) provides that, after January 1, 2005, FDA may propose that ODS products containing a particular active moiety are nonessential if the moiety no longer meets the essential-use criteria in § 2.125(f). Even if a current essential-use active moiety is not reformulated, sufficient alternative products may exist in the future to fully meet the needs of patients. FDA would designate any remaining active moieties marketed in ODS formulations as nonessential. FDA will consult with an advisory committee and provide the opportunity for public comment before making such a determination.

3. Products for Which Non-ODS Alternatives Containing the Same Active Moiety Are Developed

Under § 2.125(g)(3) and (g)(4), a moiety can remain on the essential-use list until:

- 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;
- Supplies and production capacity for the alternative(s) exist or will exist at levels sufficient to meet patient need;
- Adequate U.S. postmarketing data exist; and

• Patients who medically require the ODS product are adequately served by available alternatives.

In addition, a CFC–MDI with an active moiety that is marketed under more than one new drug application (NDA) will not be removed from the essential-use list under § 2.125(g)(4) unless at least two non-ODS products with the same active moiety are marketed under more than one NDA.

a. *Same indication*. In evaluating indications, FDA will require a non-ODS alternative to have a broader indication or an indication or indications identical 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. 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.

b. *Same level of convenience of use*. In evaluating whether an alternative has approximately the same level of convenience of use compared to the ODS product containing the same active moiety, FDA will consider whether:

• The product has approximately the same or better portability;

• The product requires approximately the same amount of or less preparation before use; and

• The product requires approximately the same or less physical effort and dexterity.

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

d. *Postmarketing data*. 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 encourages 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 encourages 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.

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.

e. *Patients adequately served*. 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 data for the available alternatives exist for the indicated populations and other populations known to medically rely on the ODS product. FDA anticipates that ODS products of the same active moiety marketed in different strengths will need to be replaced by non-ODS products of the same active moiety with more than one strength to adequately serve patients. 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.

4. Opportunity for Public Comment

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 patients.

III. Changes From the Proposed Rule

Based on the comments it received on the proposed rule, FDA has made some changes in this final rule.

FDA is finalizing § 2.125(g)(2) to permit FDA to evaluate all remaining ODS products after January 1, 2005, instead of just those products that are not available without an ODS. FDA is making this change in response to comments. FDA believes this change is important to cover active moieties marketed as ODS products and represented by two or more NDAs but for which only one non-ODS replacement is marketed, as well as active moieties for which a non-ODS replacement is developed that does not alone meet all of the criteria in § 2.125(g)(3). Under § 2.125(g)(2), FDA will examine the entire marketplace of products available to treat asthma and COPD in determining whether an ODS product remains essential. By entire marketplace, FDA means to include replacements containing the same active moiety, other non-ODS products, as well as remaining CFC products.

FDA is finalizing § 2.125(g)(3)(iii) to require adequate U.S. postmarketing data instead of at least 1 year of postmarketing data. FDA is making this change in response to comments pointing out that more or less data may be necessary depending on factors such as the amount of foreign data available on the same product and the amount of U.S. data that would be available by the time FDA finalized removal of an essential use.

FDA is eliminating the proposal that § 2.125(g)(4) require active moieties marketed as ODS products and represented by multiple strengths be replaced by at least two non-ODS products. FDA is making this change in response to comments. FDA made this proposal to account for different subpopulations that may require different strengths. FDA believes it can adequately account for this need by requiring that replacements adequately serve patients who medically require the ODS product (see § 2.125(g)(3)(iv)).

For consistency, FDA is also finalizing § 2.125(g)(3) to eliminate the phrase ''and one strength:''.

FDA is maintaining the requirement in § 2.125(g)(4) to require active moieties marketed as ODS products and represented by two or more NDAs to be replaced by at least two non-ODS products.

FDA has determined, on its own initiative, that this rule will go into effect 180 days after publication, rather than 1 year after publication as was originally proposed. This change is

being made because of the length of this rulemaking process, the anticipated length of future rulemakings to remove essential-use exemptions, and the importance of eliminating ODSs in a timely manner. The agency has also determined that the elimination of the essential-use exemption for metered-dose steroid human drugs for nasal inhalation will apply 1 year after the date of publication of this rule. Several CFC-containing nasal steroid MDIs are still being marketed. The agency believes that a 1-year period to dispose of existing stocks and to complete the transition to non-ODS-containing alternatives remains appropriate.

IV. Comments on the Proposed Rule

FDA sought comments on the proposed rule. In particular, FDA requested comment on the following issues:

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

FDA received 22 written comments on the proposed rule and held one public meeting at the November 22, 1999, session of the Pulmonary and Allergy Drugs Advisory Committee (PADAC). Comments were submitted by individuals, health care providers, patient groups, prescription drug manufacturers, professional associations, Congress, and a union. A summary of the comments received and the agency's responses follow.

A. General Comments About the Proposed Rule

(Comment 1) Two comments supported the proposed rule as reasonable and protective of patient choice. One comment noted that it is difficult for patients to switch therapies and supported the proposed rule as minimally disruptive of patient care. One comment supported the proposed rule as protective of patients and the environment. One comment supported the proposed rule as a reasonable and measured approach. One comment encouraged FDA to finalize the proposed rule as quickly as possible. One comment supported the proposed rule as an improvement over the ANPRM (62 FR 10242, March 6, 1997) FDA published on the same topic. PADAC members were generally supportive of the proposed rule (Ref. 1, page 122 of the transcript).

FDA is generally adopting the rule as proposed, with the changes noted in section III of this document.

B. Number of Alternatives Proposed

(Comment 2) Eight comments supported the moiety-by-moiety approach. Two comments supported the moiety-by-moiety approach, including listing each individual active moiety deemed essential. PADAC was generally supportive of the moiety-by-moiety approach (Ref. 1, pp. 203 and 204 of the transcript).

FDA is using the moiety-by-moiety approach overall, including listing each individual active moiety deemed essential.

(Comment 3) Two comments said that FDA should make essentiality determinations on a product-by-product rather than a moiety-by-moiety approach. One of these comments argued that FDA applies such a product-by-product approach to discontinued products and products outside the classes listed in the proposal. One comment said that FDA should not remove an essential use for an active moiety unless there is a non-ODS alternative available. One comment requested that FDA not remove a product from the essential-use list until it was no longer marketed.

FDA notes that some companies are unlikely to reformulate their CFC products into non-ODS products because of economic considerations. Therefore, FDA did not propose using a product-by-product approach or waiting until a product was no longer marketed because such approaches would not accomplish the eventual phaseout of CFC–MDIs as agreed to by the United States.

FDA disagrees that drugs outside the classes listed in the proposal and discontinued products are treated differently from drugs within the classes. FDA is not listing particular products, but rather active moieties. Although some of these active moieties are represented by one product, as are most of the moieties within the classes listed in the proposal, FDA is using the active moiety within the product as a basis for classification, not the product itself.

(Comment 4) One comment stated that FDA should list as essential uses all currently approved and available asthma-related MDIs, including cromolyn. The comment also stated that some of the active moieties included in table 1 of the proposed rule (64 FR 47719 at 47740, September 1, 1999) were not proposed as essential uses.

FDA proposed, and is including in this final rule, an essential use for cromolyn at § 2.125(e)(4)(iv). In evaluating this comment, FDA compared table 1 in the preamble of the proposed rule with the proposed codified language and found that the active moieties isoetharine and isoproterenol were referenced in the table but not in the proposed codified language. FDA did not include these active moieties in the proposed codified language because the moieties are no longer marketed in CFC formulations. FDA also researched whether any active moieties listed in table 1 of the proposed rule are no longer marketed. FDA has determined that terbutaline is no longer marketed in an ODS formulation and, therefore, is finalizing this rule without including terbutaline in the codified portion of this final rule.

(Comment 5) One comment requested that FDA provide additional details regarding how it would treat over-the-counter (OTC) bronchodilator products.

The only active moiety available as an OTC bronchodilator is epinephrine. Epinephrine CFC–MDIs are manufactured under multiple NDAs. FDA will evaluate the essentiality of epinephrine the same way it will evaluate the essentiality of all active moieties manufactured under multiple NDAs. FDA will not initiate rulemaking to eliminate the essential-use designation for any individual active moiety marketed under multiple NDAs until at least two non-ODS alternatives exist that contain the same active moiety or, after January 1, 2005, until adequate alternatives exist, as described in § 2.125(g). FDA further notes that any reexamination of the appropriateness of continuing the OTC status for bronchodilators is quite separate from determinations on the essential-use status of epinephrine CFC–MDIs.

(Comment 6) Five comments supported the proposal that more than one non-ODS product be available for an active moiety for which more than one CFC product is available currently. One comment stated that FDA should clarify that under § 2.125(g)(4) more than one product is required only for active moieties represented by two or more NDAs. PADAC supported this proposal generally but noted that the replacement products should be adequate to serve the populations that were served by the ODS product (Ref. 1, pp. 196 through 199 of the transcript).

FDA is including in this final rule a requirement that more than one non-ODS product be available for active moieties currently available under two or more NDAs. FDA acknowledges that it may be difficult to argue that a higher strength replacement is an adequate replacement for a product available in

multiple strengths if a population exists that specifically requires a lower strength product (Ref. 1, pp. 197 and 198 of the transcript). Therefore, FDA is removing the requirement that multiple-strength ODS products be replaced by replacement products represented by multiple NDAs. Instead, FDA will consider whether a multiple-strength ODS product is adequately replaced by a non-ODS product by determining whether patients are adequately served by the replacement.

(Comment 7) One comment asked FDA to require that before a multiple-strength ODS product is found to be nonessential it must be replaced by either one non-ODS product with the same active moiety in at least two strengths, or two different non-ODS products with the same active moiety in different strengths.

At the time FDA drafted the proposed rule, FDA considered carefully whether to propose requiring replacing multiple strength ODS products with multiple strength non-ODS products. Instead the agency decided to require replacement by multiple non-ODS products for active moieties for which more than one different product is currently available. FDA chose not to propose to specifically require multiple strength alternatives for multiple strength ODS products because of the difficulty of equating therapeutic need with strengths. For example, if an active moiety were available in two low potency strength alternatives, it would meet the letter of the regulation, but might not meet the therapeutic need for a high-potency formulation. On the other hand, if a replacement product were twice as effective at half the strength, requiring the replacement to be marketed in the same strength would not necessarily serve the same population. FDA believes this reasoning is still valid and declines to adopt the suggestion, but will rather examine all aspects of an alternative's acceptability as a replacement.

(Comment 8) One comment stated that proposed § 2.125(g)(4) could preclude replacement of a multiple-strength CFC–MDI by one non-ODS product with two strengths.

FDA agrees that proposed § 2.125(g)(4) could have prevented a multiple-strength CFC–MDI from being replaced by one non-ODS product with two strengths filed under the same NDA. Therefore, FDA is finalizing § 2.125(g)(4) to require only that ODS products represented by two or more NDAs be replaced by at least two non-ODS products. This criterion could be met by two products that differ in strength and that are approved under one NDA. FDA is eliminating the proposal that active moieties marketed in multiple distinct strengths be replaced by at least two non-ODS products. FDA's intent in proposing that multiple strengths be replaced by multiple products was to ensure that patients who require different strengths are adequately served by replacements. Section 2.125(g)(3)(iv) already requires that patients who medically required the ODS product to be adequately served by the non-ODS product(s) containing that active moiety and other available products. Therefore, FDA does not believe that its original proposal adds any additional protection. For consistency, FDA is also eliminating the phrase ''and one strength'' from § 2.125 (g)(3).

C. Specific Comments on the Proposed Criteria for Phaseout

(Comment 9) One comment stated that FDA should establish a procedure to reinstate an essential use if a replacement is found inadequate after removal of that essential use.

Section 2.125 does provide a mechanism to reinstate an essential use if replacements are found inadequate after removal of that essential use. A petitioner will need to apply under § 2.125(f) to add the essential use to § 2.125(e).

(Comment 10) One comment stated that FDA should permit FDA-regulated products using any ODS to remain on the market.

As explained below in detail in response to comment 52 of this document, FDA-regulated products containing an ODS cannot remain on the market once they are no longer essential.

(Comment 11) One comment stated that FDA should not propose removal of an essential-use listing for an active moiety that does not have a non-ODS replacement after January 1, 2005, unless FDA states the criteria it will use to conclude that alternatives are adequate.

FDA will use notice-and-comment rulemaking if it proposes removal of an essential-use listing for an active moiety that does not have a non-ODS replacement. As part of this rulemaking, FDA will state the criteria it will use to conclude that alternatives are adequate.

(Comment 12) One comment recommended that FDA establish an expert panel to monitor all aspects of the transition. One comment stated that FDA should state the qualifications of the people on the advisory committee and should include members of the expert panel assembled by the National Institutes of Health (NIH) and professionals selected by the House Committee on Commerce's Subcommittee on Health and the Environment.

PADAC comprises individuals possessing recognized expertise and judgment in the fields of pulmonary and allergy medicine. Members have the training and experience necessary to evaluate information objectively and to interpret its significance under various, often controversial, circumstances. Voting members of PADAC have expertise, as demonstrated by training, education, and experience in pulmonary and allergy medicine. To the extent feasible, voting members possess skill and experience in the development, manufacture, or use of the types of drugs to be referred to the committee. FDA strives to ensure that the group of voting members reflects a balanced composition of scientific expertise through members with diverse professional education, training, and experience (21 CFR 14.80(b)(1)). Ad hoc committee members who are representatives of consumer or patient interests, or who have expertise in the particular disease or condition for which the drug under consideration is proposed to be indicated, will be voting members if: (1) They have the requisite scientific or technical expertise, and (2) their participation is not prevented by conflict of interest laws and regulations. Because of inherent conflict of interest concerns, representatives of the drug manufacturing industry will not be voting members of the committee. No person who is a regular full-time employee of the U.S. Government and engaged in the administration of the act may be a voting member of an advisory committee (section 505(n)(3) of the act (21 U.S.C. 355(n)(3))).

The names and qualifications of the current members of PADAC are available at each meeting and by written request mailed or faxed to the following address: Food and Drug Administration, Freedom of Information Staff (HFI–35), 5600 Fishers Lane, Rockville, MD 20857, FAX 301–443–1726.

FDA may invite other individuals, such as members of the expert panel assembled by NIH or professionals selected by the House Committee on Commerce's Subcommittee on Health and the Environment, to serve as ad hoc PADAC members if appropriate.

(Comment 13) Four comments supported proposed § 2.125(g)(2). Three comments recommended FDA undertake an evaluation of all ODS–MDI products after January 1, 2005. One comment stated that FDA should not limit proposed § 2.125(g)(2) to products without a non-ODS replacement.

FDA agrees with these comments and has therefore revised § 2.125(g)(2) to permit the agency to undertake an evaluation of all ODS products after January 1, 2005, not just those products without a non-ODS replacement.

(Comment 14) Three comments stated that FDA should permit manufacturers to demonstrate an ability to meet patient need through a single manufacturing site before requiring multiple manufacturing sites. One comment supported FDA's proposal to require adequate supplies and production capacity, but asked FDA to clarify that a single facility could be adequate to meet patient demand.

FDA did not propose and is not finalizing in this rule a requirement that replacement products be manufactured at multiple sites. This final rule requires only that supplies and production capacity for the non-ODS product exist at levels sufficient to meet patient need. FDA notes, however, that multiple manufacturing sites increase the likelihood that a manufacturer will be able to supply the replacement drug in the event of an unforseen circumstance that shuts down one site.

(Comment 15) Three comments supported the proposal that an alternative be acceptable only if patients are adequately served and the alternative is marketed for the same route of administration, for the same indication, and with approximately the same level of convenience of use as the product it is replacing.

In this final rule, FDA will not eliminate an essential use under § 2.125(g)(3) or (g)(4) unless patients are adequately served by alternatives and an alternative is marketed for the same route of administration, for the same indication, and with approximately the same level of convenience of use as the product it is replacing.

(Comment 16) One comment asked FDA to confirm that only significant variations in convenience that materially impede patient compliance are a basis for consideration of whether a product has approximately the same level of convenience of use.

FDA confirms that only significant variations in convenience that materially impede patient compliance are a basis for consideration of whether a product has approximately the same level of convenience of use. For example, it is possible that a non-ODS MDI may use a mouthpiece that is different from its CFC–MDI counterpart. Such a difference would not normally constitute a significant inconvenience. On the other hand, FDA is aware that physicians and patients value the compact size and ease of use of MDIs. Therefore, a non-ODS product that needed to be plugged in to be used would not have the same level of convenience of use as a portable MDI.

(Comment 17) One comment supported FDA's statement that approximately the same level of convenience of use should mean approximately the same or better portability and the same amount of or less preparation time.

In evaluating whether an alternative has approximately the same level of convenience of use compared to the ODS product containing the same active moiety, FDA will consider whether:

1. The product has approximately the same or better portability;

2. The product requires approximately the same amount of or less preparation before use; and

3. The product does not require significantly greater physical effort or dexterity.

(Comment 18) One comment asked FDA to revise the rule to state that a non-ODS product need only provide a level of convenience that would not significantly impair safe and effective use.

FDA is not revising this rule to state that convenience of use means only that a non-ODS product does not significantly impair safe and effective use. Although products exist already that are safe and effective without providing the same level of convenience of use as CFC–MDIs, such products do not represent sufficient treatment options. For example, solutions for nebulization safely and effectively treat asthma and COPD. However, nebulizers are generally not readily portable and usually require an external power source to work. If such solution products were the only means to treat asthma and COPD, patients with these diseases would be highly restricted in where and how they could receive their treatment. FDA does not believe such restrictions are reasonable or medically appropriate.

(Comment 19) One comment asked that FDA eliminate essential uses based on indications. One comment argued that FDA should eliminate essential uses on an indication-by-indication basis and require revised labeling accordingly.

FDA is not eliminating essential uses based on indications. It is extraordinarily difficult to control to whom marketed drugs are prescribed. FDA believes such an effort would be ineffective. Therefore, FDA is not adopting this suggestion.

(Comment 20) Three comments supported removing essential use designations for products no longer marketed.

FDA is removing the essential-use designations for products no longer marketed and will continue to propose removal of such designations under § 2.125(g)(1) as products are removed from the market.

(Comment 21) One comment stated that FDA should not eliminate an essential use unless alternatives are found to be as safe, effective, well tolerated, and inexpensive as CFC–MDIs.

In general, the criteria cited in this comment match the criteria in this final rule. Although rigid cost comparison is not planned, FDA will consider cost under the criterion of whether patients are adequately served by the non-ODS alternatives.

(Comment 22) One comment suggested that FDA modify § 2.125(f) to specify that a petition to remove an essential use must submit compelling evidence that the criteria in § 2.125(g)(3) or (g)(4) are met.

FDA is finalizing § 2.125(g) to clarify that a petitioner must submit compelling evidence that an essential use should be removed from § 2.125(e). If FDA grants the petition, FDA will propose removal of that essential use through notice-and-comment rulemaking. During the rulemaking period, the public will have the opportunity to comment on the adequacy of the evidence in support of the proposal to remove the essential use.

(Comment 23) One comment supported requiring that all patient groups be adequately served.

FDA agrees with this comment and therefore is including in this final rule a requirement that patients who medically required the ODS product are adequately served by the non-ODS product(s) containing that active moiety and other available products (§ 2.125(g)).

(Comment 24) One comment asked that FDA revise § 2.125(g)(4) to add the word ''each'' to clarify that each replacement product is subject to independent evaluation using the substitution criteria.

FDA is not adding the word ''each'' to § 2.125(g)(4). It is not FDA's intent that each replacement product be subject to independent evaluation using the substitution criteria. Rather, it is FDA's intent to ensure that patients are adequately served by available options.

D. Patient Subpopulations

(Comment 25) One comment stated that every subpopulation is significant. One comment asked that FDA consider the severity of impact on patients rather

than the numbers in a subpopulation. PADAC noted that some subgroups that might require particular attention are the elderly, pregnant women, urban patients, low-income patients, minority populations, and people who cannot cooperate at all in using a device because of neurological or other health problems (Ref. 1, pages 171 to 196 of the transcript). However, PADAC also acknowledged that these same groups have problems with existing products and stated that FDA should not set a standard for new products that cannot be met by existing products (Ref. 1, pp. 187 and 196 of the transcript).

FDA recognizes that each patient is important. FDA also recognizes that patients' asthma management programs are individualized and that changes in these programs require patience, education, and consultation with health care providers. FDA encourages patients to try appropriate new therapies as they become available and will ask patients to provide first-hand feedback to FDA as part of notice-and-comment rulemaking proposing to remove an essential use. FDA will carefully consider all such comments in determining whether a use remains essential. However, FDA notes that, just as all patients are not served by one CFC–MDI, all patients will not be served by a single alternative product. Therefore, FDA does not believe it is appropriate to make essential-use determinations on a patient-by-patient basis, just as the agency would not make determinations about whether a drug should remain on the market based on the experience of one patient or a small handful of patients.

(Comment 26) One comment stated that FDA proposed to determine essentiality based on the needs of patients who use the product for unapproved uses and asked that FDA limit its evaluations to approved uses. The comment cited the statement ''for the indicated populations and other populations known to medically rely on the ODS product'' (64 FR 47719 at 47723).

Although FDA will generally concentrate on those populations for whom a product is indicated in approved labeling, FDA also recognizes that there are populations that medically rely on CFC–MDIs even though the CFC–MDIs are not labeled for their use. FDA will consider information from these populations in making its essential-use determinations.

(Comment 27) One comment requested that FDA confirm that alternatives would have to cover all significant indications before being considered acceptable.

FDA confirms that the available alternatives should cover all significant indications before the agency removes an essential use. In general, non-ODS 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 as young as age 6 but the non-ODS alternatives are only labeled for children age 12 and above, a significant patient subpopulation would exist that might 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. FDA notes, however, that FDA will examine all available treatment options, not just the non-ODS product(s) containing the moiety for which FDA proposes eliminating an essential use, in determining whether patients are adequately served. FDA will examine all replacement products, as well as remaining ODS products.

(Comment 28) One comment recommended that FDA revise § 2.125(g)(3)(i) to replace the word ''indication'' with ''indication(s)''.

After consideration, FDA has decided not to replace the words ''indication'' with ''indication(s)'' in § 2.125(g)(3)(i). Multiple non-ODS products may replace the ODS product, and FDA does not intend to require each of those products to carry each of the indications approved for the ODS product. Instead, FDA will examine whether all of the products together cover the same indications as the ODS product.

E. Postmarketing Data and Suggested Duration

(Comment 29) One comment stated that FDA must use methods in addition to MedWatch to collect postmarketing data.

FDA plans to use methods in addition to MedWatch to collect postmarketing data. 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 but not limited to FDA's MedWatch data.

(Comment 30) One comment supported use of foreign postmarketing data in support of U.S. data.

FDA will consider foreign data supportive of U.S. postmarketing use data if U.S. and foreign formulations, patient populations, and clinical practices are the same or substantially similar.

(Comment 31) Two comments asked that FDA reduce the requirement for 1 year of U.S. postmarketing data if foreign postmarketing use data is sufficient to support a finding that a CFC–MDI is no longer essential. One comment asked that FDA permit the use of foreign data in combination with U.S. data to make a total of 1 year of postmarketing data.

In response to these comments, FDA has finalized § 2.125(g)(3)(iii) to require that adequate U.S. postmarketing data exist for the non-ODS product. FDA may find that less than 1 year is adequate if foreign data is relevant to the U.S. market. FDA notes that it is interested in the acceptability of a product in the U.S. population, its actual use in the United States, and its relation to other products marketed in the United States. Foreign data may be used to augment U.S. data when appropriate.

(Comment 32) One comment stated that FDA should use a longer than 1-year period to collect postmarketing data.

FDA is requiring adequate postmarketing data. This may mean more or less than 1 year, depending on the particulars of the product under consideration and the status of other alternatives.

(Comment 33) One comment stated that it does not support phase 4 studies in the postmarketing period. One comment supported FDA's postmarketing requirements, but asked that FDA clarify that postmarketing information need not necessarily be obtained through phase 4 studies. One comment supported the proposal that a postmarketing study not be required if other data are adequate to establish the acceptability of an alternative. PADAC members had differing points of view on the value of conducting formal postmarketing studies (Ref. 1, pp. 136 through 171 of the transcript).

In general, FDA does not anticipate that sponsors will need to conduct formal phase 4 studies in the postmarketing period to provide adequate postmarketing data. FDA does anticipate, however, that sponsors will need to collect some postmarketing data beyond standard postmarketing surveillance to determine the acceptability of an alternative.

(Comment 34) One comment asked that FDA retract its suggestion that new data, and possibly new clinical studies, may be required to ensure an additional level of proof of safety and effectiveness.

FDA will not require an additional level of proof of safety and effectiveness in evaluating alternatives. FDA makes a determination that a non-ODS product is safe and effective when FDA approves the product for marketing. The question of whether the non-ODS product is an acceptable alternative to an ODS-product is a separate question, which FDA will answer by using the criteria set forth in § 2.125(g).

F. Timing of Phaseout

(Comment 35) One comment requested that FDA accord priority review to NDAs for non-ODS products. One comment stated that non-ODS products should undergo expedited review.

The agency is committed to the timely review of all drug applications. FDA does not believe that NDAs for non-ODS replacement products meet the criteria for priority review at the current time.

(Comment 36) One comment stated that education is a very important part of the transition process and asked FDA to take a leadership role in continuing education.

FDA recognizes the need to educate patients, health care providers, and interested parties about the planned phaseout of CFC–MDIs for the transition to non-ODS products to occur as smoothly as possible. FDA has been involved in public education on this issue for the past several years. Members of the Center for Drug Evaluation and Research's Division of Pulmonary and Allergy Drug Products have made presentations and participated in panel discussions on the phaseout of CFCs at national scientific and professional society meetings and will continue to do so.

The division has also worked in close cooperation with the National Asthma Education and Prevention Program (NAEPP), an ongoing comprehensive 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 CFCs. The NAEPP Coordinating Committee formed a CFC Workgroup to educate patients and physicians about the CFC phaseout. The NAEPP CFC Workgroup, in cooperation with the International Pharmaceutical Aerosol Consortium, developed a ''fact sheet'' for patients entitled ''Your Metered-Dose Inhaler Will Be Changing * * * Here Are the Facts.'' The fact sheet is available on the Internet at 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 CFCs in FDA Consumer, Journal of the American Medical Association, 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.

(Comment 37) One comment asked that FDA work with others to outline clear deadlines and strategies for a complete transition to facilitate necessary patient and health care provider education. One comment stated that FDA should provide a detailed timeframe for the transition.

FDA understands that patients and health care providers are very interested in knowing exactly when the transition will be complete. However, FDA cannot provide an exact date at this time because the U.S. transition is largely dependent on the availability of alternative products. However, as described above, FDA will develop and participate in patient and health care provider education that is appropriate for each stage of the transition and as more information becomes available regarding the timing of the transition.

(Comment 38) One comment requested that FDA carefully prepare its regulatory materials; provide patient, medical professional, and public education; and allow ample opportunity for interaction with FDA advisory bodies and personnel before proposing removal of an essential-use designation for an active moiety without a non-ODS replacement containing that active moiety.

FDA plans to take all of these steps before proposing removal of an essential-use designation under § 2.125(g)(2) for an active moiety without a non-ODS replacement containing that moiety. FDA notes, however, that if an active moiety is no longer marketed in a CFC formulation, FDA will propose removal of the essential-use designation under § 2.125(g)(1) without necessarily taking the additional steps suggested in the comment.

(Comment 39) One comment asked that FDA reiterate that it will determine the effective date of the removal of an essential use from § 2.125 on a case-by-case basis.

FDA will determine the effective date of the removal of an essential use from § 2.125(e) on a case-by-case basis determined as a part of notice-and-comment rulemaking.

G. Nasal Steroids

(Comment 40) Three comments supported removal of the essential-use designations for nasal steroids. PADAC supported the removal of the essential-use designations for nasal steroids (Ref. 1, pp. 235 though 240 of the transcript).

In this final rule, FDA is eliminating the essential-use designations for nasal steroids. This means that after the applicability date of this rule, no ODS formulation of a nasal steroid may be sold or distributed, or offered for sale or distribution, in the United States (see 40 CFR 82.64(c) and 82.66(d)).

(Comment 41) One comment supported removal of nasal steroids generally, but noted that only one nasal steroid containing CFCs is approved to age 4 and asked that FDA not remove the essential use for this product.

In response to this comment, FDA has reviewed the labeling for nasal steroids. Fluticasone and mometasone, both available as non-ODS products, are labeled for children as young as ages 4 and 3, respectively. No CFC nasal products are approved for children as young as age 4. Therefore, FDA does not believe it is medically necessary to retain the essential use for any nasal steroid.

H. Incentives for Development of Alternatives

(Comment 42) One comment requested that FDA cooperate with other government entities to implement suggestions outside of its authority. The same comment asked FDA to seek changes to the Montreal Protocol if necessary to protect patient health.

FDA is working closely with EPA and with the Department of State to ensure that the transition is smooth. If FDA finds that patient health is at risk as the transition progresses, FDA will take steps within its own authority and will seek the assistance of other authorities to continue to protect patient health.

I. Cost of New Products

(Comment 43) One comment stated that cost should be a priority in determining whether non-ODS alternatives are adequate. One comment stated that economic impacts must be taken into account before removal of an

essential-use designation. One comment argued that FDA has not adequately assessed the impact on public health from removal of generic CFC–MDIs. Three comments stated that FDA should not consider cost in determining essentiality. PADAC members agreed generally that cost alone should not be a reason for retaining an essential use and that the United States should work to find a way to deliver appropriate drugs to people who cannot afford the medicine (Ref. 1, pp. 226 through 235 of the transcript).

FDA recognizes that cost is a concern for many patients and health care providers. In part due to considerations such as those raised in these comments, FDA is requiring that multiple-source CFC–MDI products be replaced by at least two non-ODS alternative products. FDA will also consider cost in determining whether alternatives meet patient needs. In addition, FDA expects that the price for most non-ODS products will approximate the price for branded CFC products. FDA bases this expectation on statements by manufacturers.

J. Environmental Impact of CFC–MDI Use

(Comment 44) One comment argued that the elimination of CFC–MDIs is not justified by the *de minimis* environmental benefit that will result.

The United States evaluated the environmental effect of eliminating the use of all CFCs in an environmental impact statement (EIS) in the 1970s (see 43 FR 11301, March 17, 1978). As part of that evaluation, FDA concluded that the continued use of CFCs 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 CFCs over time (see Title VI (enacted November 15, 1990)). FDA notes that the environmental impact of individual uses of nonessential CFCs must not be evaluated independently, but rather must be evaluated in the context of the overall use of CFCs. 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 ODS use and therefore should be exempted, the elimination of CFC use in MDIs is only one of many steps that are part of the overall phaseout of ODS 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.

K. Generics

(Comment 45) Two comments stated that FDA should not eliminate an essential use unless a non-ODS generic is available for that essential use.

Only one CFC-MDI, albuterol, is available in a generic formulation. FDA is not requiring that more generics be available in non-ODS formulations than are available in CFC formulations. It would seem inappropriate to require the availability of a non-ODS generic drug product when there is no generic version currently on the market and we have no guaranty that a generic drug will ever be developed for any given active moiety. 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, by the approvability of any particular generic drug application, and by the manufacturers' eligibility to receive ODSs under the Montreal Protocol and the Clean Air Act.

(Comment 46) Three comments said that FDA should not approve a new CFC-containing MDI drug product if the active moiety in the drug product is already marketed and appears on the essential-use list. Three comments stated that FDA should not approve generic versions of existing essential-use products. One comment stated that FDA should approve generic versions of existing essential-use products. One comment stated that patients will not be adversely affected in terms of out-of-pocket cost of medications or quality of life if approval of generic medications should cease. One comment said that FDA should not approve any new CFC-containing drug product unless it provides an unavailable important public health benefit. One comment requested that FDA require all new drug products to demonstrate clinically significant value before approval.

Section 505 of the act directs FDA to approve new drug and generic products if all of the requirements in the act are met. There is no exception in the act permitting FDA to refuse to approve new drug or generic products simply because they contain an ODS. Therefore, FDA will continue to approve new drug and generic applications that meet the current requirements of the act.

(Comment 47) One comment stated that FDA should require companies using essential-use designations to demonstrate that they are actively pursuing reformulation.

FDA is not requiring companies to demonstrate that they are actively pursuing reformulation to maintain the essential-use designation of their products. However, after January 1, 2005, FDA may propose to remove the essential-use designation for an active moiety even if it has not been reformulated.

L. New Essential Uses

(Comment 48) One comment supported the criteria in the proposed rule for the addition of new essential uses.

FDA is adopting the criteria for addition of new essential uses that it had proposed.

(Comment 49) One comment supported the compelling evidence standard generally but asked that FDA approve new essential uses if the product offers a compelling therapeutic benefit to a significant, albeit small, subpopulation.

FDA will consider adding a new essential use if the use is for a product that will provide an unavailable important public health benefit. FDA believes it is possible, under this criterion, for a product that offers a compelling therapeutic benefit for a significant, albeit small, subpopulation to qualify for an essential use. FDA would carefully evaluate any evidence in support of such an essential use.

M. Additional Comments

(Comment 50) Three comments supported changing the designation of ODS products not listed from adulterated and misbranded to nonessential. One comment asked that FDA revoke the statements made in the preamble to the proposed rule regarding the continued applicability of the adulterated and misbranded provisions of the act. One comment stated that FDA should retain the express authority to find a nonessential product adulterated or misbranded if it contains CFCs.

The agency is amending § 2.125 to state that a product in a self-pressurized container that contains an ODS is not essential. This change should not be interpreted to mean that FDA no longer believes that such products are adulterated and/or misbranded. 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 § 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 the Clean Air Act.

(Comment 51) One comment argued that the transition will force patients to abandon safe and effective products.

FDA is finalizing this rule to fulfill its responsibilities under the Clean Air Act. Although it is true that CFC–MDIs are safe and effective as approved, CFCs also deplete the ozone layer which has a detrimental effect on the public health and the environment. The United States has determined that, as a result, CFC–MDIs should be phased out.

(Comment 52) One comment asked for clarification on whether elimination of an essential use from § 2.125 would prohibit use of stockpiled CFCs.

This comment raises questions under the Clean Air Act. Under 40 CFR 82.64(c), no person may sell or distribute, or offer to sell or distribute, in interstate commerce any nonessential product. Under 40 CFR 82.66(d), any aerosol product or other pressurized dispenser that contains a CFC is a nonessential product. Medical devices listed in § 2.125(e) are exempted from this prohibition (40 CFR 82.66(d)(2)(i)). However, once a medical device is removed from the listing in § 2.125(e), it can no longer be marketed (40 CFR 82.64(c)). FDA notes that it plans to include an implementation period once the agency determines that a use is no longer essential. The length of this implementation period will be determined through the notice-and-comment rulemaking in which the essential use is eliminated.

(Comment 53) One comment stated that FDA must comply with Executive Order 12898 on environmental justice.

Executive Order 12898 requires agencies to identify and address disproportionately high adverse human health or environmental effects on minority populations and low-income populations. As discussed in the economic analysis prepared for this rule, the agency does not anticipate that this final rule will have any adverse effects on human health or the environment (see section VII of this document).

(Comment 54) One comment stated that FDA must comply with Executive Order 12866 on economic and social cost-benefit assessments.

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).

(Comment 55) One comment stated that FDA must comply with Executive Order 12630 on effects on private property. One comment argued that the government cannot preclude the use of stockpiled CFCs because to do so would result in a taking.

Executive Order 12630 requires government agencies to evaluate whether a regulation has any takings implications. FDA does not believe that this regulation has any takings implications. This regulation simply sets the standard FDA will use to determine whether an ODS use remains essential. The Clean Air Act then prevents marketing of those ODS-containing products. The use of stockpiled CFCs is governed by the Clean Air Act.

(Comment 56) One comment stated that FDA needs to complete an EIS under the National Environmental Policy Act of 1969 (NEPA), as amended (42 U.S.C. 4321–4347).

FDA has complied with NEPA. The agency has evaluated the environmental effects of eliminating ODS-containing products and provided opportunities for public comment on these issues. An EIS was prepared on this issue (see 43 FR 11301, March 17, 1978). In addition, environmental assessments (EAs) were prepared in conjunction with the NDA approval process for products that are viewed as alternatives to metered-dose steroid drugs for nasal inhalation containing ODSs. Finally, FDA issued both an ANPRM (62 FR 10242) and a proposed rule (64 FR 47719) as part to this rulemaking. Both of these documents discuss the environmental effects of eliminating ODS-containing products. The agency received large numbers of comments and responded to them in the proposed rule or this document. This document further discusses the environmental effect of eliminating ODS- containing products.

Furthermore, those portions of the rule that set out the processes for adding new essential uses and for determining that existing uses are no longer essential are covered by a categorical exclusion from NEPA's requirements. Section 25.30(h) of FDA's NEPA regulations (21 CFR 25.30(h)) provides that the ''[i]ssuance, amendment, or revocation of procedural or administrative regulations * * *'' does not require the preparation of an EIS or an EA. Finally, in the future, when FDA undertakes rulemaking to add or remove an essential use, the agency will prepare an EA and/or an EIS if required by NEPA.

However, to ensure that the public is given the fullest opportunity to comment on this rulemaking, interested parties may submit comments on the environmental effects of removing the essential-use designations for products that are no longer being marketed and for metered-dose steroid drugs for nasal inhalation for a period of 30 days after publication of this rule. Unless the agency receives a comment that leads it to believe that a change in the rule is appropriate, the effective date of this rule will be January 20, 2003.

(Comment 57) One comment asked that FDA revise the proposal to clarify that the nonessentiality determination applies only to products marketed in the United States and not to exports.

FDA is not revising § 2.125 to reflect that the nonessentiality determination applies only to products in the United States and not to exports because the act has specific provisions that address when a product that would otherwise be adulterated and misbranded may still be exported. Under section 801(e)(1) of the act (21 U.S.C. 381(e)(1)):

> A food, drug, device, or cosmetic intended for export shall not be deemed to be adulterated or misbranded under this Act if it—
>
> (A) accords to the specifications of the foreign purchaser,
>
> (B) is not in conflict with the laws of the country to which it is intended for export,
>
> (C) is labeled on the outside of the shipping package that it is intended for export, and
>
> (D) is not sold or offered for sale in domestic commerce.

A manufacturer seeking to export nonessential products could do so under the act so long as the products for export met the requirements of section 801 of the act.

FDA has consulted with EPA to determine whether EPA rules currently allow export of nonessential products. FDA understands that current EPA rules do not allow such export. However, depending on the pace of transition in other countries and their possible continued short-term need to have a small amount of additional time to effectuate their timely and thoughtful phaseout, EPA may consider changing its rule at some future date.

(Comment 58) One comment argued that the Clean Air Act requires notice-and-comment rulemaking for addition of each drug product rather than each moiety.

Section 601(8) of the Clean Air Act states that each ''medical device'' must

have been determined to be essential. The section defines ''medical device'' as ''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 * * *.'' Section 201(g)(1) of the act defines ''drug'' as:

(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and

(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

(C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and

(D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

* * *

This definition permits the word ''drug'' to be read to mean either ''drug product,'' ''drug substance'' or ''active moiety.'' FDA has read the word drug to have a specific meaning depending on the context in which it is used. In this case, FDA believes it is appropriate to read the word ''drug'' to mean ''active moiety.''

(Comment 59) Two comments stated that neither the Clean Air Act nor the Montreal Protocol requires an eventual end to any and all essential uses of CFCs within the United States.

In light of these comments, FDA has revisited the text of the Clean Air Act, its legislative history, the text of the Montreal Protocol, and decisions by the Parties to the Protocol. FDA also further discussed its understanding of the Clean Air Act and the Protocol with the EPA.

The text of the Clean Air Act states that EPA will, after notice and opportunity for public comment and ''to the extent such action is consistent with the Montreal Protocol, authorize the production of limited quantities of class I substances solely for use in medical devices * * *.'' (section 604(d)(2) of the Clean Air Act). The Clean Air Act does not state specifically whether such essential-use exemptions may continue indefinitely or must terminate at some future time. However, the legislative history for this section of the Clean Air Act makes it clear that the exemption is only permitted for a limited time. The Senate Conference Report for this section of the Clean Air Act states:

The Administrator [of EPA] is authorized on a conditional basis to grant limited extensions of the termination date for production of limited quantities of class I substances, to the extent such action is consistent with the Montreal Protocol for: * * * medical devices; * * *.

* * * * *

The centerpiece of the stratospheric ozone protection program established by this title is the phaseout of production and consumption of all ozone depleting substances.

(136 Cong. Rec. S16895 at 16946 and 16947 (daily ed. Oct. 27, 1990).)

These statements are consistent with the Montreal Protocol. The Preamble to the Protocol states that the Parties are:

Determined to protect the ozone layer by taking precautionary measures to control equitably total global emissions of substances that deplete it, *with the ultimate objective of their elimination* on the basis of developments in scientific knowledge, taking into account technical and economic considerations and bearing in mind the developmental needs of developing countries.

(Preamble to the Montreal Protocol (emphasis added).)

Decision IV/25 of the Protocol also indicates that essential-use exemptions are temporary. This decision asks the Technology and Economic Assessment Panel to determine an estimated duration for each essential use, the steps necessary to ensure alternatives are available as soon as possible, and whether previously qualified essential uses should no longer qualify as essential.

Finally, FDA confirmed with EPA that it is also their understanding that the Clean Air Act and the Montreal Protocol do not permit essential-use exemptions to continue forever.

Thus, although it is true that there is no set date for termination of essential-use exemptions, it is also clear that the exemptions will not exist forever.

V. Legal Authority

This final rule to determine when FDA-regulated products using ODSs are essential is authorized by the Clean Air Act. EPA regulations implementing the provisions of section 610 of the Clean Air Act contain a general ban on the use of CFCs 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) (section 610(e) of the Clean Air Act; 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 ODS 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 CFCs, halons, carbon tetrachloride, methyl chloroform, methyl bromide, and other chemicals not relevant to this document (see 40 CFR part 82, appendix A to subpart A). Class II substances include hydrochlorofluorocarbons (see 40 CFR part 82, appendix B to subpart A).

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 rule provides a mechanism for FDA to remove products from the essential-use list in an orderly and rational fashion.

EPA has reviewed this rule and agrees with its issuance.

VI. Implementation Plan

This final rule is effective January 20, 2003. After January 20, 2003, FDA will 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.

VII. Analysis of Impacts

FDA has examined the impacts of the final 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 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 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 determined that the final rule is consistent with the principles set forth in the Executive order and in these statutes. The final 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 regulation would not result in a significant economic impact on a substantial number of small entities. Thus, the agency need not prepare a final regulatory flexibility analysis.

FDA published a detailed analysis of impacts when this regulation was proposed in September 1, 1999 (64 FR 47719). No further information has been submitted that would alter the findings of the analysis submitted with the proposed regulation.

FDA is removing the essential-use designation for metered-dose steroid human drugs for nasal inhalation. Four manufacturers market CFC-nasal inhalation products, which constitute a small proportion of the nasal inhalation product market. The affected CFC containing drug products contain either beclomethasone, budesonide, or triamcinolone. All three active moieties are also marketed in non-CFC formulations by the same manufacturers of the CFC nasal inhalation products. Several other steroid human drugs for nasal inhalation are marketed in non-CFC formulations. These drug products provide therapeutic alternatives to the CFC containing products.

FDA is also removing the essential-use designations for drug products that are either no longer being marketed or are no longer being marketed in a formulation containing ozone depleting substances.

In addition to removing these essential uses, this regulation articulates the standards used by FDA to determine whether the use of ozone-depleting substances in metered dose inhalers remains essential under the Clean Air Act. The regulation has limited direct economic impact because it primarily establishes the criteria FDA would use to make essential use determinations. However, future application of the procedure described in this regulation will generate both regulatory benefits and costs. FDA has discussed the potential nature of these impacts with the proposed rule and briefly describes them below.

A. Regulatory Benefits

The benefits of the procedure described in this regulation are the environmental gains associated with the diminished use of ozone-depleting substances in medical products. The Environmental Protection Agency has estimated (in prior regulatory analyses) that the aggregate public health benefit of phasing out the use of ozone-depleting substances due to reduced cases of skin cancer, cataracts and other health effects ranges between $8 and $32 trillion. FDA has crafted the procedure described in this regulation to achieve a small fraction of these benefits while maintaining adequate supplies of reformulated products for patients treated for asthma and COPD. Most important, the regulation ensures that adequate supplies of reformulated products with comparable therapeutic roles are available prior to rescission of an essential use designation. Although FDA cannot speak with certainty about future events, the agency does not anticipate that significant decreases in purchases of non-ODS alternatives, as compared to purchases of CFC–MDIs, will occur after an essential-use exemption is removed under the procedures set forth in this rule.

Similarly, removal of essential-use designations for steroid nasal inhalation products would not affect the public health. Adequate supplies of reformulated products with comparable therapeutic roles exist with prices that are approximately the same as the CFC products on a dose basis.

B. Regulatory Costs

FDA considers the costs of reformulation to be direct consequences of the statutory requirements of the Clean Air Act rather than forthcoming FDA regulatory activity. Sponsors who elect to reformulate their products may incur costs to collect detailed clinical data, but FDA has no empirical information to confirm the extent of these costs. Manufacturers are well aware of the mandate to eliminate ozone-depleting substances and are already engaged in the development of reformulated products.

The same manufacturers that currently market steroid nasal inhalation products containing CFCs also market non-CFC alternatives. Thus, FDA does not anticipate a regulatory cost due to this regulation.

FDA realizes that the future elimination of essential-use exemptions could have significant distributional and regulatory impacts on various economic sectors. The agency will prepare detailed analyses of impacts as part of each of these future rulemakings. The role that the Montreal Protocol and the Clean Air Act will play in the eventual prohibition of the production or importation of ODSs must also be kept in mind.

C. Distributive Impacts

Potential distributive impacts will not be triggered until the completion of future rulemaking on each specific product currently using ozone-depleting substances. FDA plans on conducting specific market analyses to determine the approximate magnitude of these effects prior to removing essential use designations for specific products.

The agency recognizes that generic albuterol CFC-MDIs are currently marketed and that these products cost less than currently marketed albuterol sulfate MDI's which use hydrofluoroalkane (HFA) as a propellant. At the appropriate time, FDA will evaluate the essential-use status of albuterol under criteria established by this rule. In determining whether patients are adequately served by non-ODS products containing albuterol as the active moiety, FDA will consider the cost of potential alternatives, such as the albuterol sulfate HFA-MDIs.

The agency does not believe that cost will be a significant factor in determining whether patients are adequately served by non-ODS products containing active moieties other than albuterol. There are currently no generic versions for these other products and FDA expects that the price for most non-ODS products will approximate the price for branded CFC products. FDA bases this expectation on statements by manufacturers.

FDA does not anticipate distributive impacts due to the removal of essential-use designations for steroid nasal inhalation products. The same manufacturers also currently market substitute, non-CFC products at approximately the same price.

D. Small Business Impact

FDA conducted an interim Regulatory Flexibility Analysis that resulted in a determination that this regulation would not have a significant economic impact on a substantial number of small entities. This analysis was included with the proposed regulation (64 FR 47719). There are relatively few small manufacturers of products that could potentially be affected. In addition, pharmaceutical wholesalers and retailers are unlikely to be significantly affected because this regulation will affect only a few of the thousands of products sold by these firms. FDA

received no comments on the interim analysis. FDA also notes that this regulation simply articulates a procedure that will be used in the future to assess whether or not ozone-depleting substances in metered dose inhalers are essential.

FDA further certifies that the removal of essential-use designations for steroid nasal inhalation products that contain CFCs will not have a significant impact on a substantial number of small entities. The four affected manufacturers currently market alternative products at comparable prices. Therefore no net impact is expected from this regulation.

VIII. The Paperwork Reduction Act of 1995

This final 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 number 0910–0183, which expires on February 28, 2003 (see 65 FR 12014, March 7, 2000).

IX. Reference

The following reference has been placed on display in the Dockets Management Branch (HFA–305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. The reference may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Food and Drug Administration, Center for Drug Evaluation and Research, Pulmonary and Allergy Drugs Advisory Committee Transcript, Friedman & Associates, November 22, 1999.

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, after consultation with the Administrator of the Environmental Protection Agency, 21 CFR part 2 is amended as follows:

PART 2—GENERAL ADMINISTRATIVE RULINGS AND DECISIONS

1. The authority citation for 21 CFR part 2 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 ODSs 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) 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 request that FDA initiate rulemaking to amend paragraph (e) of this section to add an essential use. FDA may initiate notice-and-comment rulemaking to add an essential use on its own initiative or in response to a petition, if granted.

(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 ODSs;

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

(iii) Use of the product does not release cumulatively significant amounts of ODSs 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 ODSs;

(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 ODSs into the atmosphere or the release is warranted in view of the high probability of an unavailable important public health benefit.

(g) Any person may file a petition under part 10 of this chapter to request

that FDA initiate rulemaking to amend paragraph (e) of this section to remove an essential use. FDA may initiate notice-and-comment rulemaking to remove an essential use on its own initiative or in response to a petition, if granted. If the petition is to remove an essential use from paragraph (e) of this section, the petitioner must submit compelling evidence of any one of the following criteria:

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

(2) After January 1, 2005, FDA determines that the product using an ODS 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):

(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) Adequate 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 NDAs:

(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: April 15, 2002.

Lester M. Crawford,

Deputy Commissioner.

[FR Doc. 02–18610 Filed 7–18–02; 3:38 pm]

BILLING CODE 4160–01–S

DEPARTMENT OF JUSTICE

Bureau of Prisons

28 CFR Part 523

[BOP–1106–F]

RIN 1120–AB05

District of Columbia Educational Good Time Credit

AGENCY: Bureau of Prisons, Justice.

ACTION: Interim final rule.

SUMMARY: In this document, the Bureau of Prisons (Bureau) describes procedures for awarding educational good time credit consistent with D.C. Code § 24–221.01 (DCEGT). This rule will apply to D.C. Code offenders in Bureau institutions or Bureau contract facilities under the National Capital Revitalization and Self-Government Improvement Act of 1997 (D.C. Revitalization Act), D.C. Code § 24–101(b), who committed their offenses before August 5, 2000. Through this rule, we will allow inmates sentenced under the D.C. Code to retain benefits permitted by the D.C. Code while fulfilling our statutory mandate to provide for their custody consistent with the sentence imposed.

DATES: This rule is effective on July 24, 2002. Comments are due by September 23, 2002.

ADDRESSES: Rules Unit, Office of General Counsel, Bureau of Prisons, 320 First Street, NW., Washington, DC 20534.

FOR FURTHER INFORMATION CONTACT: Sarah Qureshi, Office of General Counsel, Bureau of Prisons, phone (202) 307–2105.

SUPPLEMENTARY INFORMATION:

What Will This Rule Do?

Through this rule, the Bureau of Prisons (Bureau) will add a subpart D to its regulations in 28 CFR part 523, on Computation of Sentence. The new subpart D will establish procedures for awarding educational good time credit consistent with D.C. Code § 24–221.01. (We refer to educational good time credit consistent with the D.C. Code as ''DCEGT.'')

This rule will apply to D.C. Code offenders who committed their offense before August 5, 2000 and are in Bureau institutions or Bureau contract facilities under the D.C. Revitalization Act.

Why Are We Making This Rule?

We are making this rule to comply with the D.C. Revitalization Act, enacted August 5, 1997. This Act makes the Bureau responsible for the ''custody, care, subsistence, education, treatment and training'' of ''the felony population sentenced pursuant to the District of Columbia Code'' (D.C. Code offenders). (D.C. Code § 24–101(b)) D.C. Code offenders in Bureau custody are subject to Federal laws and Bureau regulations as long as they are ''consistent with the sentence imposed.''

In August of 1997, when the D.C. Revitalization Act was enacted, the Bureau began absorbing approximately 8000 D.C. Code offenders. It was unclear at that time to what extent, if any, the Bureau would be bound by D.C. Code legislation which purported to direct Bureau functions.

As numerous D.C. Code provisions were analyzed for applicability to Bureau functions, it was generally concluded that the Bureau would have to follow D.C. Code sentence calculation provisions (e.g., good time, jail credit, etc.) to the extent non-compliance would result in an ex post facto violation of the offender's sentence. The Bureau based this approach on the provision in D.C. Revitalization Act requiring the Bureau to apply Federal laws to D.C. Code offenders ''consistent with the sentence imposed.''

The Bureau concluded that D.C. Code offenders who committed their offenses before August 5, 2000 are entitled to educational good time sentence credit. As a result, we developed these rules to give effect to the D.C. Code educational good time sentence credit (DCEGT) provisions in the Bureau's education and sentence calculation systems.

Section 24–221.01 of the D.C. Code provides for ''educational good time credits of no less than 3 days a month and not more than 5 days a month'' when a D.C. Code offender completes an educational program and obeys institution rules. This provision applies when a D.C. Code offender completes an educational program on or after April 11, 1987, when section 24–221.01 was enacted.

Section 24–403.01(d) of the D.C. Code, enacted April 23, 1998, however, requires that D.C. Code offenders who committed their offense on or after August 5, 2000, receive good time credit ''only as provided in 18 U.S.C. 3624(b).'' This statute in the Federal Criminal Code directs the Bureau how to award good time credit to U.S. Code offenders. Bureau regulations implementing this provision are in 28 CFR 523.20.

D.C. Code offenders who successfully complete an educational program on or after April 11, 1987, and who committed their offense before August 5, 2000, may receive educational good time credit consistent with D.C. Code