Executive Order 12291 was revoked by Executive Order 12866 section 11. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. The agency has complied with this requirement to the extent necessary (see section VII of this document).

Executive Order 12606 was revoked and replaced by Executive Order 13045 section 7–702. Executive Order 13045 applies only to regulatory actions initiated after the date of the Executive Order (Executive Order 13045 section 2–202). The ANPRM was published on March 6, 1997, before the Executive Order was signed on April 21, 1997. Accordingly, this proposed regulatory action is exempt from Executive Order 13045. In addition, Executive Order 13045 applies only to significant regulatory actions that concern an environmental health risk or safety risk that an agency has reason to believe may disproportionately affect children. First, this proposal is not a significant regulatory action because it is not anticipated that it will have an annual net effect on the economy of $100 million or more, nor would it adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities. Second, the phaseout of CFC–MDI's is not an environmental health risk. Rather, the phaseout constitutes an environmental health benefit, since reduction in CFC use could decrease ongoing damage to the ozone layer and thereby decrease related health problems. In particular, children will benefit from a phaseout because they are more susceptible to skin cancers due to increased sensitivity and lifetime exposure. Therefore, Executive Order 13045 does not apply to this proposal.

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

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

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

The primary purpose of the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) is to end the imposition of unfunded Federal mandates on other governments without the full consideration of the Federal Government (2 U.S.C. 1501(2)). However, the Unfunded Mandates Reform Act does also ask agencies to estimate the impact of unfunded Federal mandates on the private sector (2 U.S.C. 1501(3)). As part of that estimate, the agency is to examine the effect of the Federal mandate on health, safety, and the natural environment. FDA has complied with this requirement (see section VII of this document). In addition, FDA believes that environmental benefits are analyzed with the regulations implementing the Clean Air Act.

IV. Legal Authority

FDA's proposal to determine when CFC uses are essential in medical devices is authorized by the Clean Air Act. EPA regulations implementing the provisions of section 610 of the Clean Air Act (42 U.S.C. 7671i) contain a general ban on the use of CFC's in pressurized dispensers (40 CFR 82.64(c) and 82.66(d)). The Clean Air Act and EPA regulations exempt from the general ban ''medical devices'' that FDA considers essential and that are listed in § 2.125(e) (42 U.S.C. 7671i(e); 40 CFR 82.66(d)(2)). Section 601(8) of the Clean Air Act defines ''medical device'' as any device (as defined in the act), diagnostic product, drug (as defined in the act), and drug delivery system, if such device, product, drug, or drug delivery system uses a class I or class II ozone-depleting substance for which no safe and effective alternative has been developed (and, where necessary, approved by the Commissioner of Food and Drugs (the Commissioner)); and if such device, product, drug, or drug delivery system has, after notice and opportunity for public comment, been approved and determined to be essential by the Commissioner in consultation with

the Administrator of EPA (the Administrator). Class I substances include CFC's, halons, carbon tetrachloride, methyl chloroform, methyl bromide, and other chemicals not relevant to this document (see 40 CFR part 82, appendix A to subpart A). Class II substances include hydrochlorofluorocarbons (HCFC's) (see 40 CFR part 82, appendix B to subpart A). Essential-use products are listed in § 2.125(e). Although § 2.125 includes a mechanism for adding essential-use products to the regulations, the regulations do not include a mechanism for removing products from the essential-use list. This proposed rule, if enacted, would provide a mechanism for FDA to remove products from the essential-use list in an orderly and rational fashion.

V. Proposed Implementation Plan

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

VI. Request for Comments

Interested persons may, on or before (*insert date 90 days after date of publication in the* **Federal Register**), submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In particular, FDA seeks comment on the following issues:

1. The criteria FDA should use to determine whether a subpopulation is significant;

2. The type of postmarketing information FDA should consider in evaluating the adequacy of alternatives; and

3. The timing of the removal of the essential-use designation for nasal steroids.

VII. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs regulatory agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Unless the agency certifies that the rule is not expected to have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant economic impact of a rule on small entities. Section 202 of the Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million in any one year (adjusted annually for inflation). The agency has conducted analyses of the proposed rule, and has determined that the rule is consistent with the principles set forth in the Executive Order and in these statutes. FDA finds that this proposed rule will not result in costs in excess of $100 million, and therefore no further analysis is required under the Unfunded Mandates Reform Act. In addition, FDA certifies that this proposed regulation would not result in a significant economic impact on a substantial number of small entities. Thus, the agency need not prepare an interim Regulatory Flexibility Analysis.

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

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

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

B. Economic Impacts

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

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

1. Regulatory Benefits

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

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

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

increased following the introduction of generic competition (Ref. 3). Consequently, FDA does not anticipate a significant decrease in the total number of prescriptions purchased due to curtailment of generic competition. However, these impacts may vary for particular products or markets and FDA asks for public comment on this issue, with particular attention to evaluating effects on patient affordability.

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

2. Regulatory Costs

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

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

3. Distributive Impacts

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

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

[7] Data indicate this to be true in both absolute and proportional terms.

manufacturers could experience overall sector losses due to the removal of a product from the essential-use list in § 2.125.

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

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

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

C. Small Business Impact

1. Initial Analysis

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

2. Description of Impact

The objective of the proposed regulation is to provide the basis for essential-use designations for ODS's in FDA-regulated products, without jeopardizing the public health. The proposed

regulation would accomplish this objective by articulating the standards to be used for revising essential-use designations for approved drug products. The statutory authority for the proposed rulemaking is discussed in section IV of this document.

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

Table 1 of this document shows that seven drug substances will be eligible for generic competition in the next several years. However, even in the absence of any FDA decision, many of these drug substances are unlikely to attract generic competition because of their relatively small market share and the knowledge that ODS's are to be removed from the market. In fact, several drug substances that have lost market exclusivity have not been subject to generic competition.

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

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

3. Analysis of Alternatives

FDA examined several alternatives to the proposed rule. First, FDA considered denying new essential-use designations but allowing currently exempted drug products to continue to use ODS's.

This alternative would continue the availability of current therapies at no additional transfer of costs. However, there would be no incentive to reformulate products. Thus, this alternative would not meet the environmental requirement to eliminate the use of ODS's.

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

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

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

D. Conclusion

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

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

TABLE 1.—DESCRIPTION OF THE AFFECTED DRUG SUBSTANCE (AS OF SEPTEMBER 1998)[1]

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

[1] Source: FDA CDER data and *Approved Therapeutic Drug Products*, 19th ed.
[2] Including 34.96 million generic and relabeled prescriptions.
[3] Percentages do not add to 100 percent because data are not available for epinephrine and isoproterenol.

VIII. The Paperwork Reduction Act of 1995

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

IX. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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

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

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

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

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

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

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

8. Frank, R. G., and D. S. Salkever, ''Generic Entry and the Pricing of Pharmaceuticals,'' *Journal of Economics and Management Strategy*, 6:1(75–90), 1997.

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

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

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

List of Subjects in 21 CFR Part 2

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

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

PART 2—GENERAL ADMINISTRATIVE RULINGS AND DECISIONS

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

Authority: 15 U.S.C. 402, 409; 21 U.S.C. 321, 331, 335, 342, 343, 346a, 348, 351, 352, 355, 360b, 361, 362, 371, 372, 374; 42 U.S.C. 7671 *et seq.*

2. Section 2.125 is revised to read as follows:

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

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

(b) Except as provided in paragraph (c) of this section, any food, drug, device, or cosmetic that is, consists in part of, or is contained in, an aerosol product or other pressurized dispenser that releases an ODS is not an essential use of the ODS under the Clean Air Act.

(c) A food, drug, device, or cosmetic that is, consists in part of, or is contained in, an aerosol product or other pressurized dispenser that releases an ODS is an essential use of the ODS under the Clean Air Act if paragraph (e) of this section specifies the use of that product as essential. For drugs, including biologics and animal drugs, and for devices, an investigational application or an approved marketing application must be in effect, as applicable.

(d) [Reserved]

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

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

(i) Beclomethasone.

(ii) Dexamethasone.

(iii) Flunisolide.

(iv) Fluticasone.

(v) Triamcinolone.

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

(i) Albuterol.

(ii) Bitolterol.

(iii) Metaproterenol.

(iv) Pirbuterol.

(v) Terbutaline.

(vi) Epinephrine.

(3) [Reserved]

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

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

(iii) Anesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(2) After January 1, 2005, the product is not available without an ODS and FDA determines that the product no longer meets the criteria in paragraph (f) of this section after consultation with a relevant advisory committee(s) and after an open public meeting; or

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

(i) At least one non-ODS product with the same active moiety is marketed with the same route of administration, for the same indication, and with approximately the same level of convenience of use as the ODS product containing that active moiety;

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

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

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

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

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

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

Dated: AUG 19 1999

August 19, 1999

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 99–???? Filed ??–??–99; 8:45 am]

BILLING CODE 4160–01–F

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL