January 29, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Pursuant to 21 CFR § 10.30, this petition is submitted by the undersigned organizations, representing patients with asthma, chronic obstructive pulmonary disease ("COPD") and other respiratory diseases, physicians specializing in the treatment of these diseases, respiratory therapists, and other healthcare professionals specializing in respiratory care. This petition requests the Commissioner of Food and Drugs to initiate rulemaking by July 28, 2003 to remove metered-dose inhalers ("MDIs") containing the active moiety albuterol from the list of essential uses of ozone-depleting substances ("ODS") set forth in the Food and Drug Administration's ("FDA") regulation at 21 CFR § 2.125(e)(2). The FDA regulation provides that:

> Any person may file a petition under [21 CFR part 10] to request that FDA initiate rulemaking to amend paragraph (e) of this section to remove an essential use. FDA may initiate notice-and-comment rulemaking to remove an essential use...in response to a petition, if granted.[1]

21 CFR § 10.30 establishes the procedures and format for citizen petitions to FDA. This provision also specifies that FDA must respond to a petition within 180 days and, if the response is affirmative, must "concurrently take appropriate action (e.g., publication of a Federal Register notice) implementing the approval."[2]

A. ACTION REQUESTED

For the reasons discussed in section B, this petition requests the Commissioner to issue a proposed rule by July 28, 2003 to amend 21 CFR § 2.125(e)(2) to read as follows:

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

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1 21 CFR 2.125(g). See also Use of Ozone Depleting Substances: Essential Use Determinations. 67 Fed. Reg. 48370, 48384-5 (July 24, 2002) (final rule) (hereinafter "Essentiality Regulation").

2 See 21 CFR § 10.30(e)(2).

(i) [Removed and Reserved]
(ii) Bitolterol.
(iii) Metaproterenol.
(iv) Pirbuterol.
(v) Epinephrine.

B. STATEMENT OF GROUNDS

As discussed below in subsection 1, removing albuterol MDIs containing chlorofluorocarbons ("CFCs") from FDA's list of essential uses of ODS will benefit patients with asthma or COPD. Moreover, as discussed in subsection 2, sufficient information exists concerning the criteria established by the Essentiality Regulation with respect to CFC-free albuterol MDIs for FDA to initiate rulemaking to de-list albuterol as set forth above.

1. Deeming CFC Albuterol MDIs Non-Essential Benefits Patients

Phasing out CFC albuterol MDIs serves the best interests of asthma and COPD patients in several ways: increased health benefits from reduced depletion of the ozone layer, increased certainty that their asthma and COPD medications will be available in the future, and improved management of their diseases.

a. Health Benefits

First, patients will benefit from reduced depletion of the ozone layer. The destructive impact of CFCs on the stratospheric ozone layer and resulting increase in ultraviolet radiation are well established scientifically.[3] The Environmental Protection Agency ("EPA") has confirmed that increased exposure to ultraviolet rays (UV-B) due to ozone depletion increases the risk of severe human health effects – including malignant melanoma, which often is fatal.[4] Other human health effects include nonmelanoma skin cancer, actinic keratoses, immune suppression, cataracts, and premature aging of the skin.[5] Asthma and COPD patients – like all inhabitants of the planet – will benefit from

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[3] See Protection of Stratospheric Ozone: Phaseout of Chlorobromomethane Production and Consumption, 67 Fed. Reg. 65916, 65917 (Oct. 29, 2002) (not. prop. rule) (hereinafter "CBM Proposed Rule"); Protection of Stratospheric Ozone, 58 Fed. Reg. 4768, 4769 (Jan. 15, 1993) (final rule); see also Environmental Protection Agency, "Science of Ozone Depletion", *available at* <http://www.epa.gov/ozone/science/index.html>, *visited on* December 19, 2002 (incorporating numerous links to information regarding CFCs and other ODS and ozone depletion).

[4] *Health Effects of Overexposure to the Sun*, U.S. Environmental Protection Agency, *available at* <http://www.epa.gov/sunwise/uvandhealth.html>, *visited on* Dec. 18, 2002.

[5] Id.

the additional protection of the ozone layer that will result from phasing out CFC albuterol MDIs.

Depletion of stratospheric ozone also contributes to increased formation of damaging ground-level ozone in polluted areas,[6] which – as the key ingredient of smog[7] – particularly impacts asthma and COPD patients. FDA itself has stated that the continued use of CFCs in medical products like MDIs poses an unreasonable risk of long-term biological and climactic impacts.[8] Albuterol MDIs account for approximately half of the CFCs used in the United States.[9] Therefore, asthma and COPD patients will benefit directly from the reduction of CFC emissions from CFC albuterol MDIs.

In addition to this direct benefit to patients, there is also likely an indirect effect of U.S. action in this regard – improved worldwide ozone layer protection. The Montreal Protocol's Technology and Economic Assessment Panel ("TEAP"), an independent panel of experts, has concluded that "[U.S.] de-listing [of CFC albuterol MDIs] will have a very significant impact on the use of CFCs."[10] This is true not only because of the direct reduction of U.S. CFC emissions, but also because a determination by the United States that albuterol is non-essential would send an unambiguously positive signal to the international community that the U.S. still takes protection of the ozone layer seriously. With both developed and developing countries looking to the U.S. for leadership, the impact of strong U.S. resolve to eliminate all remaining uses of ODS should not be underestimated. Asthma and COPD patients in the U.S. also will benefit from this secondary effect from an FDA determination that CFC albuterol MDIs are non-essential.

b. Increased Certainty About Medication Supply

Patients also will benefit from the increased certainty that will result from FDA's initiation of the non-essentiality determination process for CFC albuterol MDIs. Currently, there is considerable uncertainty as to how many CFC producers will

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6 See United Nations Environment Programme, Environmental Effects of Ozone Depletion, 1998 Assessment at 137 (Nov. 1998). See also CBM Proposed Rule, 67 Fed. Reg. 65917; Protection of Stratospheric Ozone, 58 Fed. Reg. at 4769.

7 See Environmental Protection Agency, Office of Air Quality Planning and Standards, "How Ground-Level Ozone Affects the Way We Live and Breathe" (Nov. 2000), *available at* <http://www.epa.gov/air/urbanair/ozone/index.html>, *visited on* December 18, 2002.

8 Essentiality Regulation, 67 Fed. Reg. at 48380.

9 See United Nations Environment Programme, Report of the Technology and Economic Assessment Panel at 45 (April 2002) (hereinafter "2002 TEAP Report").

10 Id.

continue to supply pharmaceutical-grade CFCs, due to declining demand[11] and/or government mandates.[12] Indeed, the Protocol Parties in Decision XIII/10 stated their concern that "the end of . . . production [of CFCs] could come unexpectedly."[13] Given this uncertainty about continued supply of CFCs for MDIs, it is not in the interests of patients who need MDIs to continue to rely on the CFC versions of those products and then, possibly, to be made to switch with little advance warning because the CFC version is no longer available.

A transparent, planned, orderly transition with a clearly defined timeframe – which FDA's non-essentiality rulemaking would provide – is the best means of moving patients from CFC MDIs to the non-CFC alternatives that are available. The Essentiality Regulation establishes an orderly process for promulgating a regulation to remove essential uses from the regulations via notice-and-comment rulemaking. The alternative is that MDI production, in response to the reduction or cut-off in CFC supply, would be decided based solely on commercial factors – possibly leaving physicians and patients with insufficient information or preparation time to smoothly transition to non-CFC MDIs.

c. Improved Disease Management

A third important benefit to asthma and COPD patients from FDA's initiation of an albuterol non-essentiality rulemaking will be that patients would be encouraged to visit their physicians to review their treatment regimens. In testimony to FDA's Pulmonary and Allergy Drugs Advisory Committee ("PADAC") in 1999, the American Lung Association's past president noted that "[t]he transition to CFC-free [MDIs] provides a unique opportunity for the entire pulmonary-allergy community to refocus attention on the proper diagnosis and management of asthma [and COPD] and to revitalize the relationship between physicians and other health care providers and patients . . . ."[14]

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[11] See *e.g.*, id. at 124-125 (discussing the Montreal Protocol-mandated 50% reduction from baseline levels in CFC consumption for basic domestic needs in developing countries in 2005, stating that the resulting competition between uses for CFC supplies "may compromise supply of CFCs for MDIs"); United Nations Environment Programme, Report of the Technology and Economic Assessment Panel at 28 (April 2001) (stating that "CFC producers are evaluating the economic viability of their individual production facilities, and some may close as CFC requirements continue to decline").

[12] For example, the government of The Netherlands ordered production of CFC-11 and CFC-12 cease on or before December 31, 2005 at Honeywell's facility in Weert – a critical supplier of CFC-11 and CFC-12 for MDI manufacture. See 2002 TEAP Report at 56.

[13] United Nations Environment Programme, Report of the Thirteenth Meeting of the Parties to the Montreal Protocol, UNEP/OzL.Pro.13/10, at 39 (Decision XII/10) (Oct. 26, 2001).

[14] Statement of Dr. Alfred Munzer, Meeting of the Pulmonary and Allergy Drugs Advisory Committee to Discuss FDA Proposed Rule on Essential Use Determinations, (Nov. 22, 1999) at 105 (hereinafter "1999 PADAC Meeting Transcript"); see also Statement of Mary E. Worstell, MPH,

This revitalized relationship will allow doctors to assess their patients' health and adjust their treatment as necessary for the patients' well-being. For example, physicians on PADAC have expressed to FDA their concern that some patients may be relying too heavily on albuterol "rescue" inhalers and might benefit from regular maintenance products.[15] By encouraging patients to discuss their treatment plans with their doctors, a non-essentiality determination for albuterol has the potential to improve the well-being of asthma and COPD patients.

2. Sufficient Information Exists Regarding the Criteria Established by the Essentiality Regulation With Respect to CFC-Free Albuterol MDIs for FDA to Issue a Notice of Proposed Rulemaking

Albuterol is an individual active moiety marketed as an ODS product represented by multiple new drug applications ("NDAs"). Current CFC albuterol MDIs on the market include Ventolin® and Proventil®, which are marketed under different NDAs.[16] Each contains CFC 11 and 12, which are ODS under the Clean Air Act ("CAA").[17] Pursuant to the Essentiality Regulation, a petitioner seeking the removal of an essential use relating to an individual active moiety marketed as an ODS product and represented by two or more NDAs must submit "compelling evidence" that:

(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) [regarding adequate supplies and production capacity], (g)(3)(iii) [regarding postmarketing data] and (g)(3)(iv) [regarding adequate service of patients] of this section are met.[18]

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id. at 111-112; Comments on Behalf of the Stakeholders Group on Metered-Dose Inhalers, Doc. No. C9612 at 1, FDA Docket No. 97N-0023 (Nov. 30, 1999) (hereinafter "Stakeholders' NPR Comments").

15 See *e.g.*, Statements of Drs. Sessler, Fink, and Kelly, 1999 PADAC Meeting Transcript at 205, 219.

16 See NDA #18-473 and NDA #17-559, respectively.

17 See 42 U.S.C. § 7671a(a). See also 40 CFR Part 82, Subpart A, Appendix A.

18 21 CFR § 2.125(g)(4); Essentiality Regulation 67 Fed. Reg. at 48385.

As demonstrated below, many of the foregoing requirements for removal of the use of ODS in albuterol MDIs from the essential-use listing in 21 CFR § 2.125(e) already have been met. With respect to the remaining requirements, sufficient information now exists for FDA to initiate rulemaking on albuterol non-essentiality.

a. Same Active Moiety

To remove an ODS essential use for an active moiety represented by two or more NDAs, the Essentiality Regulation requires that at least two non-ODS products containing the same active moiety are being marketed.[19] There are currently two non-ODS products containing the active moiety albuterol marketed in the United States: Ventolin® HFA and Proventil® HFA.[20] Therefore, the Essentiality Regulation's first criterion has been met.

b. Same Route of Delivery

The Essentiality Regulation next requires that the non-ODS products have the same route of delivery as the applicable ODS products.[21] With regard to MDIs, FDA has stated that this means the non-ODS products "would have to be . . . inhalation drug product[s]."[22] Both Ventolin® HFA and Proventil® HFA are MDIs, which use the inhaled route of delivery,[23] the same as CFC albuterol MDIs.[24] Thus, the Essentiality Regulation's second criterion has been met.

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19 21 CFR § 2.125(g)(4)(i); Essentiality Regulation, 67 Fed. Reg. at 48385.

20 Ventolin® HFA was launched on the market in February of 2002 and Proventil® HFA was first marketed in late 1996.

21 21 CFR § 2.125(g)(4)(i); Essentiality Regulation, 67 Fed. Reg. at 48385.

22 Statement of Dr. Babatunde Otulana, FDA Medical Officer, Pulmonary Division, Meeting of the Pulmonary-Allergy Drugs Advisory Committee to Discuss FDA ANPR on Essential Use Determinations (April 11, 1997) at 56 (commenting on the analogous provision in the Advance Notice of Proposed Rulemaking, a precursor to the Essentiality Regulation. See Chlorofluorocarbon Propellants in Self Pressurized Containers; Determinations that Uses Are No Longer Essential, 62 Fed. Reg. 10242 (March 6, 1997) (adv. not. prop. rule)).

23 See FDA "Electronic Orange Book" entries for Ventolin HFA® and Proventil HFA®, *available at* <http://www.fda.gov/cder/ob/default.htm>, *visited on* Jan. 21, 2003 (application numbers 020983 and 020503, respectively) (showing "Inhalation" as the route of delivery).

24 See FDA "Electronic Orange Book" entries for Ventolin® and Proventil®, *available at* <http://www.fda.gov/cder/ob/default.htm>, *visited on* Jan. 21, 2003 (application numbers 018473 and 017559, respectively) (also showing "Inhalation" as the route of delivery).

c. Same Indication

Under the Essentiality Regulation, the non-ODS products must also be for the same indication as the ODS product for which a non-essentiality determination is requested.[25] FDA has stated:

> In evaluating indications, FDA will require a non-ODS alternative to have a broader indication or an indication or indications identical to that of the ODS product containing the active moiety to be removed from the list of essential uses, except for minor wording changes that do not materially change the meaning of the indication. For example, the non-ODS product could be indicated for treatment of asthma and chronic obstructive pulmonary disease (COPD) whereas the ODS product might only be indicated for asthma.[26]

CFC albuterol MDIs are approved for the prevention and relief of bronchospasm in patients with reversible obstructive airway disease and exercise-induced bronchospasm, and are indicated for pediatric use.[27] Ventolin® HFA and Proventil® HFA are both approved for these indications as well.[28] Therefore, the Essentiality Regulation's third criterion has been met.

d. Approximately Same Level of Convenience

Pursuant to the Essentiality Regulation, the non-ODS alternatives must have approximately the same level of convenience of use as the ODS products.[29] FDA has stated that in determining whether this criterion has been met, FDA will examine whether the product "has approximately the same or better portability;" "requires approximately the same amount of or less preparation before use;" and "does not require significantly greater physical effort or dexterity" compared to the ODS product(s).[30] FDA previously has stated that it "considers non-ODS MDIs . . . to have approximately the same level of convenience of use as [ODS] MDIs."[31]

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25 21 CFR § 2.125(g)(4)(i); Essentiality Regulation, 67 Fed. Reg. at 48385.

26 Essentiality Regulation, 67 Fed. Reg. at 48374.

27 See Thompson PDR, Physicians' Desk Reference, (57th ed. 2003), pp. 16745, 3064 (hereinafter "PDR") (showing indications and usage information for Proventil® and Ventolin®).

28 Id. at 1677, 3069 (showing indications and usage information for Proventil® HFA and Ventolin® HFA).

29 21 CFR § 2.125(g)(4)(i); Essentiality Regulation, 67 Fed. Reg. at 48385.

30 Essentiality Regulation, 67 Fed. Reg. at 48377.

31 See Use of Ozone-Depleting Substances; Essential Use Determinations, 64 Fed. Reg. 47719, 47722 (Sept. 1, 1999) (prop. rule).

Ventolin® HFA and Proventil® HFA, like their CFC-based counterparts, are MDIs. These non-CFC versions have the same portability[32] and require the same preparation as the CFC MDIs, with no more effort or dexterity needed for use. Hence, the Essentiality Regulation's fourth criterion has been met.

e. Adequate Supplies and Production Capacity

The Essentiality Regulation requires evidence that "[s]upplies and production capacity for the non-ODS product(s) exist or will exist at levels sufficient to meet patient need."[33] FDA has stated that in determining whether adequate supplies and production capacity exist it will "consider whether a manufacturer of a non-ODS alternative is able to manufacture the non-ODS alternative in sufficient quantities to satisfy patient demand once the ODS product containing the same active moiety is no longer marketed."[34] Further, FDA has stated that it "generally will expect the non-ODS product to be manufactured at multiple manufacturing sites if the ODS product was manufactured at multiple manufacturing sites."[35]

Specific information on production capacity is proprietary and therefore not publicly available. Generally though, the Petitioners are aware that multiple manufacturing sites exist because both GlaxoSmithKline (producer of Ventolin® HFA) and 3M Pharmaceuticals (producer of Proventil® HFA) have established manufacturing sites for their respective products. We believe that this information, as well as other information that FDA can obtain pursuant to the notice-and-comment process for an albuterol non-essentiality determination, will establish that the supply and production capacity for non-CFC albuterol MDI products either now exists, or will exist, at levels sufficient to meet patient need, by the time a final ruling of non-essentiality becomes effective.

f. Adequate Postmarketing Use Data

The Essentiality Regulation requires evidence that "[a]dequate U.S. postmarketing use data is available for the non-ODS product(s) . . . ."[36] FDA has stated that it "will look at a composite of all available information" and "will consider foreign data supportive of U.S. postmarketing use data if U.S. and foreign formulations, patient

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32 For example, the weight of the HFA MDIs approximate the weight of the CFC MDIs. See generally, PDR, pp.1674, 1676, 3063, and 3071.

33 21 CFR § 2.125(g)(3)(ii); Essentiality Regulation, 67 Fed. Reg. at 48385 (new).

34 Essentiality Regulation, 67 Fed. Reg. at 48374.

35 Id.

36 21 CFR § 2.125(g)(3)(iii); Essentiality Regulation, 67 Fed. Reg. at 48385.

populations, and clinical practices were the same or substantially similar."[37] If the foreign postmarketing data are found to be applicable to the U.S. market, "FDA may find that less than 1 year [of U.S. use data] is adequate . . . ."[38]

> Regarding the types of data required, FDA has stated that it
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> will encourage sponsors to seek data regarding patient subpopulations not fully represented in premarketing clinical trials. FDA will also evaluate data on acceptance, device performance, tolerability, adverse events, and effectiveness by using postmarketing studies and postmarketing use and surveillance data, including but not limited to FDA's MedWatch data.[39]

Also,

> FDA does not anticipate that sponsors will need to conduct formal phase 4 studies in the postmarketing period to provide adequate postmarketing data. FDA does anticipate, however, that sponsors will need to collect some postmarketing data beyond standard postmarketing surveillance to determine the acceptability of an alternative.[40]

Ventolin® HFA has been on the market for 11 months,[41] and Proventil® HFA has been on the market since late 1996, *i.e.*, six years.[42] Therefore, FDA should either now have or be able to obtain adequate postmarketing data for both of the non-CFC albuterol MDIs currently marketed in the United States.

Moreover, several years of non-U.S. postmarketing data undoubtedly exist for HFA albuterol MDIs. Nearly five years ago, TEAP reported that 3M Pharmaceuticals was marketing its HFA albuterol[43] MDI in more than 40 countries and that Glaxo

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37 Essentiality Regulation, 67 Fed. Reg. at 48374.

38 Id. at 48378.

39 Id.

40 Id.

41 See *GlaxoSmithKline's Ventolin HFA, albuterol sulfate HFA inhalation aerosol, environmentally friendly reformulation of a widely used asthma medication, now available in U.S.*, Business Wire, February 20, 2002.

42 See *Schering-Plough in Agreement to Market 3M Pharmaceuticals' CFC-free Albuterol Inhaler*, PR Newswire, August 16, 1996.

43 Note that "albuterol" is also known as "salbutamol". See RxList Description for Albuterol Inhalation, *available at* <http://www.rxlist.com/cgi/generic/albut1.htm>, *visited on* December 11,

Wellcome (now GlaxoSmithKline) had filed registration applications for its HFA albuterol MDI in more than 20 countries.[44] Currently, the International Pharmaceutical Aerosol Consortium ("IPAC") lists 59 countries in which GlaxoSmithKline's product Ventolin® HFA is available.[45] Also, according to the 2002 TEAP Report, non-CFC albuterol MDIs have been introduced and commercialized "around the world."[46] Thus, long-term postmarketing data for HFA albuterol MDIs from numerous other countries unquestionably are available.

Taken together, the U.S. and foreign postmarketing data for HFA albuterol MDIs are more than adequate for FDA to confirm that these products are an acceptable substitute for currently marketed CFC albuterol MDIs. Therefore, the Essentiality Regulation's sixth criterion has been met.

g. Patients are Adequately Served

FDA's Essentiality Regulation requires evidence that "[p]atients who medically required the ODS product are adequately served by the non-ODS product(s) containing [the same] active moiety and other available products . . . ."[47] FDA has stated that it will consider "whether adequate safety, tolerability, effectiveness, and compliance data for the available alternatives exist for the indicated populations and other populations known to medically rely on the ODS product" in determining whether patients are adequately served by non-ODS products.[48]

As noted above, significant data exist with regard to HFA albuterol MDIs. The Petitioners believe that these data establish that HFA albuterol MDIs are safe, well-tolerated, effective, and that patient compliance in using these products is high for the indicated populations and other populations known to medically rely on the CFC product.

2002 (noting that the World Health Organization's recommended name for albuterol is salbutamol).

44 United Nations Environment Programme, Technology and Economic Assessment Panel Progress Report at 118-119 (April 1998).

45 International Pharmaceutical Aerosol Consortium, "World-Wide Availability of CFC-Free MDIs of IPAC Companies", *available at* <http://www.ipacmdi.com/documents/Worldwide_HFCMDIs.pdf>, *visited on* December 12, 2002. Because 3M Pharmaceuticals is not an IPAC member, similar data for Proventil® HFA are not included.

46 2002 TEAP Report at 120.

47 21 CFR § 2.125(g)(3)(iv); Essentiality Regulation, 67 Fed. Reg. at 48385.

48 Essentiality Regulation, 67 Fed. Reg. at 48374.

While FDA has indicated that cost is not likely to be a factor for active moieties other than albuterol, the Agency has stated that in the case of non-ODS albuterol products, it will consider cost as part of an assessment on whether patients are adequately served.[49] Specifically with regard to albuterol MDIs, FDA has stated:

> The agency recognizes that generic albuterol CFC-MDIs are currently marketed and that these products cost less than currently marketed albuterol sulfate MDI's which use hydrofluoroalkane (HFA) as a propellant. At the appropriate time, FDA will evaluate the essential-use status of albuterol under criteria established by this rule. In determining whether patients are adequately served by non-ODS products containing albuterol as the active moiety, FDA will consider the cost of potential alternatives, such as the albuterol sulfate HFA-MDIs. * * * FDA expects that the price for most non-ODS products will approximate the price for branded CFC products.[50]

Regarding the cost of the non-CFC versus the CFC-containing albuterol MDI, the Petitioners agree with the Agency that ensuring adequate patient access to treatment should be part of the consideration of whether to remove an essential use exemption. In this regard, the Petitioners supported the requirement found in the Essentiality Regulation requiring that multiple-source CFC-MDI products be replaced by at least two non-ODS alternative products.[51] As FDA indicated, it included the requirement for multiple sources in part in response to concerns raised about the cost of non-ODS alternatives.[52] By maintaining competition between MDI manufacturers, this requirement offers large institutional purchasers leverage when negotiating the price of CFC-free drugs, in the same way they are able to negotiate high volume discounts for all drugs where there is a competitive market.

As FDA has noted, it has a legal obligation to consider the benefits as well as the costs of any non-essentiality determination.[53] In the context of this specific criterion – whether patients are adequately served – a rulemaking is the proper place to consider the many aspects of this issue, including among other things, potential costs savings from reduced overall costs of asthma treatment, impact on key populations, and the health benefits resulting from less depletion of the ozone layer.

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49 Id. at 48377.

50 Id. at 48383.

51 Stakeholders' NPR Comments at 3; see Essentiality Regulation at 48380.

52 Essentiality Regulation at 48380.

53 Id at 48382.

In short, as FDA's Pulmonary Advisory Committee has concluded – "cost alone should not be a reason for retaining an essential use..."[54] During the proposed rule's notice and comment period, the Petitioners look forward to assisting the Agency as it conducts specific market analyses to determine and weigh the approximate magnitude of the range of costs and benefits on all relevant sectors.

C. ENVIRONMENTAL IMPACT

FDA has stated that, "in the future, when FDA undertakes rulemaking to add or remove an essential use, the agency will prepare an . . . EIS [environmental impact statement] if required by NEPA."[55] NEPA – *i.e.*, the National Environmental Policy Act – generally requires federal agencies to include environmental impact statements in any proposal for "major Federal actions significantly affecting the quality of the human environment."[56]

There are exceptions to this general rule, however. Specifically, 15 U.S.C. § 793 provides that "[n]o action taken under the Clean Air Act . . . shall be deemed a major Federal action significantly affecting the quality of the human environment within the meaning of the National Environmental Policy Act of 1969 . . . ."[57] The courts have consistently held that this provision exempts actions taken under the CAA from the EIS requirement of NEPA.[58] FDA has acknowledged that it is acting under the CAA in making essentiality determinations.[59] Therefore, FDA's essentiality determinations are expressly exempted from the EIS requirement of NEPA.

In any case, the net environmental impact that will result from the removal of the use of CFCs in albuterol MDIs from the essential-use listing in FDA's regulations will be positive. As FDA has stated in the preamble to the Essentiality Regulation:

> The United States evaluated the environmental effect of eliminating the use of all CFC's in an environmental impact statement (EIS) in the 1970s (see 43 FR 11301, March 17, 1978). As part of that

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54 Id at 48380 (citing 1999 PADAC Meeting Transcript at 226-35).

55 Id. at 48381 (emphasis added).

56 42 U.S.C. § 4332.

57 15 U.S.C. § 793(c)(1).

58 See, *e.g.*, American Trucking Associations, Inc. v. EPA, 175 F.3d 1027, 1041 (D.C. Cir. 1999), *rev'd in part on other grounds*, Whitman v. American Trucking Associations, 531 U.S. 457 (2001); Ethyl Corp. v. EPA, 541 F.2d 1, 53 (D.C. Cir. 1976), *cert. denied* Ethyl Corp. v. EPA, 426 U.S. 941, 96 S.Ct. 2663 (1976); South Terminal Corp. v. EPA, 504 F.2d 646 (1st Cir. 1974).

59 See Essentiality Regulation, 67 Fed. Reg. at 48370, 71, 81, 82.

> evaluation, FDA concluded that the continued use of CFCs in medical products posed an unreasonable risk of long-term biological and climatic impacts (see Docket No. 96N-0057). Congress later enacted provisions of the Clean Air Act that codified the decision to fully phase out the use of CFCs over time (see Title VI (enacted November 15, 1990)). [60]

Concerning the incremental impact of eliminating CFC emissions from MDIs, FDA has made it very clear that:

> [T]he environmental impact of individual uses of nonessential CFCs must not be evaluated independently, but rather must be evaluated in the context of the overall use of CFCs. Cumulative impacts can result from individually minor but collectively significant actions taking place over a period of time (40 CFR 1508.7). Significance cannot be avoided by breaking an action down into small components (40 CFR 1508.27(b)(7)). Although it may appear to some that CFC-MDI use is only a small part of total ODS use and therefore should be exempted, the elimination of CFC use in MDIs is only one of many steps that are part of the overall phaseout of CFC use. If each small step were provided an exemption, the cumulative effect would be to prevent environmental improvements.[61]

The action the Petitioners are requesting in this petition will eliminate the use of CFCs in one type of MDI, which happens to be the single largest use of all MDI active ingredients. As such, this action by FDA will, in FDA's words, constitute one of the "small step[s]" that will have a "collectively significant" positive impact on the environment by leading to the elimination of CFC emissions that are harmful to the ozone layer.

D. ECONOMIC IMPACT

Pursuant to 21 CFR § 10.30(b), information under this section is to be submitted only when requested by the Commissioner following review of the petition.

E. CERTIFICATION

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies,

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60 Id. at 48380.

61 Id.

and that it includes representative data and information known to the petitioners that are unfavorable to the petition.

F. CONCLUSION

For the foregoing reasons, the Petitioners request that this petition be granted, and that by July 21, 2003 FDA issue a notice of proposed rulemaking to remove albuterol MDIs from the list of essential uses in 21 CFR § 2.125(e)(2).

Respectfully Submitted,

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