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

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

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

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

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

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

11. Four comments stated that two different active moieties within a therapeutic class were not sufficient, but did not explain why or offer an alternative number. One comment stated that the therapeutic class approach would not permit sufficient alternatives to serve all patient subgroups because it would reduce the number of products available once three non-CFC products were

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

After careful consideration of the public comments, FDA has decided not to propose to use the therapeutic class approach. Rather, FDA is proposing to use a moiety-by-moiety approach. This means that FDA would not propose eliminating the essential use for an active moiety unless patients had access to the same active moiety in at least one non-ODS product. FDA is proposing to require at least two different non-ODS products for an active moiety if an active moiety is marketed under multiple NDA's or exists in multiple strengths.

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

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

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

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

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

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

15. One comment stated that anti-inflammatories, also called corticosteroids, are the mainstay of asthma control, and therefore FDA should not phase out CFC corticosteroids until there are sufficient non-CFC corticosteroids.

As explained previously, FDA is not proposing to eliminate the essential-use designation for any individual active moiety until at least one non-CFC alternative exists that contains the same

active moiety or, after January 1, 2005, until adequate alternatives exist, as described in proposed § 2.125(g).

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

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

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

FDA agrees that interactions between spacers and non-ODS–MDI's and CFC–MDI's may differ, given the different pharmaceutical properties of these products. However, spacers and holding chambers are usually approved for general use rather than for use with specific products.

A patient decides with his or her health care practitioner whether to use such a device with an MDI, regardless of whether the MDI is a CFC–MDI or a non-CFC alternative.

2. Specific Comments on the Proposed Criteria for Phaseout

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

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

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

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

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

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

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

FDA agrees generally that non-CFC products with the same active moiety should be approved for the same indications as their CFC counterparts prior to being considered as alternatives. For example, if a CFC–MDI is approved for use in the pediatric population down to age 6 but non-

ODS products are only labeled down to age 12, a significant patient subpopulation would exist that would not be adequately served by non-ODS products. Absent other data, the agency would not eliminate the essential-use designation for the CFC–MDI based on this factor alone.

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

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

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

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

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

FDA will continue to require NDA's to comply with all applicable new drug laws and regulations (see, e.g., section 505 of the act (21 U.S.C. 355)). As with all new drug products, FDA is requiring clinical data from adequate and well-controlled trials to establish the safety and effectiveness of non-CFC products prior to approval. FDA is also requiring at least 1 year of postmarketing data on the use of alternatives by the general population before it will propose removing the essential-use designation for any CFC–MDI.

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

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

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

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

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

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

3. Intolerance or Allergy to Drug Products or Propellants

28. Eleven comments pointed out that many asthmatics are allergic to propellants and inactive ingredients such as alcohol, sulfate, oleic acid, trisorbitan oleate, lecithin, and lactose. Two comments stated specifically that albuterol alone was not a sufficient alternative because of patient

intolerance. One comment requested that, with a doctor's written authorization, patients be permitted to continue to use CFC–MDI's until a non-CFC alternative to which they were not allergic was available. One comment noted that some patients develop a potentially fatal addiction to the aerosol component of MDI's and requested that FDA require manufacturers to put warnings on CFC–MDI labels and develop nonaerosol alternatives.

FDA acknowledges that intolerance and sometimes true allergies or addiction to drug products or components are a concern for patients any time new medications are used, regardless of whether the medication is CFC-based. To address this concern, FDA is requiring at least 1 year of postmarketing data to ensure that subpopulations are served by the available alternatives without widespread intolerance or allergy. If subpopulations of patients cannot use a product because of intolerance or allergic reactions and no other medically suitable options exist for those patients, that product would not be considered an acceptable alternative to the CFC–MDI counterpart.

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

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

4. Patient Subpopulations

a. *Children*

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

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

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

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

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

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

33. One comment noted that, in the past, new products have generally been marketed without a pediatric indication and asked how FDA would address this issue.

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

b. *Elderly*

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

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

c. *Other subpopulations*

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

FDA is aware of epidemiological data that show minorities and inner-city residents disproportionately experience asthma morbidity and mortality compared to the general population. FDA intends to take into account the needs of the entire asthma population. FDA plans to take into account the medical needs of demographic subgroups, including racial and ethnic groups, economic groups, or other socioeconomic or medical groups.

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

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

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

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

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

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

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

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

5. Experimental Nature of Alternative MDI's

40. One comment stated that the person had seen an alternative MDI manufactured by Glaxo Pharmaceuticals in limited use and that the alternative did not receive a favorable response from most of the patients who tried it. Another comment stated that the person had participated in Glaxo

Wellcome studies on the non-CFC Ventolin and found that the delivery method was not as effective. One comment stated that the person had participated in a University of Arizona study to test a new drug and had to drop out before the 12-week study was over because he did not do as well with the new drug. One comment stated that five new studies on potential asthma medications were being conducted at the University of Nebraska Medical Center and that the studies should be have been completed in late 1997.

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

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

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

42. One comment stated that the long-term effect of using other medications with CFC replacements is unknown and that replacements may be endocrine disruptors or have other adverse effects.

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

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

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

6. Choice of Technically Feasible Alternatives

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

≤60 l/minute, which may not be possible for all patients. One comment said that DPI's should not be considered a substitute because not all drugs are available as powders. One comment said that DPI's cannot be used with spacers to reduce systemic side effects and oral candidiasis and dysphonia. One comment said that Swedish experience shows that DPI's can be used by 80 to 90 percent of asthma patients. One comment said that DPI's are better than CFC–MDI's and their use should be expedited.

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

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

FDA cannot predict which products will be acceptable alternatives to CFC–MDI's. FDA anticipates that non-CFC MDI's will be the primary replacements for CFC–MDI's. However, advances in technology may mean that manufacturers develop new alternatives that are even better

than CFC–MDI's. In addition, non-MDI products can serve at least a portion of the patient population, even if they cannot serve the entire population. Accordingly, FDA is not limiting the rule to require that all CFC–MDI's be replaced by non-CFC MDI's. FDA will consider such products as part of an overall determination regarding whether the patient population is adequately served by available alternatives.

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

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

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

7. Proventil HFA

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

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

8. Postmarketing Data and Suggested Duration

48. Many comments suggested varying lengths of time to collect postmarketing data. One comment suggested that CFC–MDI's should be banned immediately. One comment stated that patient acceptance should be judged in a shorter time than 1 year. One comment suggested collecting data during the first 6 to 12 months of marketing. One comment suggested 12 months for phaseout of individual products and 6 months for phaseout of classes. One comment said that FDA should require at least 1 year of postmarketing data on alternatives before removing any comparable inhalers. One comment said FDA should wait to ban any CFC–MDI's until 1 year after all the replacements are in place. Two comments said that a postmarketing evaluation cannot be completed in less than 1 year. One comment said that inhalers should be phased out within 18 months of availability of an alternative. Two comments said FDA should require 2 to 3 years of postmarketing data. One comment recommended at least 5 years notice before banning CFC–MDI's. One comment requested that the phaseout not be completed until 2005. Three comments said FDA should allow a 10- to 15-year phaseout period. Two comments said that 1 year of postmarketing data is insufficient because most asthmatics must try a number of medications and different seasons affect the efficacy of medications. Four comments said that 1 year of postmarketing data is insufficient because it will not reveal the side effects of long-term usage.

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

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

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

50. One comment said that MDI's should not be phased out until manufacturers produce a full range of MDI products with highly effective delivery, at practical prices, and a sound degree of availability. One comment requested that phaseout not occur until patients have sufficient experience with alternatives. One comment said that phaseout should not occur until replacements: (1) Are as effective as the present products, (2) are tested by FDA, and (3) cost the same as the products they replace.

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

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

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

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

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

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

Patients and their health care providers can now and will continue to be able to choose any product available on the market. However, the Clean Air Act will not allow CFC products to remain on the market if the products are not essential. FDA is required by U.S. law and regulations to determine, in conjunction with EPA, whether a medical product remains an essential use of CFC's. FDA wants to ensure through development of a planned transition strategy that the transition occurs in a manner that protects the safety of patients.

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

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

55. One comment said that postmarketing data should address not only market penetration but also physician education; patient education; patient acceptance, particularly in the

subpopulations of children and the elderly; and patient compliance. One comment said that FDA should contact patients through their doctors and have them complete a survey to determine what kind of asthmatic they are, what substitute medications have already been tried, and the result. Another comment suggested that FDA survey a representative sample of all allergists, including private practitioners, rather than relying on drug companies or selected clinics in assessing the adequacy of replacements. Another comment said that FDA should let pharmacists, not MDI manufacturers, determine the adequacy of supplies, effectiveness, and other criteria through customer surveys. One comment said that new products should contain an insert that makes comment possible or that consists of a brief ''satisfaction survey'' to be filled out. Another comment said that FDA should require objective postmarketing studies that include a sample of at least 20 percent of diagnosed asthmatics. One comment said that any postmarketing study should be limited to showing that adverse events related to a new CFC-free formulation, but not found in the CFC product's labeling: (1) Occur at very low rates; (2) do not develop in patient populations not generally included in premarketing trials; or (3) expose drug-drug or drug-disease interactions not seen in the pivotal clinical trials, as determined by the equivalent of 100,000 patient years of exposure or a more formal postmarketing surveillance study, at the manufacturer's discretion.

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

dimensions; mechanical performance of inhalation device; and confidence that the new product is a dependable replacement. One comment simply said that FDA should disclose the types of studies that it believes are necessary to demonstrate product comparability for phaseout purposes.

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

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

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

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

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

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

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

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

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

9. Timing of Phaseout

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

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

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

FDA is proposing this rule to fulfill its obligation under the Clean Air Act to make essential-use determinations that will lead to the eventual phaseout of CFC–MDI's. Once FDA has determined that a product is essential, a consumer can use the product for the essential use as needed and prescribed.

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

The Parties to the Montreal Protocol, through the Technical and Economic Assessment Panels, have asked that all Parties develop transition strategies. Parties were required to present a draft