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

Re: NAS 0; Not Product Specific
General Correspondence: Docket No. 03P-0029
Citizen Petition: Requesting FDA to Initiate Rulemaking to Remove CFC Albuterol MDIs from FDA's List of Essential Uses of Ozone-Depleting Substances

Dear Sir or Madam:

GlaxoSmithKline (GSK) hereby submits the enclosed comments on the January 29, 2003 Citizen Petition submitted by the US Stakeholders Group on MDI Transition. That Petition requested that FDA publish a notice of proposed rulemaking by July 28, 2003 to remove the active moiety albuterol from the agency's list of essential uses for ozone-depleting substances (ODS) at 21 CFR § 2.125(e)(2). GSK supports the action requested by the Petition.

GSK is one of the largest manufacturers of metered-dose inhalers (MDIs) for the treatment of asthma and chronic obstructive pulmonary disease (COPD). In response to the US commitment under the Montreal Protocol to phase out all ODS, GSK has made a significant investment, over more than a decade, to develop and seek approval for non-ODS MDIs, and to withdraw its ODS MDIs from the market. As a result, GSK leads the world in providing non-ODS MDIs. In the US, GSK is one of two companies that has an approved non-ODS albuterol MDI on the market. GSK has voluntarily ceased US production of its ODS albuterol MDI and will soon cease sale and distribution in the US market.

GSK agrees with the Petition that deeming albuterol non-essential would yield substantial health and environmental benefits. We also agree with the Petition's conclusion that sufficient information exists concerning the criteria specified by FDA at 21 CFR § 2.125 for FDA to initiate rulemaking to de-list albuterol. Our comments provide further information on the criteria involving company-specific information which, understandably, the Petition could not fully address. There is now sufficient information

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Comments on Citizen Petition
on Removing Albuterol MDI from FDA's List of Essential ODS Uses
(FDA Docket 03P-0029)
Submitted by GlaxoSmithKline

This paper provides information relevant to the January 29, 2003 Citizen Petition submitted by the US Stakeholders Group on MDI Transition, which requested FDA to initiate rulemaking on the non-essentiality of chlorofluorocarbon (CFC)-containing albuterol metered dose inhalers (MDIs). The Citizen Petition was submitted pursuant to FDA's regulation on essentiality determinations at 21 CFR § 2.125 ("ODS Regulation"), which was promulgated by a final rule issued by FDA in July 2002 that entered into force on January 20, 2003 ("Final Rule").[1] As discussed herein, GlaxoSmithKline (GSK) agrees with the Petition and believes that FDA should issue the proposed rule as requested by the Stakeholders by July 28, 2003.

1.0 INTRODUCTION

GSK has conducted a lengthy, resource-intensive, and technically difficult effort to reformulate its CFC-containing MDIs and bring to market new chemical entities in new delivery systems such as hydrofluoroalkane (HFA)-containing MDIs and/or dry powder inhalers (DPIs). To a great extent, this effort was undertaken in response to US laws and international agreements that call for the phase-out of ozone-depleting substances (ODS). FDA has put the pharmaceutical industry on clear notice that "the Montreal Protocol and the Clean Air Act mandate an eventual complete ban on the production of ODS" and that "the essential-use exemptions allowed under the Protocol are clearly not intended, or expected, to be permanent".[2]

In furtherance of this mandate, GSK has submitted new drug applications (NDAs) for several non-ODS products and FDA has approved NDAs for Serevent Diskus, Advair Diskus, and Ventolin HFA on September 19, 1997, August 20, 2001, and April 19, 2001 respectively. In addition, GSK is voluntarily withdrawing its CFC-containing MDIs for

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[1] Use of Ozone-Depleting Substances; Essential-Use Determinations, 67 Fed. Reg. 48370 (July 24, 2002) (final rule).

[2] *Regulatory Efforts to Phaseout Chlorofluorocarbon-Based Metered Dose Inhalers: Hearing Before the Subcomm. on Health and Environment of the House Committee on Commerce*, 105th Cong., pp. 50-51 (May 6, 1998) (prepared statement of John Jenkins, Director, Division of Pulmonary Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services); see also *Advance Notice of Proposed Rulemaking: Meeting of the Pulmonary and Allergy Drug Advisory Committee*, meeting transcript, p. 19 (April 11, 1997) (statement of John K. Jenkins, Director, Division of Pulmonary Drug Products, Food and Drug Administration) ("the Montreal Protocol and the Clean Air Act . . . mandate the phaseout of the use of CFCs in all products").

which it has a non-ODS alternative product on the market. Recent GSK actions in the US include the phase-out of Beconase Nasal Inhalation Aerosol and Serevent CFC MDI. In addition, GSK will cease sale and distribution of Ventolin CFC by September 2003. As a result, by the end of 2003, GSK will have transitioned more than 80% of its total respiratory portfolio to non-ODS products, with only Flovent MDI remaining in CFC form. These voluntary actions by GSK have resulted in a dramatic decline in essential use CFC volumes licensed to GSK for new production of CFCs: from 858.1 MT for 2001 to zero MT for 2005.

While GSK has transitioned its own products without the need for regulatory intervention by FDA, transition of the entire US albuterol market will not occur without regulatory action. As discussed below, the albuterol market is dominated by generic CFC MDIs, which generally are sold at a lower price than branded HFA albuterol MDIs. Because of this price differential, the albuterol market will not transition as a result of market forces alone. Two alternative HFA albuterol MDIs have now been on the market for more than one year, but still over 90% of albuterol MDIs sold or distributed in the US use CFCs.[3] CFC albuterol MDIs represent approximately 50% of the 1902 MT of the 2005 US request for essential use CFCs.[4] Although overall CFC volumes requested by the United States to the Montreal Protocol Parties have declined in recent years, this decline is due primarily to GSK's voluntary actions described above: over 70% of the US decline is due to GSK alone.[5] Without further regulatory action by the federal government, this decline in overall US CFC demand for use in MDIs is not likely to continue.

In other major markets around the world, actions by GSK local operating companies alone also have not been sufficient to transition an entire market. More often than not, market-wide transitions have succeeded only where the government has taken regulatory steps to deem particular active ingredients or therapeutic classes non-essential, and/or has set firm phase-out deadlines. Currently, the governments of twelve European countries as well as Canada, Australia and Japan have eliminated the use of CFCs in albuterol MDIs and taken other steps to advance the transition.

2.0 VENTOLIN TRANSITION

The development of alternatives to CFC MDIs has been underway at GSK since the late 1980s and continues today. As a result, GSK's albuterol MDI containing the non-ozone-depleting propellant HFA 134a has been launched in 67 countries around the world, including the United States ***(see Appendix I)***.

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[3] May 2003 TEAP Report at p.14.

[4] Id.

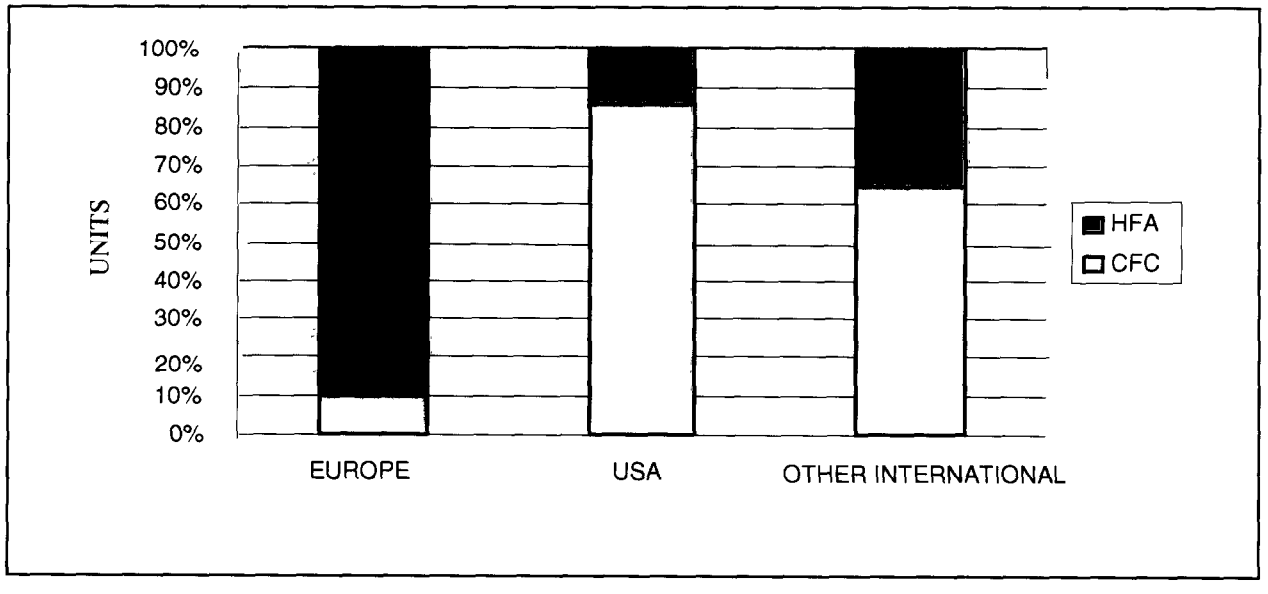
[5] April 1999 TEAP Report at p. 110; May 2003 TEAP Report at p. 14 (showing a decline of 1,199 MT in the US EUA nominations from 2001 to 2005); Protection of Stratospheric Ozone: Allocation of Essential Use Allowances for Calendar Year 2001, 66 Fed. Reg. 1462, 1466 (Jan. 8, 2001) (showing GSK's EUA in 2001 was 858.1 MT). GSK has requested no essential use volumes for 2005. 858.1 ÷ 1,199 = 71.6%.

2.1 Global Markets

Globally, GSK's transition to a CFC-free albuterol MDI is progressing well. To date, regulatory approvals have been obtained in 115 countries, and the product has been launched in 67 countries. Additional launches are planned. In 50 countries, the GSK local company's corresponding CFC product has been withdrawn after the company's CFC-free albuterol MDI was launched ***(see Appendix I)***. In a few cases, the phase-out of the CFC product has taken over a year (e.g., the UK), but in most countries phase-out of GSK's albuterol CFC product was accomplished within 3 to 6 months of launching the HFA product.

Now, almost 60% of GSK's global Ventolin MDI business (by volume) is in the form of the HFA MDI. This represents some 75 million canisters sold annually. The chart below indicates that GSK's transition to Ventolin HFA in Europe (including Eastern Europe) is now almost 90% complete and is over 30% complete in other GSK international markets. Note that this latter group includes some countries where the albuterol transition is virtually complete – e.g., Australia, Canada – as well as developing country markets in Latin America, the Middle East, etc., which are not required under the Montreal Protocol to phase out CFCs generally until 2010.

Global Albuterol HFA/CFC unit mix
GSK Markets
(Dec. 2002)



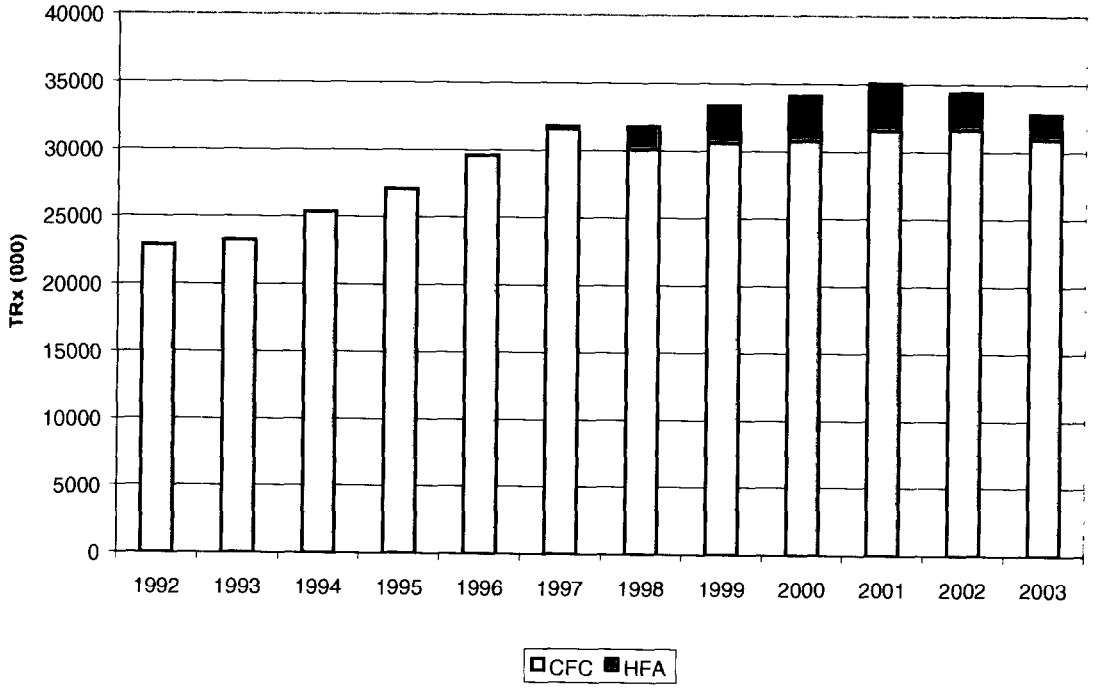
2.2 Current US Albuterol Market

The US albuterol aerosol market is currently valued at around $376M.[6] Over the past year, the number of albuterol aerosol market units sold has seen a decline of 5% after growing by as much as 3% in previous years.

This market is dominated by generic products, which make up 89% of all albuterol units sold. Of this 89%, Warrick Pharmaceuticals (generic subsidiary of Schering-Plough Corporation) provides the majority of generic albuterol MDIs, holding a 69% share in generic units sold over the past 12 months. The remaining 11% of the albuterol aerosol prescriptions are being filled with branded products, of which Proventil and Ventolin (both CFC and HFA) currently hold a 74% share.

Of all the albuterol MDIs sold in the US market, two products, Proventil HFA and Ventolin HFA, are CFC-free. The uptake of these two CFC-free products has been slow, however. Launched in 1996, Proventil HFA is the larger of the two brands, but currently holds only a 5% share of the total albuterol aerosol market. Ventolin HFA, launched in February 2002, accounts for less than 1% of the total albuterol MDI market. In addition, as the following chart shows, the total number of HFA albuterol inhalers sold has declined by 28% over the past year.[7]

Albutrol Inhaler Prescription Volume (CFC vs. HFA)



[6] MAT February 2003, IMS.

[7] Verispan, Source™ Prescription Audit ("SPA"), April 1992 – 2003.

The low market penetration of the HFA albuterol inhalers is due in large part to the cost structure of this market. The inhaled albuterol market will continue to be dominated by CFC MDIs unless regulatory action is taken to remove CFC-containing products from the marketplace. Market forces alone will not be enough to transition the albuterol market.

3.0 FDA REGULATION OF ODS-CONTAINING PRODUCTS

GSK US has introduced Ventolin HFA to the market and will deplete its inventory of Ventolin CFC in the second half of 2003. However, CFC MDIs will continue to dominate the US albuterol market until FDA deems CFC albuterol MDIs non-essential by removing albuterol from the agency's list of essential ODS uses codified in the ODS Regulation at 21 CFR §2.125(e)(2).

In the ODS Regulation, FDA establishes four categories for removing an ODS use from the essential list. Albuterol is in the category for "individual active moieties marketed as ODS products and represented by two or more NDAs".[8] For products in this category, at least two non-ODS products must be available with the same active moiety, with the same route of delivery, for the same indication(s), and with approximately the same level of convenience of use as the ODS products that they will replace. In addition, the non-ODS products must meet the following criteria: (1) adequate supplies and production capacity, (2) adequate US postmarketing data, and (3) patients who medically require the ODS products are adequately served by the non-ODS products containing the same active moiety and other available products.[9] Although some of these criteria are straightforward, others are subject to interpretation.

3.1 Same Active Moiety

To remove a use from the essential use listing, the ODS Regulation requires that, for active moieties represented by two or more NDAs, at least two non-ODS products are being marketed with the same active moiety.[10] GSK agrees with the Petition's discussion of this criterion and the Petition's conclusion that the first criterion set forth in the ODS Regulation has been met.

3.2 Same Route of Administration

The ODS Regulation also requires that the non-ODS alternatives have the same route of delivery as the ODS-containing products.[11] GSK agrees with the Petition's discussion on this criterion and concurs that it has been met.

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[8] 21 CFR § 2.125(g)(4).

[9] Id.

[10] 21 CFR § 2.125(g)(4)(i).

[11] Id.

3.3 Same Indications

The ODS Regulation requires that the non-ODS alternative products have the same indication as the ODS-containing products.[12] In the preamble to the Final Rule, FDA stated that "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."[13]

The indications and usage sections of the ODS-containing products, represented by the reference drugs Ventolin CFC and Proventil CFC, are provided in ***Table 1*** below. Indications and usage section wording for generic albuterol CFC inhalation aerosol products is not provided since the wording is (necessarily) very similar to the branded products.

Table 1

Product	Indications and Usage
Ventolin CFC	Ventolin inhalation aerosol is indicated for the prevention and relief of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.
Proventil CFC	Proventil inhalation aerosol is indicated in patients 12 years of age and older, for the prevention and relief of bronchospasm in patients with reversible obstructive airway disease, and for the prevention of exercise-induced bronchospasm.

The indications and usage sections of the two non-ODS alternative products, Ventolin HFA and Proventil HFA, are provided in ***Table 2*** below.

Table 2

Product	Indications and Usage
Ventolin HFA	Ventolin inhalation aerosol is indicated for the prevention and relief of bronchospasm in adults and children 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.
Proventil HFA	Proventil HFA inhalation aerosol is indicated in adults and children 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for prevention of exercise-induced bronchospasm.

As shown above, the non-ODS albuterol MDI products are approved for the same or broader indications and in the same age groups as the ODS-containing albuterol MDI products. Therefore, GSK agrees with the conclusion in the Petition that this criterion has been met.

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[12] Id.

[13] 67 Fed. Reg. at 48374.

3.4 Approximately the Same Level of Convenience of Use

The ODS Regulation further requires that the non-ODS alternatives have approximately the same level of convenience of use as the ODS-containing products.[14] GSK believes the discussion in the Petition regarding this criterion is accurate and therefore agrees with the Petition's conclusion that this criterion has been met.

3.5 Adequate Supplies and Production Capacity

The preamble to the Final Rule states that, in evaluating whether supplies and production capacity for the non-ODS product(s) exist or will exist to satisfy patient need, FDA will consider whether the manufacturer(s) of a non-ODS alternative is/are able to manufacture the non-ODS alternative(s) in sufficient quantities to satisfy patient demand once the ODS product(s) containing the same active moiety is/are no longer marketed.[15] GSK manufactured Ventolin CFCs for the US market solely at its production facility in Zebulon, North Carolina. Similarly, GSK manufactures Ventolin HFA for the US market solely at its Zebulon, North Carolina facility.

GSK has estimated a range of possible future production capacity requirements based on market size, approved HFA NDAs, and potential effective dates for removal of albuterol MDIs from the list of essential ODS uses. GSK has conducted a detailed review to identify how it would support Ventolin HFA in the US market from a demand perspective, including internal expansion of manufacturing (filling and packing) and external supply of cans, valves, propellant, actuators, and other third party supplies. Notwithstanding the significant commitment of energy and resources entailed, GSK is confident that additional internal and external capacity can be installed to ensure adequate supplies and production capacity for Ventolin HFA. An expansion of Ventolin HFA supply and production capacity, to a combined level consistent with the mid-range of our developed scenarios, could be completed within 12 - 18 months.

As indicated in the introduction, GSK has made a significant overall commitment to transitioning its MDIs to non-ODS formulations, consistent with the goals of the Montreal Protocol and the US law. However, in view of the advance planning issues and the significant financial commitment required to expand current production capacity, GSK will need some assurance of the timing and probability of the removal of albuterol MDIs from the list of essential ODS uses. After GSK has reviewed any comments submitted on a proposed rule on albuterol non-essentiality, the company would be willing to meet with FDA to review plans for expansion of its production and supply chain capacity. At that point, GSK would be in a position to commit the substantial resources needed to ensure that an adequate combination of Ventolin HFA supply and production capacity is in place by the time that a final rule removing albuterol MDIs from the list of ODS essential uses enters into effect. As coordination of manufacturing resource and

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[14] 21 CFR § 2.125(g)(4)(i).

[15] 67 Fed. Reg. at 48374.

timing of an effective date for albuterol non-essentiality necessarily go hand in hand, FDA may want to consider making the effective date of the final rule on albuterol non-essentiality contingent upon confirmation by the agency of adequate supply and production capacity of both GSK and 3M (the manufacturer of Proventil HFA).

FDA has further stated that it generally will expect the non-ODS product(s) to be manufactured at multiple manufacturing sites if the ODS product(s) was/were manufactured at multiple manufacturing sites.[16] However, in addressing comments about this criterion, FDA stated that "FDA did not propose and is not finalizing in this rule a requirement that replacement products be manufactured at multiple sites. The ODS Regulation requires only that supplies and production capacity for the non-ODS product(s) exist at levels sufficient to meet patient need. FDA notes, however, that multiple manufacturing sites increase the likelihood that a manufacturer will be able to supply the replacement drug in the event of an unforeseen circumstance that shuts down one site."[17]

In this regard, it should be noted that many medically essential products are manufactured at a single site throughout the pharmaceutical industry. Our current manufacturing site for Ventolin HFA, Zebulon, has experience in HFA MDI manufacture, US supply, new product introduction activities, and rapid scale-up, in addition to single sourcing critical products. However, in the unlikely event of a potential interruption of GSK's primary supply to the US market, GSK would be able to work with the Agency to make use of alternate, non-US GSK supply sites which manufacture HFA Ventolin for other markets. In this regard, it should be noted that GSK's European manufacturing facilities in Evreux, France, Aranda, Spain and Poznan, Poland supply the entire rest of world GSK supply of Ventolin HFA.

Finally, as the agency has acknowledged, there is no guarantee that supply of pharmaceutical-grade CFCs will be adequate in the future, nor is there any guarantee that other CFC MDI components will remain in supply. There remains only one supplier to the US of pharmaceutical grade CFC-11 and CFC-12. That supplier, in the Netherlands, is scheduled to shut down operations in 2005 or earlier. Although other CFC producers have expressed an interest in supplying the US market, there is no guarantee of continued CFC supply of acceptable quality. In addition, supply of other CFC MDI components – valves, canisters, etc. – is becoming increasingly uncertain. Therefore, rather than being driven to transition albuterol at the "Eleventh Hour" due to the lack of CFCs or CFC MDI components, FDA should ensure a safe and orderly transition with deliberate action sooner rather than later without interruption to supply.

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[16] Id.

[17] Id. at 48377.

3.6 Adequate Postmarketing Use Data

The ODS Regulation states that in order to support a non-essentiality determination, adequate US postmarketing use data must be available for non-ODS product(s).[18] FDA has also stated that, in evaluating the adequacy of US postmarketing data, it will look at a composite of all postmarketing information that is available. This information may include foreign data if US and foreign formulations, patient populations, and clinical practices are the same or substantially similar. FDA has concluded that if such foreign data are relevant to the US market it will consider them along with US data.[19]

3.6.1 Postmarketing Study of Ventolin HFA in the United Kingdom

GSK has conducted a large postmarketing study in the UK of adults and children with asthma that monitors the transition from a CFC-containing MDI (Ventolin MDI) to an HFA-MDI (Ventolin Evohaler).[20] ***(See Appendix 2)***

The Ventolin Evohaler in the UK is essentially equivalent to Ventolin HFA in the US. Due to variations in national regulatory requirements, however, there are some minor differences in the manufacturing, labeling or packaging of the product, as outlined below:

Comparison of Ventolin HFA & UK Evohaler

	UK Evohaler	**US Ventolin HFA**
Shelf-Life and Storage Conditions	24 months No in-use restrictions expiry Stored below 30 c Protect from frost Protect from direct sunlight	18 months 3 month in-use expiry Stored between 15 and 25 c
Packaging	No foil overwrap No desiccant	Foil overwrap Desiccant added

The primary objective of the postmarketing study was to determine if incidence densities of events measured after the introduction of Ventolin Evohaler in the UK were similar to those events prior to Evohaler introduction. A secondary objective of the study was to provide information on incidence densities of events among users of Ventolin Evohaler relative to users of Ventolin MDI within the same study period.

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[18] 21 CFR § 2.125(g)(4)(ii) and (3)(iii).

[19] 67 Fed. Reg. at 48374.

[20] Craig-McFeely PM, Wilton LV, Soriano JB, Maier WC, Shakir SAW, *Prospective observational cohort safety study to monitor the introduction of a non-CFC formulation of salbutamol with HFA 134a in England*, 41 Int. J. Clinical Pharm. and Therapeutics 67-76 (2003).

Patients who received regular repeat prescriptions for Ventolin MDI (at least two inhalers during 1998) were recruited by general practitioners in the UK. The study recruited 10,472 patients, of which 8973 completed the study. The study included both adults and children with asthma.

The results of this postmarketing surveillance study, after adjustment for confounding factors such as possible under-reporting of events, found no evidence of any difference in the incidence or types of events occurring after the introduction of Ventolin Evohaler to the UK market. The pattern of events and incidence densities occurring during the course of the study and any differences observed between Ventolin MDI and Ventolin Evohaler appeared to be related largely to the combined effects of residual confounding by severity, seasonality and improved reporting of events by physicians as the study progressed. No paradoxical bronchospasm was reported during the course of the study. No deaths or adverse pregnancy outcomes have been attributed to the use of either inhaler. There were no differences in event incidence densities in any comparison in the sub-group of children. Thus, the results of this study suggested that the Ventolin Evohaler was as well-tolerated as Ventolin MDI.

3.6.2 Ventolin HFA - Worldwide Spontaneous Reports

To date, Ventolin HFA has been approved in over 60 countries outside of the United States for the treatment of bronchospasm associated with asthma. Ventolin HFA was approved for this same indication in the US on April 19, 2001, and introduced to the US marketplace in February of 2002. As of January 2003, worldwide patient exposure to Ventolin HFA has been estimated to be 16 million patient years.

As of January 2003, approximately 1100 spontaneous reports have been received worldwide in association with the use of Ventolin HFA, of which 6% meet the adverse event reporting criteria for being "serious."

Six percent (6%) of the worldwide HFA reports are serious and 18% of the worldwide CFC reports are serious. The most frequently reported adverse events are consistent with the product labeling for Ventolin HFA and CFC.

3.6.3 Ventolin HFA - US Spontaneous Reports

Since US launch of Ventolin HFA in February 2002 through January 2003 there have been approximately 110,000 prescriptions written and eight spontaneous reports received. None of the reports contained serious adverse events. These reports have all been, or will be, submitted to FDA pursuant to 21 CFR § 314.80.

3.6.4 Proventil HFA - US Spontaneous Reports

GSK recognizes that FDA will need to evaluate postmarketing data for Proventil HFA when considering the essential-use status of albuterol. Proventil HFA was introduced to the US market in 1996 for the treatment of bronchospasm associated with asthma. GSK has completed a preliminary review of postmarketing surveillance data obtained from FDA's MedWatch/AERS database, which includes all serious and non-serious reports from US sources and regulatory-mandated foreign serious reports for Proventil HFA.

Disproportionality analysis (DuMouchel, *Proc. KDD, 2001*) of the FDA's Adverse Event Reporting System (AERS) public release database was performed for albuterol HFA, excluding Ventolin brand HFA.

A total of 207 reports, containing 543 events, were identified for albuterol HFA through 1Q02. Six events were identified as having an increased reporting ratio. These events are labeled, or similar to labeled events currently described in the approved Prescribing Information for both the CFC and HFA formulations of Proventil.

3.6.5 Postmarketing Data – Conclusion

In conclusion, postmarketing data on Ventolin HFA from markets outside the United States are substantial and suggest no difference in the safety profile of this non-ODS product relative to its ODS counterparts. A large postmarketing trial in 10,472 patients found no evidence of an important safety signal attributable to the HFA formulation after introduction of the Ventolin Evohaler (equivalent to Ventolin HFA in the US) in the UK. As of January 31, 2003, approximately 1100 spontaneous reports have been received worldwide in association with Ventolin HFA. The most frequently occurring adverse events associated with Ventolin HFA use are consistent with the product's labeling and that of its ODS counterparts. Although Ventolin HFA was successfully launched in the US in February of 2002, very few spontaneous reports of adverse events have been received to date.

GSK expects that adverse event reports associated with Ventolin HFA MDI in the United States will remain quite limited throughout the time FDA is considering the essential use-status of albuterol MDIs. Therefore GSK expects that FDA will need to rely on the postmarketing data obtained from worldwide markets for Ventolin HFA MDI, as well as accumulated experience with Proventil HFA MDI, to support a non-essentiality determination for albuterol.

A preliminary review of the FDA's AERS public release database was performed on Proventil HFA. The adverse events identified were consistent with those described in the product's labeling and that of CFC-containing counterparts. Taken together, the available postmarketing data on Ventolin HFA and Proventil HFA are supportive of a non-essentiality determination for albuterol.

3.7 Patients Adequately Served

3.7.1 Health and Safety Issues

The ODS Regulation states that patients who medically require the ODS product must be adequately served by the non-ODS product(s) containing the same active moiety and other available products.[21] The preamble to the Final Rule states that FDA will evaluate this criterion in part by determining whether adequate safety, tolerability, effectiveness and compliance data for the alternatives exist for the indicated populations known to medically rely on the ODS product(s).[22]

Ventolin HFA and Proventil HFA were both subject to FDA review and approval prior to market introduction in the US. The data contained in each product's new drug application (NDA) provide ample evidence of safety, tolerability and efficacy. The postmarketing data described above also provide ample evidence of the safety, tolerability and efficacy of these products in actual clinical practice.

The preamble to the Final Rule further states that FDA anticipates that ODS products containing the same active moiety marketed in different strengths will need to be represented by non-ODS products also containing the same active moiety with more than one strength in order to adequately serve patients.[23] The CFC-containing albuterol formulations are each available in single dosage strengths. Similarly, Ventolin HFA and Proventil HFA are each available in single dosage strengths. Therefore, patients will be adequately served by the available dosage strengths.

3.7.2 Cost and Accessibility Issues

The preamble to the Final Rule states that FDA will also consider whether a high-priced non-ODS product is effectively unavailable to a portion of the patient population if they cannot afford to buy the product.[24] GSK has conducted a preliminary assessment of the possible impact of albuterol non-essentiality on the various patient segments that comprise the current US albuterol MDI market. Our preliminary assessment, discussed in more detail below, is that some but not all patients may experience some increase in cost of treatment, at least in the short run, due to an FDA determination on albuterol non-essentiality. However, the competition likely to ensue between the HFA albuterol products subsequent to that determination would create downward price pressure. In addition, for particularly vulnerable patient populations, such as indigent, the elderly and children, there are numerous public and private programs to help to ensure that such patients will not be denied access to treatment.

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[21] 21 CFR § 2.125(g)(4)(ii) and (3)(iv).

[22] 67 Fed. Reg. at 48374.

[23] Id.

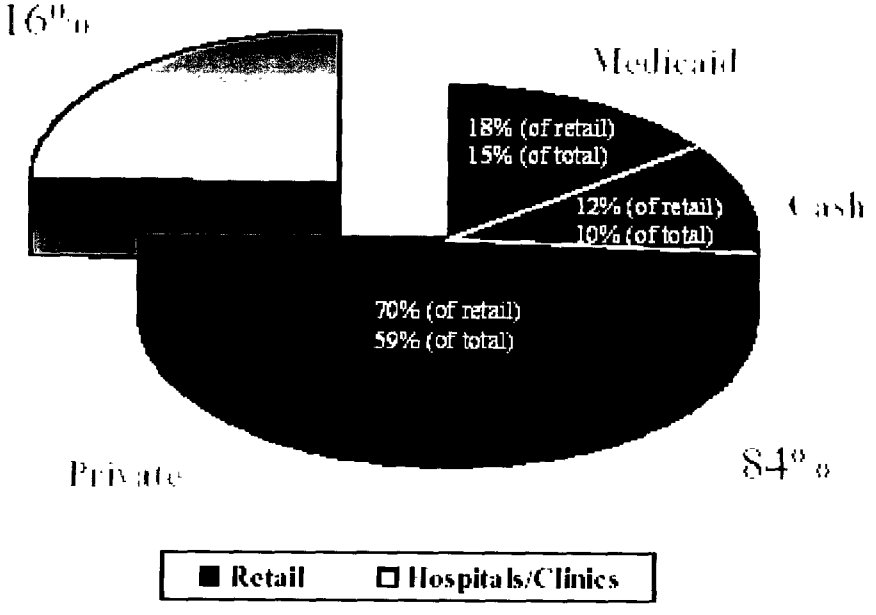
[24] Id.

3.7.2.1 Patient Access Routes for Albuterol

Patients' access to albuterol MDIs can take many routes. Currently 84% of albuterol MDI units are obtained through a retail setting (e.g., retail pharmacy or mail order). The remaining 16% of albuterol MDI units are obtained through either federal or non-federal hospitals or clinics.[25]

3.7.2.1.1 Retail Access Route

Patients obtaining albuterol MDIs through retail settings pay for their treatments in various ways: 12% of albuterol MDIs are cash-only purchases, 70% are covered by private payers, and 18% are covered by Government programs such as Medicaid.[26] Additionally, a number of privately funded programs exist to help the elderly or very poor obtain prescription medications at no cost or a reduced cost. The following chart illustrates the various patient access routes.



3.7.2.1.1.1 Retail Route – Cash Payers

FDA stated that it expects that CFC-free products will be offered at prices comparable to branded CFC products.[27] The published average wholesale price (AWP) of Ventolin HFA is $35.06, the same as the AWP for Ventolin CFC.[28] This compares to an AWP

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[25] Weighted average MAT 2001, 2002, Jan.-Feb. 2003, IMS.

[26] Verispan. SPA, May 2003.

[27] 67 Fed. Reg. at 48380.

[28] Drug Topics Red Book 2002.

range for generic CFC albuterol MDIs of $21.41-$29.85.[29] The actual wholesale price paid by retail outlets can vary considerably from these averages, due to, e.g., discounts applied through various channels.

The average retail price is $22.61 for generic CFC albuterol MDIs and $38.62 for branded HFA albuterol MDIs.[30] Thus, in theory, the approximately 10% of the total albuterol patient population (.84 x .12) that are cash payers would experience an average $16.00 price increase. However, that is an over-simplification, because some patients in this cash-only segment are already purchasing branded albuterol MDIs and thus would experience no increase in price. In addition, there are significant differences in retail price based on retail outlet and region of the country – even between the same generic or same branded product. Therefore, it is extremely difficult to predict with a high degree of certainty what the impact of FDA action on CFC albuterol will be on all-cash payers.

3.7.2.1.1.2 Retail Route – Private Payer Programs

The approximately 59% of the albuterol patient population (.84 x .70) who are covered by insurance or other private payer programs will experience a modest impact of a switch from a generic to a branded albuterol market. For such patients, out-of-pocket costs for prescriptions are generally limited to pre-determined co-payments. In 2003, a majority of patients will participate in a three-tiered copay system. The remainder will participate in a percentage copay system where the copay is based on a percentage of the price of the prescription. In a tiered system, the average copay for tier one is $10, tier two $22, and tier three $40 – for generic, preferred, and non-preferred products respectively.[31] After CFC albuterol is deemed non-essential, if private payer programs place Ventolin HFA and Proventil HFA in tier 2, the copay for patients in these programs could increase by approximately $12 (i.e., from $10 to $22). This estimated increase is based on the conservative assumption that insurance and other private payer programs do not modify their policies to accommodate patients. Note that any increase to patients in this segment would be independent of the prices paid by wholesalers for Proventil HFA and Ventolin HFA.

3.7.2.1.1.3 Retail Route – Government Programs to Ensure Patient Access

For the approximately 15% of the albuterol patient population (.84 x .18) that are neither cash payers nor covered by private payer programs, there are numerous governmental programs that provide prescription drug coverage with no or minimal out-of-pocket copays.

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[29] Id.

[30] Verispan, SPA, May 2003.

[31] Health Strategies Group, Strategic Health Plans Update 2002.

For example, the programs administered by the Centers for Medicare and Medicaid Services (CMS) – including child health programs – provide benefits to more than 80 million Americans.[32] This represents more than a quarter of the US population. Moreover, these programs are targeted specifically at low-income individuals, the elderly, and children – precisely those groups that are most susceptible to respiratory tract diseases like asthma and COPD, and who would be most affected by price considerations.

Similarly, the Department of Defense provides prescription drug benefits to military beneficiaries through outpatient pharmacies, the TRICARE program, and the National Mail Order Pharmacy program.[33] These benefits cover both active-duty and retired military personnel and their families. Active-duty members never pay a co-pay for prescriptions. The cost that other military personnel and their families pay for prescriptions depends on the place of service. There is no co-pay for either generic or brand when the prescription is obtained at a military treatment facility. For the TRICARE Mail Order Pharmacy (for a three month supply) or TRICARE Retail Network (for a one month supply) the co-pay is $3 or $9 for generic or brand respectively. Additionally, a patient may go to a non-network pharmacy and pay $9 or 20% of the drug cost, whichever is higher. Thus, patients in this sector are not likely to experience a substantial change in price from an FDA determination that albuterol is non-essential.

3.7.2.1.1.4 Retail Route – GSK Programs to Ensure Patient Access

For those patients without federal or state government assistance or private insurance coverage, GSK offers Orange Card^{SM}, Together Rx™, or Bridges to Access™ programs.

The GSK Orange Card^{SM} offers GSK products, including Ventolin HFA, to eligible Medicare beneficiaries at point-of-sale discounts up to 40%. The discount program is available for Medicare beneficiaries without any other prescription coverage and incomes of up to $30,000 for an individual and up to $40,000 for a married couple.

Together Rx™, modeled after the GSK Orange Card^{SM}, is a multi-company discount program that is also available for Medicare beneficiaries without any other prescription coverage. It provides discounts up to 40% and is available for individuals with incomes below $28,000 for a single person and $38,000 for a married couple.

GSK is also an industry leader in Patient Assistance Programs (PAP). GSK provides medicines, including Ventolin HFA, through its "Bridges to Access"™ program at no cost or at a minimal retail pharmacy-dispensing fee to qualified patients with incomes up to $25,000 or families below 250% of the Federal Poverty Level. This program is designed to ensure that no low-income patient goes without the medicine he or she needs.

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[32] See Centers for Medicare and Medicaid Services, "CMS at a Glance", *available at* <http://cms.hhs.gov/about/overview.asp>, *visited on* April 21, 2003.

[33] See TRICARE, "Pharmacy Co-Pays", *available at* <http://www.tricare.osd.mil/pharmacy/newcopay.cfm>, *visited on* June 27, 2003.

3.7.2.1.2 Hospital and Clinic Route

The approximately 16% of the total albuterol patient population obtaining albuterol through the hospital and clinic route pay no or a low copay. Thus, patients in this sector are not likely to experience any material change in price from an FDA determination that albuterol is non-essential.

3.7.2.1.3 Summary of Possible Short-Term Cost Effects

To summarize the possible short-term impacts on different payer segments of an FDA determination that albuterol is non-essential:

- The 59% of patients covered by insurance or other private payers could see an average increase in copay of approximately $12, assuming insurance or other private payers do not modify their policies;
- 31% of patients, those covered via hospitals/clinics (16%) or other various government-funded programs (15%), would be unaffected or only minimally affected;
- Of the remaining 10% of patients that pay cash only, those not already purchasing branded products would see an increase in cost, with the magnitude dependent on regional and retailer variations; in addition, numerous private programs exist to ensure patient access to needed treatment.

3.7.2.1.4 Potential Effect of Competition on Cost

The estimated short-term impacts discussed above do not take into account the potential mitigating role of competitive market forces, in a market where institutional buyers have market power. In this regard, it is important to note that the United States has already experienced a branded albuterol market for 14 years. From 1981 to 1995, Proventil CFC and Ventolin CFC were the only two albuterol products on the market and during that time active price competition occurred between the two producers. Given the bargaining power of both public and private buyers, it is likely that the intense competition seen during that period will resume after CFC albuterol is deemed non-essential.

It is also important to note that when the albuterol market became genericized, there was no increase in the total number of albuterol MDI units sold.[34] A similar result can be expected if CFC albuterol MDIs are deemed non-essential.

3.7.2.2 Other Considerations

The price of albuterol alone should not be the controlling consideration in an assessment of whether patients will be adequately served by a CFC-free albuterol market. GSK agrees with the Petitioners that the potential benefits of removing albuterol from the list

[34] MAT 1996-2002, IMS.

of essential ODS uses also must be considered. Specifically, an albuterol non-essentiality determination will encourage patients currently using CFC albuterol MDIs to consult with their physicians, creating an opportunity for a reevaluation of treatment.

Moreover, although the criteria being discussed focuses on a possible risk of treatment being effectively unavailable as a result FDA action, there is also a potential risk of needed treatment being unavailable due to FDA inaction. As noted above, there is no guarantee that supply of pharmaceutical-grade CFCs will be adequate in the future, nor is there any guarantee that other CFC MDI components will remain in supply. The best way to reduce both potential risks to patients is to publish a proposed rule in the timeframe requested by patients' representatives.

4.0 SUMMARY AND CONCLUSION

In summary, GSK agrees with the rationale and objectives of the January 29, 2003 Stakeholders Petition and we support the request of the Petition that FDA should initiate rulemaking by July 28, 2003 to remove albuterol MDIs from its list of essential uses.

GSK is a corporate steward to the US commitment under the Montreal Protocol to phase out all ozone-depleting substances. It is for this and the foregoing reasons that GSK requests that this Petition be granted and that FDA issue a notice of proposed rulemaking by July 28, 2003 to remove albuterol MDIs from the list of essential uses in 21 CFR § 2.125(e)(2).