transition strategy no later than January 31, 1999, and were encouraged to present a strategy before January 31, 1998. In publishing the ANPRM, FDA provided a draft proposal for public comment and consideration domestically and internationally. FDA recognizes that rulemaking can take many months or years to complete. FDA published the ANPRM early to give the public time to comment and to give FDA time to develop a final rule that would be most protective of public health.

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

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

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

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

65. One comment said that as more people use non-ODS products, CFC use will decrease and the problem of CFC use will solve itself.

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

10. Nasal Steroids

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

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

For the reasons set forth previously, FDA is proposing to remove the essential-use designation in current § 2.125(e)(1) for metered-dose steroid human drugs for nasal inhalation. FDA notes that the Parties to the Montreal Protocol have not granted essential-use exemptions for manufacture of nasal steroid CFC–MDI's since the general ban on CFC production went into effect in industrialized nations on January 1, 1996. The Parties do not consider CFC-based nasal steroids to be medically essential products because of the available alternatives. Any CFC-based nasal steroids currently being manufactured are presumably being manufactured with CFC's manufactured prior to 1996. In addition, the indications for which these products are approved and used are not life threatening.

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

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

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

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

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

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

11. Miscellaneous Comments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12. Incentives for Development of Alternatives

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

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

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

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

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

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

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

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

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

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

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

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

85. One comment stated that inventors of non-CFC products should be rewarded with the same patent protections as all other inventors. One comment stated that non-CFC formulations of CFC–MDI's should not be patented.

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

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

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

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

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

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

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

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

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

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

Manufacturers may advertise claims supported by adequate evidence.

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

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

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

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

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

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

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

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

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

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

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

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

13. Cost of New Products

97. Two comments stated that FDA should consider whether lack of competition will increase costs. Another comment requested that FDA not allow phaseout unless alternative products are manufactured by at least two independent manufacturers. A third comment requested that FDA not allow phaseout until there are at least three competitors available in each of the three categories: Quick-acting, 12-hour, and cortisone-based inhalers. One comment asked that FDA not eliminate CFC–MDI's until generic competition for the non-CFC products exists. Two comments said that if CFC substitutes are produced using proprietary technology, phaseout should not be mandated until the technology is in the public domain. Another comment asked that asthma medicine continue to be available at the lowest possible prices. One comment stated that non-CFC products would likely be higher priced than current MDI's. Five comments stated that FDA's proposal, if implemented, would have an enormous financial impact for state Medicaid drug costs, Medicare

patients, and uninsured or inadequately insured individuals who could not afford the new non-CFC agent. Another comment evaluated their institution's cost of replacing generic albuterol CFC–MDI's with Proventil HFA and concluded that the annual cost for albuterol MDI's would increase from approximately $25,000 to more than $200,000.

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

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

FDA has completed an analysis of the economic impact of its proposal that addresses these issues (see section VII.B of this document).

99. Four comments stated that FDA should undertake a cost/benefits study comparing the benefits of removing CFC–MDI's from the market to the benefits of allowing continued marketing of CFC devices. One comment stated that FDA should determine whether to eliminate CFC

products based on sound science that includes a cost/benefit study whose methodology is published in the **Federal Register**.

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

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

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

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

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

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

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

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

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

14. Environmental Impact of CFC–MDI Use

104. One comment claimed that a continuing exemption for MDI's is permitted under the Montreal Protocol, Title VI of the Clean Air Act, and the regulatory and policy actions of EPA.

The comment went on to question whether termination of the essential-use exemption for MDI's will materially advance stratospheric ozone protection and whether this benefit outweighs the potential social and economic costs of phaseout.

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

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

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

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

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

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

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

One comment stated that stratospheric ozone is our main global protectant against ultraviolet B light (UVB), and international restrictions on CFC releases will allow the progressive destruction of stratospheric ozone to cease and begin to rebuild in the early 21st century. The comment also noted that the current generation of children face a 1:70 risk of melanoma. In addition, the comment stated that basal and squamous cell carcinoma, cancer precursor lesions, premature skin aging (spotting, wrinkling, fragility, sallow color, sagging), photo-induced medication reactions, autoimmune disease (i.e. lupus), immune suppression, porphyria, and regular sunburn are all exacerbated by the UVB rays in sunlight, which will become more intense on an increasing basis by 2010 due to ozone depletion.

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

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

The United States evaluated the environmental effect of eliminating the use of all CFC's in an environmental impact statement in the 1970's (see 43 FR 11301, March 17, 1978). As part of that evaluation, FDA concluded that the continued use of CFC's in medical products posed an unreasonable risk of long-term biological and climatic impacts (see Docket No. 96N–0057). Congress later enacted provisions of the Clean Air Act that codified the decision to fully phase out the use of CFC's over time (see 42 U.S.C. 7671 *et seq.* (enacted November 15, 1990)). FDA notes that the environmental impact of individual uses of nonessential CFC's must not be evaluated independently, but rather must be evaluated in the context of the overall use of CFC's. Cumulative impacts can result from individually minor but collectively significant actions taking place over a period of time (40 CFR 1508.7). Significance cannot be avoided by breaking an action down

into small components (40 CFR 1508.27(b)(7)). Although it may appear to some that CFC–MDI use is only a small part of total CFC use and therefore should be exempted, the elimination of CFC use in MDI's is only one of many steps that are part of the overall phaseout of CFC use. If each small step were provided an exemption, the cumulative effect would be to prevent environmental improvements. FDA is merely fulfilling its obligation to make essential-use determinations for FDA-regulated products, in accordance with the Clean Air Act.

FDA notes that CFC–MDI's do release CFC's as part of their intended use. Tube spacers, inhalation techniques, and other factors do not alter this release.

15. Proposed Mechanism for Phaseout

105. One comment requested that FDA publish this proposed rule by September 1997.

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

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

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

107. One comment requested that, as part of the phaseout procedure, FDA require industry to educate physicians and patients that: (1) CFC's serve no medical purpose, and (2) the transition is not about removing drugs but about getting rid of CFC's. Two comments said that FDA should require patient and physician education. One comment said that a seamless transition scheme should be developed and should include patient and health care provider educational resources and programs as well as public awareness campaigns well before projected phaseout dates. Another comment said that transition should be undertaken as a joint project by FDA, the National Asthma

Education and Prevention Program (NAEPP) of the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH), industry (e.g., International Consortium of Pharmaceutical Aerosol Manufacturers (IPAC), professional organizations (e.g., American Lung Association) and patient advocacy groups (e.g., Mothers of Asthmatics) to ensure dissemination of consistent information. The comment went on to say that educational efforts should include presentations at national scientific and professional meetings and seminars, consultations with public interest groups, one-on-one instruction, and publications in professional as well as lay media (e.g., flyers, posters, newspaper articles, videos, stories, plays). One comment said that FDA should consider psychological factors that could result in slow acceptance of new products. Ten comments said that patients, physicians, and managed care companies need education.

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

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

/www.fda.gov/cder/mdi/. The NAEPP CFC Workgroup is continuing to broaden its educational effort. FDA provides appropriate advice and assistance to the NAEPP CFC Workgroup.

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

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

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

FDA uses the procedures in 21 CFR 314.200 to withdraw approval of a drug. Under proposed § 2.125, FDA is not proposing to withdraw approval of any drug. FDA is simply proposing a process for determining whether the use of an ODS in a particular medical device continues to be essential. To maximize public input, FDA will use notice-and-comment rulemaking to evaluate whether a moiety should remain on the list of essential uses.

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

FDA has disclosed in the ANPRM and in this proposed rule the data and technical information upon which it relied in drafting this proposal.

16. International Mandate (Montreal Protocol)

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

Although FDA did not publish this proposed rule before the November 1998 meeting, it has continued to work to develop the proposal. The Parties to the Montreal Protocol suggested that Parties requesting essential-use allowances submit an initial transition strategy by January 31, 1998,

and required these Parties to submit an initial strategy no later than January 31, 1999. FDA is acting now to ensure that patients in the United States are not put at risk by the phaseout.

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

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

17. Legal Arguments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

specifically that it does not apply to medical devices as defined in the Clean Air Act (42 U.S.C. 7671(8)).

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

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

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

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

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

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

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

FDA did express concern about the differences between MDI's in the OTC proposed rule. FDA noted that the differences meant that all new MDI's should be approved by FDA under

an NDA supported by clinical trials designed to examine the effect of MDI differences. In recognition of the complexities of this dosage form, FDA is requiring each non-CFC MDI to be reviewed as a new NDA, rather than as a supplement to an existing CFC–MDI NDA. In addition, FDA has been encouraging sponsors to include in these clinical trials comparators representing the currently available CFC-based products. FDA believes its action regarding the development of the non-ODS products is consistent with its concerns expressed in the OTC proposal of March 9, 1995.

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

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

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

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

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