

August 25, 2004



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

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398
Tel. 919 483 2100
www.gsk.com

RE: Docket No. 03P-0029
Notice of Proposed Rule: Use of Ozone-Depleting Substances; Removal of
Essential-Use Designations

Dear Sir or Madam:

On behalf of GlaxoSmithKline ("GSK"), I respectfully request FDA to note the following clarifications and corrections to GSK's submission dated August 10, 2004:

1. In footnote 33 (page 12), the following cite for the data on drugstore.com's FY2003 net sales and percent of those sales for pharmaceutical products should have been included at the end of the footnote: "Michelle L. Kirsche, *Customer focus propels drugstore.com*, Drug Store News, April 19, 2004, at 6, available at <<http://archives.lf.com/docview.cfm?A=1&DS=ARC&ID=2004110551851>>, visited on Aug. 9, 2004."
2. On page 14, in the third full paragraph, reference is made to an "Attachment E". Instead of an attachment, the following footnote should have appeared: "Center for Disease Control, *Surveillance for Asthma --- United States, 1980 -- 1999*, Morbidity and Mortality Wkly. Rep., March 29, 2002 at 1, available at <<http://www.cdc.gov/mmwr/PDF/ss/ss5101.pdf>>, visited on Aug. 9, 2004 (stating that although asthma has been increasing in prevalence since 1980, changes in rates of asthma-related morbidity since 1995 have been "limited")."
3. Footnote 50 (page 16) incorrectly reads "Statement of Dr. Anthony Marinelli . . ." That footnote should read, "Statement of Dr. Robert Meyer . . ."

Per a discussion between counsel for GSK and FDA counsel, I am enclosing a corrected copy of GSK's August 10, 2004 submission as a convenience to FDA. Please do not hesitate to call me at 919-483-4490 if you require any further information.

Sincerely,

C. Elaine Jones, Ph.D.
Vice President, US Regulatory Affairs

Enclosure

03P-0029

CR 1

**Comments on June 16, 2004 FDA Proposed Rule to
Remove Essential Use Designation for
Albuterol Metered-Dose Inhalers Containing Chlorofluorocarbons
(FDA Docket 03P-0029)
Submitted by GlaxoSmithKline**

1. Introduction and Summary

GlaxoSmithKline USA (GSK) appreciates the opportunity to provide comments on the Food and Drug Administration's (FDA's) June 16, 2004 Proposed Rule to remove the essential use designations for albuterol used in oral pressurized metered-dose inhalers (MDIs).¹ These comments are in addition to GSK's comment submitted on July 15, 2004, which served notice that GSK was immediately undertaking the work necessary to expand production capacity of its CFC-free product Ventolin[®] HFA (albuterol sulfate HFA inhalation aerosol).

GSK filed five submissions to the FDA docket regarding the January 29, 2003 Citizen Petition from the US Stakeholders Group on MDI Transition, requesting FDA to initiate rulemaking on the removal of essential use status for albuterol inhalers.² GSK understands that these submissions are part of the record for the Proposed Rule. GSK also gave an oral presentation at the June 10, 2004 public meeting of FDA's Pulmonary and Allergy Advisory Committee (PADAC), and understands that its testimony is also part of the record for the Proposed Rule. The present comments will, in some cases, update and/or augment GSK's submissions to the Citizen Petition docket and the company's testimony at the PADAC hearing.

As discussed herein, GSK believes that all of the criteria delineated by FDA at 21 C.F.R. § 2.125(g)(4), have been or will be met. In particular, in light of GSK's commitment to expand its Ventolin HFA production capacity (see section 2.1.1 below) there will be adequate production capacity for CFC-free albuterol MDIs by December 31, 2005, assuming Schering Plough makes a similar commitment. Similarly, the availability of numerous public and private programs to assist patient access, coupled with GSK's commitment to provide two million free samples of Ventolin HFA annually via GSK sales representatives whose sales territories may include lower income areas, and not to increase the price of Ventolin HFA at least through 2007, will mitigate any additional risk of patients being denied access to needed treatment after CFC albuterol MDIs are phased out.

¹ Use of Ozone Depleting Substances; Removal of Essential-Use Designations, 69 Fed. Reg. 33602 (June 16, 2004) ("Proposed Rule").

² US Stakeholders Group on MDI Transition ("Stakeholders"), Citizen Petition (Jan. 29, 2003) (FDA Docket 03P-0029, Doc. CP1) (hereinafter "Citizen Petition")

Conversely, as indicated in the Proposed Rule and supported by previous comments of the U.S. Stakeholders Group, the International Pharmaceutical Aerosol Consortium (IPAC), and others, there is a real risk that patients will be denied access to needed treatment if the transition to CFC-free albuterol MDIs is delayed beyond 2006.³

Therefore, GSK strongly recommends that FDA issue a final rule to remove CFC albuterol MDIs from the list of essential uses at 21 C.F.R. § 2.125(e)(2) effective December 31, 2005, assuming Schering Plough commits to having its production capacity ready by that date. Due to the uncertainty of future CFC supply, delaying the effective date beyond that timeframe will not materially benefit patients, and doing so could in fact increase the risk to the patient population.

2. FDA Criteria for Non-Essentiality

FDA's regulation on essential uses of ozone-depleting substances (ODS) specifies several criteria that the agency will consider in determining whether to remove a product from its essential use list.⁴ GSK agrees with FDA's conclusion in the Proposed Rule that the following regulatory criteria have been met: same active moiety, same route of administration, same indications, same level of convenience, and adequate post-marketing data.⁵ In addition, one of the two remaining criteria – adequate production capacity – will have been met by December 31, 2005, assuming Schering Plough makes a commitment to complete a scale-up of its production capacity within a timeframe similar to that of GSK. The last criterion – patients adequately served – will have been met by December 31, 2005 through numerous programs to assist patient access to needed treatment.

2.1 Adequate Production Capacity

2.1.1 GSK's Production Capacity

FDA's exact criteria on this subject is that “[s]upplies and production capacity for the non-ODS product(s) exist or *will exist* at levels sufficient to meet patient need”.⁶ Thus, under its regulation, FDA does not need to find that adequate production capacity for CFC-free albuterol MDIs exists before it can issue a final rule on CFC albuterol non-essentiality – FDA only needs to conclude that such capacity will exist by the effective date for CFC albuterol non-essentiality.

³ See Proposed Rule, 69 Fed. Reg. at 33608; Citizen Petition at 4; Stakeholders Letter to Docket 03P-0029 at 3 (July 21, 2003) (FDA Docket 03P-0029, Doc. RC1); Stakeholders Letter to Lester Crawford at 1 (April 1, 2004) (FDA Docket 03P-0029, Doc. C7); International Pharmaceutical Aerosol Consortium (“IPAC”) Letter to Docket 03P-0029 at 3 (March 8, 2004) (FDA Docket 03P-0029, Doc. Sup4).

⁴ 21 C.F.R. § 2.125(g).

⁵ Proposed Rule, 69 Fed. Reg. at 33605-07.

⁶ 21 C.F.R. § 2.125(g)(3)(ii) (emphasis added).

In the Proposed Rule, FDA indicates that the current US market for albuterol is approximately 50 million units per year.⁷ In a July 9, 2004 letter submitted to the FDA docket on July 15, 2004, GSK stated it is now undertaking an expansion of its HFA production facility at Zebulon, North Carolina to enable it to produce 30 million Ventolin HFA MDIs annually. This new production capacity will be in place and operable by December 31, 2005.

In addition, to create a margin of safety in the supply of CFC-free albuterol MDIs, GSK will begin to build up its inventory of Ventolin HFA three months prior to the effective date. If circumstances warrant, GSK will consider building this inventory sooner.

As GSK indicated in its July 15, 2004 submission, it reserves the right to re-evaluate the timing for completing its expansion of production capacity when FDA's final rule is issued and the effective date is known. If the effective date is substantially beyond December 31, 2005, it would serve no purpose for GSK to complete expansion of production capacity by that date only to have it sit idle for a long period of time.

2.1.2 Schering Plough's Production Capacity

Schering Plough's CFC-free product, Proventil HFA, currently serves 3.6% of the total albuterol market – i.e., approximately 1,738,100 MDIs annually.⁸ At the June 10, 2004 PADAC hearing, Schering Plough's representative stated that Schering Plough and its manufacturing partner, 3M Pharmaceuticals, "can have adequate supply and production capacity of Proventil HFA available again as early as December 31, 2005 or within 18 months of an established transition date."⁹

2.1.3 Conclusion Regarding Production Capacity

If Schering Plough and 3M Pharmaceuticals were to make a commitment, similar to that made by GSK, to have sufficient production capacity in place by December 31, 2005, then the "adequate production capacity" criterion will have been met by that date. If Schering Plough and 3M do not make such a commitment, then based on the statement by the Schering Plough representative at the PADAC hearing, this criterion will have been met within 18 months of the publication of the final rule: i.e., by September 2006, assuming the final rule is issued in March 2005.

⁷ Proposed Rule, 69 Fed. Reg. at 33613.

⁸ IMS HEALTH National Sales Perspectives, MAT June 2004. Data is proprietary to IMS HEALTH.

⁹ Statement of Dr. Ron Garutti, Transcript, Meeting of the Pulmonary and Allergy Drugs Advisory Committee to Discuss FDA Proposed Rule on Essential Use Determinations, at 124, 130 (Jun. 10, 2004) (hereinafter "2004 PADAC Meeting Transcript").

2.2 Patients Adequately Served

In FDA's essential use regulation, this criterion is stated as:

Patients who medically required the ODS product are adequately served by the non-ODS product(s) containing that active moiety and other available products;¹⁰

In its comment on the proposed rule that led to FDA's essential use regulation, GSK supported inclusion of a criterion to consider whether patients are adequately served by the non-ODS alternatives.¹¹ FDA did include the criterion, and stated that in applying it the agency would "consider whether a high-priced non-ODS product is effectively unavailable to a portion of the patient population because they cannot afford to buy the product."¹² GSK concurs that as part of FDA's evaluation of this criterion, it is legitimate, and indeed critically important, for FDA to consider this concern.

GSK takes very seriously the need for patients to continue to have access to needed treatment during and after the phase-out of CFC albuterol MDIs. As discussed in previous submissions and summarized below, GSK already has in place effective patient assistance programs to help patients obtain needed medicines. These are discussed in section 2.2.1.1 below. In addition, because it understands the importance of albuterol as a "rescue" medication, GSK will initiate a new patient assistance program to provide a \$10 discount on Ventolin HFA. This is discussed in section 2.2.1.1.3 below. Furthermore, GSK will initiate a comprehensive education and outreach program, described in section 2.2.3 below. Finally, as described in section 2.2.2 below, GSK has publicly committed to freeze the wholesale price of Ventolin HFA until 2008 at the earliest, and to provide two million free samples of Ventolin HFA annually, to be distributed by GSK sales representatives whose sales territories may include lower income areas.

The Proposed Rule states that any potential access problems may be ameliorated by programs such as GSK's patient assistance programs.¹³ GSK agrees: the combined effect of GSK's existing and new programs, the education and outreach actions to which GSK has committed, the assistance programs of other companies, state and federal assistance programs, GSK's price freeze and two million free samples annually, should mitigate the risk that access problems will lead to a decline in overall treatment of asthma and COPD due to a phase-out of CFC albuterol MDIs.

¹⁰ 21 C.F.R. § 2.125(g)(3)(iv).

¹¹ GlaxoWellcome Letter to Docket 97N-0023 at 11 (Nov. 29, 1999) (FDA Docket 97N-0023, Doc. C9617).

¹² Use of Ozone-Depleting Substances; Essential-Use Determinations, 67 Fed. Reg. 48370, 48374 (July 24, 2002) (hereinafter "Essentiality Regulation").

¹³ Proposed Rule, 69 Fed. Reg. at 33616.

2.2.1 Patient Assistance Programs

2.2.1.1 GSK-Sponsored Programs

2.2.1.1.1 Low Income Patients

GSK's primary assistance program for uninsured low income patients is *Bridges to Access*. This program makes available to all eligible patients all GSK medicines available for use in an out-patient setting. A qualifying patient may obtain Ventolin HFA for a one time \$10 retail co-pay for a 60-day fill, and thereafter free of charge. The program is open to all residents of the United States (including non-citizens) who are not eligible for other prescription drug benefits and meet the income eligibility requirements. Those requirements are: single person household annual income of less than or equal to \$25,000 or multi-person household income of less than or equal to 250 percent of the federal poverty level. There is no limitation on the number of patients who can enroll in this program.

GSK has taken several steps to make patients, physicians and other health care providers aware of Bridges to Access:

- Information about the program is posted on a public website: <<http://www.bridgestoaccess.gsk.com>>. The information includes eligibility requirements, documentation needed, products available and enrollment process. Sample applications are available for patients to review. Advocates also can register and download active enrollment forms from the website.
- Links to the GSK website are posted from several other websites, including the HHS website, National Council on Aging (www.benefitscheckuprx.org), Volunteers in Healthcare (www.rxassist.org), and the Pharmaceutical Research Manufacturers of America (www.helpingpatients.org). GSK works with the sponsoring agencies to make sure our information remains up to date.
- GSK has established a Customer Response Center (CRC) with a toll free number: 1-888-825-5249. Patients and advocates can speak with CRC customer service representatives 8:00am-8:00pm (ET) Monday - Friday. CRC customer service representatives are trained to respond to phone and email requests about Bridges to Access and other GSK patient assistance programs.
- GSK provides information cards on Bridges to Access to its field sales representatives to distribute to providers who request information.
- GSK works with state governments to help address patient coverage when state program changes and/or fiscal shortfalls eliminate patients from state programs.

As a result of these actions, for the first half of 2004 alone, GSK provided over \$162 million (wholesale acquisition cost) worth of medicines (including Ventolin HFA) to more than 334,000 patients. GSK's extensive, multi-faceted education and outreach program, detailed in section 2.2.3 below, should enhance awareness of the availability of this and GSK's other patient assistance programs among patients who require albuterol MDIs.

2.2.1.1.2 Senior and Disabled Patients

For seniors and disabled patients, GSK sponsors the *Orange Card*SM and participates in multi-company sponsorship of *Together Rx*TM. These two programs offer discounts on prescription medicines at the pharmacy counter that can result in savings to patients of 20 - 40 percent.¹⁴ Both programs are available to Medicare participants without other prescription coverage who meet the income eligibility requirements, which are: up to \$30,000 for an individual and up to \$40,000 for a married couple for Orange Card, and \$28,000 for an individual and up to \$38,000 for a married couple for Together Rx. These programs – which have served as a critical bridge to the availability in 2006 of the new Medicare prescription drug benefit – have also been very successful in reaching elderly or disabled patients who need assistance.

2.2.1.1.3 New Albuterol-Specific Patient Access Program

As a further means of alleviating concern about patient access during and after the phase-out of CFC albuterol MDIs, GSK will initiate a new program targeted specifically for patients that use albuterol MDIs. Under this new program, GSK will make available at least three million \$10.00 "Ventolin HFA Savings Checks" annually. The \$10.00 level was chosen based on the calculation in the study of the albuterol market by National Economic Research Associates (NERA) that cash-paying patients may pay an average increase of \$8.61 per MDI and that insured patients may pay an average increase of \$10.57 per MDI.¹⁵ Patients responsible for paying at least \$10 of the cost of their Ventolin HFA prescription themselves will be able to immediately use this savings check (very similar to a coupon) at the pharmacy upon their purchase of a Ventolin HFA MDI.¹⁶

¹⁴ Actual savings depend on the pharmacy's customary pricing for the particular drug product and on the specific discount offered by the participating manufacturer.

¹⁵ National Economic Research Associates, Inc., "The Impact on Patients and Payers of Designating Albuterol A Non-Essential Use of An Ozone-Depleting Substance" at 17 (September 8, 2003) (FDA Docket 03P-0029, Doc. C4) (hereinafter "NERA Report").

¹⁶ Certain conditions and restrictions on eligibility will apply. To cite one example, a savings check may not be used if all or any part of the prescription is covered by a Federal health care program, including Medicare and Medicaid, or any similar Federal or state program, including a state pharmaceutical assistance program. Applicable conditions and restrictions will be spelled out in full on the front and back of the check.

GSK will distribute Ventolin HFA Savings Checks through multiple channels, e.g.: directly to physician offices via GSK sales representatives whose sales territories may include lower income areas, inserted into the free Ventolin HFA samples, and by mail. Consumers will be able to request additional \$10 savings checks by providing their name and mailing address on the back of their initial savings check. Once this initial savings check is redeemed at the pharmacy, the patient's name and mailing information would be added to GSK's existing consumer database. GSK would then mail the patient additional checks for continued \$10 savings on future prescription refills of Ventolin HFA.

GSK intends to begin distribution of these savings checks three months prior to the effective date for albuterol non-essentiality and is committed to maintaining this program at least through 2009. However, should FDA choose an effective date that is later than October 2006, GSK may reevaluate the timing and scope of this program based on applicable market conditions.

2.2.1.2 Other Patient Assistance Programs

In addition to the programs sponsored by GSK, there are numerous other programs sponsored by other companies, organizations, and the state and federal governments that FDA should take into account. As shown on the PhRMA website, www.HelpingPatients.org, there are close to 300 public and private patient assistance programs in operation. An estimated 6.2 million Americans received medicines free of charge through company-sponsored patient assistance programs.¹⁷ Some examples of Government programs are detailed in GSK's July 2, 2003 submission to the FDA docket on the Citizen Petition.¹⁸ Not mentioned in that submission, but very important for FDA to take into account, is the new Medicare prescription benefit program that will be fully available on January 1, 2006.

2.2.2 Free Samples and Price Freeze

In its November 10, 2003 submission, GSK announced its commitment to provide two million free samples of Ventolin HFA annually. These samples will be distributed by GSK sales representatives whose sales territories may include lower income areas. At the June 10, 2004 PADAC hearing, FDA's Chief Economist, Dr. Lutter, stated that GSK's sampling commitment "may significantly offset the loss of canisters provided it is well targeted to the most price-sensitive patients."¹⁹ GSK cannot guarantee or track how physicians will choose to distribute the samples they request. Nevertheless, in a study of self-reported physician behavior, 86 percent of respondents agreed that drug samples are

¹⁷ PhRMA, "Profile Pharmaceutical Industry 2004" at p. viii.

¹⁸ GlaxoSmithKline Letter to Docket 03P-0029 (July 2, 2003) (FDA Docket 03P-0029, Doc. C3).

¹⁹ Statement of Dr. Randy Lutter, 2004 PADAC Meeting Transcript at 76.

a source of medications for those patients who cannot afford them; in fact, avoiding cost to the patient was the most consistent motivator for physicians to use drug samples.²⁰

Also in its November 10, 2003 submission, GSK publicly committed not to increase the wholesale acquisition cost of Ventolin HFA. GSK has committed to keep this price freeze in effect until 2008 at the earliest. The company set this date because it was making a voluntary commitment without knowing the effective date for albuterol non-essentiality.

2.2.3 Education and Outreach Programs

2.2.3.1 GSK-Initiated Actions

GSK understands the importance of increasing awareness of patient assistance programs for the phase-out of CFC albuterol MDIs. Therefore, GSK will undertake an extensive, multi-faceted program to disseminate information about the albuterol transition and the point of contact for further information on its patient assistance programs to patients directly, and indirectly through physicians, pharmacists, and other health care providers. This education and outreach program will include the actions described below.

2.2.3.1.1 Physicians and Other Health Care Providers

In order to reach as many physicians and health care providers as possible, GSK will take the following actions:

- Prior to the effective date, GSK will send letters to hospitals, indigent clinics, and private practices.
- Just prior the effective date, GSK will send a “Dear HealthCare Provider” letter to physicians, pharmacists, and other health care providers (respiratory therapists, nurses, etc.).
- GSK will print the toll-free telephone number for GSK’s Customer Response Center (CRC) on every carton of Ventolin HFA, both sample and trade pack. As noted above, CRC representatives are trained to provide details on Bridges to Access and GSK’s other patient assistance programs.

²⁰ Chew, O’Young, Hazlet, Bradley, Maynard, and Lessler, “A Physician Survey of the Effect of Drug Sample Availability on Physicians’ Behavior,” *Journal of General Internal Medicine*, Volume 15, Issue 7, July 2000, pp. 478-483.

2.2.3.1.2 Pharmacies and Pharmacists

In addition to the above actions, GSK will take several actions targeted specifically at pharmacies and pharmacists. This is critically important because pharmacists represent the third largest group of health care professionals. Consumers visit their pharmacy more often than they see their doctor. Working with pharmacists and retail pharmacies will enable GSK to reach the vast majority of patients currently using a CFC albuterol MDI. GSK actions targeted specifically to pharmacies and pharmacists will include:

- Sending information to all state and national pharmacy associations.
- Disseminating an educational brochure for pharmacy staff to hand out to patients.
- Working with pharmacy chains to deliver a point-of-sale (POS) message. An informational message will be printed out as the prescription is filled and given to the patient when the prescription is dispensed.
- Providing educational material and content to pharmacies for in-store use.
- Working with pharmacy wholesalers, pharmacy computer software vendors, and pharmacy headquarters to seek their support for providing a specific message to alert pharmacy personnel about the transition when an CFC albuterol MDI is selected during a prescription filling and/or when an order for CFC albuterol MDIs is placed with a wholesaler.

2.2.3.1.3 Direct Communication to Patients

GSK will develop an appropriate informational message on the albuterol transition and the point of contact for information on its patient assistance programs and will disseminate this message directly to consumers through the media (e.g., print, radio). This could be through public service announcements and/or paid advertisements.

2.2.3.1.4 Timing for Education and Outreach

GSK has experience with withdrawal of CFC-containing products. However, GSK understands that the phase-out of CFC albuterol MDIs presents unique challenges, which is why, even though none of the individual actions are new, the company's educational and outreach program will be extensive and multi-faceted. Work on implementation (e.g., drafting materials and content) will begin without waiting for the final rule. GSK is confident that an effective date of six months after publication of the final rule is sufficient for the company to implement this education and outreach program.

2.2.3.2 Educational Actions by the Stakeholders Group

In addition to these actions that GSK intends to take, the U.S. Stakeholders Group has expressed a willingness to conduct education and outreach:

On the part of the stakeholders, our member organizations are committed to working with the agency and the manufacturers to develop an educational strategy for communicating the availability of free and discounted albuterol. We can work with our member organizations and our network to deploy these messages in advance of the transition to patients, to specialty [physicians], general physicians and the rest of the healthcare community.²¹

2.2.4 FDA's Economic Analysis of Patient Access

The Proposed Rule provides an economic analysis which attempts to quantify the impact of a phase-out of CFC albuterol MDIs.²² While this analysis represents a thoughtful, good-faith attempt to grapple with a very difficult analytic issue, it is important to put in perspective the limitations of this analysis to the decision that FDA faces. First, this analysis likely over-estimates the potential adverse impact on patients. Second, it under-estimates potential benefits. Third, it includes several results that are not legally relevant to FDA's decision on albuterol non-essentiality, such as overall economic impact and cost/benefit comparisons. Finally, the analysis is premised on an unrealistic baseline that CFC albuterol MDIs will remain on the market indefinitely.

2.2.4.1 Over-Estimation of Potential Adverse Effects on Asthma Patients

The Proposed Rule states that two different approaches will be used to estimate the cost of earlier phase-out dates.²³ The first approach involves estimating a range of price increase when CFC albuterol MDIs are phased out and then, using various price elasticities, to estimate the theoretical decline in the number of albuterol MDIs purchased per year. The theoretical decline in sales is used as a surrogate for patients being denied access. The second approach "assumes that the effects of removing albuterol CFC MDIs from the market can be inferred from the effects of the introduction of generic products."²⁴ There are several problems with the analyses under both approaches.

²¹ Statement of Pamela Wexler, 2004 PADAC Meeting Transcript at 101-102.

²² Proposed Rule, 69 Fed. Reg. at 33609-17.

²³ Id. at 33615.

²⁴ Id.

2.2.4.1.1 Price Data

The first approach over-estimates potential adverse effects by using unrepresentative prices for generic CFC and branded HFA albuterol MDIs. These unrepresentative prices yield an unrepresentative price gap between generic and branded albuterol. The Proposed Rule expresses this price gap as a ratio of the difference in price between the generic and the branded price for an albuterol MDI to the generic price $((P_b - P_g)/P_g)$.²⁵ Based on the prices it used, the Proposed Rule calculates that these ratios range from 1.2 to 1.8. These ratios are then used to calculate a theoretical decline in sales when CFC albuterol MDIs are phased out: by multiplying the number of generic albuterol MDIs in the market (40 million) times the percent of uninsured (15%) times the presumed elasticity (.05 – 1.0) times the “price gap” ratios (1.2 – 1.8).²⁶

2.2.4.1.1.1 Lower End of Range

To derive the lower end of the price gap range (i.e., 1.2), the Proposed Rule uses prices obtained from an IMS data set.²⁷ However, the Proposed Rule cites – but does not use – Red Book data which show an average wholesale price (AWP) for generic albuterol MDIs of \$25.00 and an AWP for branded HFA albuterol of \$35.00.²⁸ Because these are wholesale prices, they likely over-estimate the price gap, given that pharmacies mark up generic products substantially more than branded products.²⁹ In any case, the ratio of the price increase to the generic price in this case ($\$10.00 / \25.00) is 0.4. Applying the lower price elasticity to this ratio yields a theoretical decline in albuterol MDI sales of only 120,000 MDIs out of a market of 40 million ($40 \text{ million} \times .15 \times .05 \times .4 = 120,000$). This theoretical decline in sales is only a third of 360,000 low end calculated in the Proposed Rule.

FDA also did not consider the prices used in the economic analysis of the albuterol market conducted by National Economic Research Associates (NERA) which

²⁵ Although the Proposed Rule states that these figures are the ratio of the branded HFA MDI price to the generic price (see Proposed Rule, 69 Fed. Reg. at 33614), in fact the 1.2 and 1.8 are ratios of the increase in price to the generic price.

²⁶ $40 \text{ million} \times .15 \times .05 \times 1.2 = 360,000$, which the Proposed Rule rounds up to 400,000; $40 \text{ million} \times .15 \times .1 \times 1.8 = 1,080,000$, which the Proposed Rule rounds down to 1 million.

²⁷ Proposed Rule, 69 Fed. Reg. at 33613.

²⁸ Id.

²⁹ See, e.g., WPVI/ABC Action News, “Special Report” (April 28, 2004) available at http://abclocal.go.com/wpvi/news/11112003_sr_drugmarkup.html, visited on Aug. 5, 2004; ABC Action News, “Pill Patrol: Generic drugs marked up as much as 3000 percent” (Nov. 27, 2003) available at <http://www.abcactionnews.com/stories/2003/11/031127pillpatrol.shtml>, visited on Aug. 5, 2004; Iowa City Press Citizen, “Generic medicines not panacea some believe” (June 18, 2003) available at <http://www.press-citizen.com/opinion/pceditorials/staffedit061803.htm>, visited on Aug. 5, 2004.

was submitted to the FDA docket on the Citizen Petition.³⁰ These prices, derived from IMS, Verispan, and SPA data, are \$26.32 for generic CFC albuterol MDIs and \$34.54 for branded HFA albuterol MDIs.³¹ The price gap in this case is \$8.22, and the price gap ratio ($\$8.22 / \26.32) is 0.3. Using this ratio, the low end of the range of theoretical decline in sales is only 90,000 MDIs out of a market of 40 million ($40 \text{ million} \times .15 \times .05 \times .3 = 90,000$).

Based on these two price sets, a more realistic low end range for the theoretical decline in sales is approximately 100,000. FDA should use this number if it continues to utilize the “theoretical sales decline” methodology for the final rule. Note, however, as discussed below, even this *de minimis* theoretical decline in sales does not take into account important mitigating factors, e.g., patients assistance programs, free samples, etc.

2.2.4.1.1.2 Upper End of Range

The higher end of the price range used in the Proposed Rule’s analysis was derived from prices found on drugstore.com. However, as Dr. Lutter noted at the June 10, 2004 PADAC hearing, these prices are not representative of the average prices paid by uninsured patients.³² Drugstore.com’s share of the prescription drug market is only 0.07 percent.³³ Moreover, the extremely aggressive pricing of certain retailers is not representative of most brick-and-mortar pharmacies which, as noted above, apply a disproportionately high mark-up to generic products.³⁴ Thus, the 1.8 price ratio derived from drugstore.com’s albuterol MDI prices is unrepresentative of the actual market, and the theoretical sales decline of 1 million MDIs derived from those prices is unrealistic, and is not appropriate for use by FDA.

³⁰ NERA Report (FDA Docket 03P-0029, Doc. C4).

³¹ NERA Report, Appendix at Exhibit A-2.

³² Statement of Dr. Randy Lutter, 2004 PADAC Meeting Transcript at 67.

³³ Total U.S. pharmacy sales for FY2003 was approximately \$205 billion. National Association of Chain Drugstores, “Industry Facts-at-a-Glance”, available at <http://www.nacds.org/wmspage.cfm?parml=507#rx>, visited on Aug. 6, 2004. Drugstore.com’s total sales in the U.S. for FY2003 were \$245 million, of which pharmacy sales represented 55% (\$135 million). Michelle L. Kirsche, *Customer focus propels drugstore.com*, Drug Store News, April 19, 2004, at 6, available at <http://archives.lf.com/docview.cfm?A=1&DS=ARC&ID=2004110551851>, visited on Aug. 9, 2004.

³⁴ See, e.g., WPVI/ABC Action News, “Special Report” (April 28, 2004) available at http://abclocal.go.com/wpvi/news/11112003_sr_drugmarkup.html, visited on Aug. 5, 2004; ABC Action News, “Pill Patrol: Generic drugs marked up as much as 3000 percent” (Nov. 27, 2003) available at <http://www.abcactionnews.com/stories/2003/11/031127pillpatrol.shtml>, visited on Aug. 5, 2004; Iowa City Press Citizen, “Generic medicines not panacea some believe” (June 18, 2003) available at <http://www.press-citizen.com/opinion/pceditorials/staffedit061803.htm>, visited on Aug. 5, 2004.

2.2.4.1.2 Effects of Competition

In addition, the price ranges used in FDA's economic analysis – at least the high end of those ranges – are unrealistic because they do not take into account the effects of market competition on prices. As noted by GSK its July 2, 2003 submission to the Citizen Petition docket, this market is characterized by large institutional buyers.³⁵ Such large-volume purchasers have the capability to induce competitive bidding among the HFA albuterol manufacturers, which will put downward pressure on prices. As GSK also noted in that submission, that is exactly what happened in the albuterol MDI market during the 14 year period before there were generics. This point was amplified by Dr. Richard Rozek, Senior Economist of NERA, testifying at the June 10, 2004 PADAC hearing. Dr. Rozek explained that when there are only two suppliers of substantially similar products, “prices do respond in a downward direction when the two are there, assuming that you have big buyers who can move market share and can extract that kind of gain.”³⁶

2.2.4.1.3 Lesson From Introduction of Generics

As noted at the outset of this section, FDA used two approaches for estimating the potential impact on patients of a phase-out of CFC albuterol MDIs. The second approach involved inferring the potential impact of phasing out generics in a market by assessing what happened to pharmaceutical markets when generic products were introduced. The most on-point example of the introduction of a generic is the 1995 transition of the albuterol market from branded to generic. The Proposed Rule notes that “[i]ncreases in total sales of albuterol MDIs around that time have been attributed to the continuing rising incidence of asthma and COPD.”³⁷

Nevertheless, the Proposed Rule neglected to consider this real-world example when conducting the “second approach” of its economic analysis. This experience is more directly applicable than a theoretically derived decline in sales based on prices and elasticities which may not be realistic, and thus it should be given more weight by FDA. The Proposed Rule does note one study of the introduction of generics into markets that “suggests that any effect on consumption by the removal of generic albuterol MDIs may be quite small.”³⁸ Although this is consistent with what actually happened when CFC albuterol MDIs entered the market, the Proposed Rule seems to conclude that this study is of limited applicability to the US albuterol market because, *inter alia*, “the number of generic albuterol MDIs currently marketed exceeds the four or five entries associated

³⁵ GlaxoSmithKline Letter to Docket 03P-0029 at 16 (July 2, 2003) (FDA Docket 03P-0029, Doc. C3).

³⁶ Statement of Dr. Richard Rozek, 2004 PADAC Meeting Transcript at 254-55.

³⁷ Proposed Rule, 69 Fed. Reg. at 33607.

³⁸ Id. at 33616.

with the peak quantity response relative to the no-generics scenario.”³⁹ However, except for Warrick (a subsidiary of Schering Plough), IVAX, and Andrx, no other generic company has more than a 1 percent share of the present albuterol MDI market.⁴⁰ Thus, in effect, the CFC albuterol market is a three-product market.

In any case, FDA should give substantially more weight to the historic example of the introduction of generics into the albuterol MDI market – the same market now under consideration – than it gives to theoretical impacts derived from price elasticities.

In addition, one key finding of that study was that at some point after the introduction of generic products, sales may actually decline due to decreased advertising by manufacturers of branded products.⁴¹ Conversely, the extensive and multi-faceted education and outreach program that GSK has committed to undertaking (see section 2.2.3 above) may have a mitigating effect, similar to advertising, on any possible decline in sales in albuterol MDIs after CFC albuterol is phased out.

Finally, it is important to note that with the introduction of generic albuterol MDIs there was no statistically significant decrease in asthma morbidity as a function of population.⁴² In other words, the introduction of generic albuterol MDIs did not bring a significant improvement in health care. FDA itself noted that:

When generic albuterol CFC MDIs first came on the market in 1995 and 1996, we did not see any clear indication that underserved patients who had not been purchasing the more expensive [branded products] began to purchase the lower-priced generics.⁴³

Given this known result of the previous shift in the albuterol market, it would be unreasonable and speculative to conclude that a phase-out of CFC albuterol will result in a significant erosion of health care.

³⁹ Id.

⁴⁰ IMS HEALTH Provider Perspective Data, January-May 2004. Data is proprietary to IMS HEALTH.

⁴¹ Proposed Rule, 69 Fed. Reg. at 33616.

⁴² Center for Disease Control, *Surveillance for Asthma -- United States, 1980 -- 1999*, Morbidity and Mortality Wkly. Rep., March 29, 2002 at 1, available at <<http://www.cdc.gov/mmwr/PDF/ss/ss5101.pdf>>, visited on Aug. 9, 2004 (stating that although asthma has been increasing in prevalence since 1980, changes in rates of asthma-related morbidity since 1995 have been “limited”).

⁴³ Proposed Rule, 69 Fed. Reg. at 33607.

2.2.4.1.4 Mitigating Effects of Patient Assistance Programs and Free Samples

FDA has acknowledged that its economic analysis ignored the likely significant off-setting effects of GSK's patient assistance programs and the 2 million/year free samples of Ventolin HFA. These programs were not taken into account because FDA concluded that the extent to which these programs would assist low income uninsured patients cannot be quantified.⁴⁴ Similarly, FDA acknowledges that its economic analysis "ignores GSK's offer to distribute free MDIs because we are unable to quantify how many of these MDIs would go to the people who would otherwise reduce MDI purchases because of the higher prices."⁴⁵

However, in evaluating whether patients would be "adequately served", FDA should consider all relevant factors, even if those factors cannot be neatly quantified. The administrative law standard of reasoned decision-making requires no less.⁴⁶

Moreover, in other parts of its analysis, the Proposed Rule makes unsupported quantitative assumptions to derive its economic conclusions: for example, the use of 3% and 7% as discount rates,⁴⁷ the use of drugstore.com prices, and the assumption that "generic albuterol MDIs containing CFC might remain on the market indefinitely"⁴⁸ despite the uncertainty of continued CFC supply (see section 3. below).

Therefore, FDA should make a good faith effort to estimate the potential impact of the GSK's patient assistance programs (including the Ventolin HFA Savings Checks) and GSK's commitment to provide 2 million free samples by making reasonable assumptions when necessary. For FDA to omit these significant factors entirely from its quantitative analysis does not meet the standard of reasoned decision-making.

Using very conservative assumptions, any theoretical decline in sales can be mitigated by the patient assistance programs and the free samples. For example, the 100,000 MDIs at the low end of the range of theoretical sales decline (see section 2.2.4.1.1.1 above) would be completely mitigated if only 5 percent of GSK's 2 million free samples reached uninsured patients. As noted in section 2.2.2 above, a primary use of samples by physicians is to assist patients who cannot afford medications.

⁴⁴ Id. at 33607, 33616.

⁴⁵ Id. at 33617.

⁴⁶ See Motor Vehicle Manufacturers Association of United States, Inc. v. State Farm Mutual Automobile Insurance Company, 463 U.S. 29, 52, 103 S.Ct. 2856, 2871 (1983); Allentown Mack Sales and Service, Inc. v. NLRB, 522 U.S. 359, 374, 118 S.Ct. 818, 826 (1998); American Trucking Associations, Inc. v. Environmental Protection Agency, 283 F.3d 355, 369-70 (D.C. Cir. 2002).

⁴⁷ Proposed Rule, 69 Fed. Reg. at 33611.

⁴⁸ Id. at 33609.

Similarly, the low end of the range of theoretical sales decline would be completely mitigated if only 5 percent of the 3 million Ventolin HFA Savings Checks (i.e., 150,000 checks) were used by the uninsured. As discussed in section 2.2.4.1.1.1 above, the price gap between generic albuterol MDIs and branded HFA albuterol MDIs is less than \$10.00 at the low end of the range, and results in a theoretical sales decline of only 100,000 MDIs.

Finally, from January through July 2004, GSK provided 79,861 Ventolin HFA MDIs through Bridges to Access. If this were to continue at the same rate for the rest of the year, GSK would be providing approximately 137,000 units of Ventolin HFA during 2004 – at a time when the albuterol MDI market is dominated by generic products and GSK’s share of that market is less than 1 percent. Therefore, it is not unreasonable to conclude that Bridges to Access could cover the lower end of the range of the theoretical decline in sales.

The above examples look at each of GSK’s programs in isolation. If these programs are taken together – and the patient assistance programs offered by Schering Plough, the Federal Government, state governments, etc., are factored in – FDA can reasonably conclude that patients will be adequately served when CFC albuterol MDIs are phased out.

2.2.4.2 Under-Estimation of Potential Benefits to Asthma Patients

The Proposed Rule’s economic analysis fails to take into account, or inadequately takes into account, certain important potential benefits to patients of phasing out CFC albuterol MDIs. As noted above, the fact that some of these benefits cannot be neatly quantified does not relieve FDA of the responsibility to take them into account in determining whether patients are adequately served.

There are two such potential benefits to asthma patients. First, the phase-out of CFC albuterol MDIs may provide an opportunity for physicians to improve treatment of their patients. It is well known that albuterol is over-used, and that proper treatment of asthma would involve less frequent use of albuterol in favor of maintenance therapy.⁴⁹ As suggested by then PADAC members at the November 22, 1999 PADAC hearing, a higher price for albuterol may lead some patients to switch to preventative treatments for asthma.⁵⁰ This point was emphasized by Dr. Meyer, Director of FDA’s Office of Drug Evaluation II, at the June 10, 2004 PADAC hearing, who noted that:

⁴⁹ See National Heart, Lung and Blood Institute, Expert Panel Report 2, Guidelines for the Diagnosis and Management of Asthma, at pp. 86 *et seq.*, National Institutes of Health Publication 97-4051 (July 1997).

⁵⁰ Statements of Drs. Sessler, Fink, and Kelly, Transcript, Meeting of the Pulmonary and Allergy Drugs Advisory Committee to Discuss FDA Proposed Rule on Essential Use Determinations at 205, 219 (Nov. 22, 1999).

One of the complications of projecting a public-health consequence of some drop in the number of albuterol MDIs distributed or used relates . . . to the possibility that when beta-adrenergic bronchodilators are overused that might, itself, have detrimental effects.⁵¹

The US Stakeholders Group stated in its Citizen Petition that 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”.⁵² As Dr. Anthony Marinelli, speaking on behalf of the American Thoracic Society at the June 10, 2004 PADAC hearing, stated:

[T]he transition provides clinicians with a teachable moment to review and improve asthma-care plans with their patients. . . . Despite my best efforts, I know many of my patients rely too much on rescue medications, underutilize their maintenance medications and don’t take the simple steps to reduce exposure to their asthma triggers. The switch from CFC to HFA albuterol gives me an opportunity to, again, teach patients to know and avoid asthma triggers and to review the proper role of the many medications needed to manage their asthma.⁵³

Second, the Citizen Petition cited EPA’s conclusion that an increase in UV-B leads to an increase in ground level pollution.⁵⁴ This will exacerbate asthma incidence and severity.⁵⁵ FDA should take both of these potential benefits to patients into account when it is considering whether patients are adequately served.

2.2.4.3 Consideration of Irrelevant Results

FDA’s economic analysis includes estimates of the overall cost to the health care system, the relative cost and benefits of taking action, the impact on small business

⁵¹ Statement of Dr. Robert Meyer, 2004 PADAC Meeting Transcript at 89-90.

⁵² Citizen Petition at 5.

⁵³ Statement of Dr. Anthony Marinelli, 2004 PADAC Meeting Transcript at 200-201.

⁵⁴ Citizen Petition at 3 (citing Environmental Protection Agency, Office of Air Quality Planning and Standards, “How Ground-Level Ozone Affects the Way We Live and Breathe” (Nov. 2000)).

⁵⁵ See World Meteorological Organization and United Nations Environment Programme, Scientific Assessment of Ozone Depletion, 2002 at Q32 (March 2003) (stating that stratospheric ozone depletion increases production of ground-level ozone due to increased UV radiation); EPA, “Health and Environmental Impacts of Ground-Level Ozone”, available at <<http://www.epa.gov/air/urbanair/ozone/hlth.html>>, visited on Aug. 5, 2004 (stating that “ground-level ozone triggers a variety of health problems including aggravated asthma, reduced lung capacity, and increased susceptibility to respiratory illnesses like pneumonia and bronchitis”).

entities, and the costs of taking action relative to industry's return on investment.⁵⁶ Although FDA may be obligated to assess some of these costs under statutes other than the Clean Air Act or the Food, Drug & Cosmetic Act, it may not take these costs into account in determining whether patients are adequately served, whether to deem CFC albuterol MDIs non-essential, and when that non-essentiality shall become effective.

FDA's authority to remove CFC albuterol MDIs from its essential use list stems from the Clean Air Act.⁵⁷ The Supreme Court has recently held that costs of regulatory actions under the Clean Air Act may not be considered unless expressly granted by the Act.⁵⁸ There is no such specific direction in subchapter VI (stratospheric ozone protection) of the Clean Air Act.⁵⁹ Similarly, to the extent that any of FDA's authority for regulating essential uses of ozone depleting substances might be derived from the Food, Drug & Cosmetic Act, there is no authority to consider costs. As Dr. Murray Lumpkin, then FDA's Deputy Director for the Center for Drug Evaluation and Research, stated in testimony before the House Subcommittee on Health and Environment, "[u]nder [our] understanding of our statutory authorities, we are not allowed to factor cost into our decisionmaking process."⁶⁰

Notwithstanding the above, as stated in section 2.2 above, GSK believes that it is legitimate for FDA to take cost into account for the specific purpose of considering whether patients are adequately served. In this specific instance, FDA would not be considering aggregate societal cost but, rather, the possible effects of cost on individual patient access. However, it is outside FDA's statutory authority to take into account any other direct and indirect costs, such as: the overall cost to the health care system, the relative cost and benefits of taking action, the impact on small business entities, and the costs of taking action relative to industry's return on investment.

2.2.4.4 Unrealistic Baseline for Analysis

The Proposed Rule states that:

Any economic analysis of prospective government actions needs to begin with a baseline from which to assess those actions. Standard practice is to

⁵⁶ Proposed Rule, 69 Fed. Reg. at 33609 *et seq.*

⁵⁷ *Id.* at 33602, 33605, 33618.

⁵⁸ Whitman v. American Trucking Associations, Inc., 531 U.S. 457, 467 (2001).

⁵⁹ See 42 U.S.C. §§ 7671 *et seq.*

⁶⁰ Statement of Murray M. Lumpkin, Dep. Dir., Ctr. for Drug Evaluation and Research, FDA; Hearing Before the Subcommittee on Health and Environment of the House Comm. on Commerce: Implementation of Title VI of the 1990 Clean Air Act Amendments and Plans for the Upcoming Meeting of the Parties to the Montreal Protocol in Montreal in September 1997, 105th Cong. 67-68 (1997).

use as a baseline the state of the world absent the rulemaking in question, or, where this implements a legislative requirement, the world absent the statute.⁶¹

FDA's rulemaking is, at one level, implementing a requirement of the Clean Air Act, but it is also implementing U.S. obligations under the Montreal Protocol.⁶² The Proposed Rule offers no support for the premise that it is "standard practice" to assume the non-existence of an international treaty obligation, particularly since continued U.S. membership in this treaty is not the subject of the economic analysis.

Whether or not the Proposed Rule's description of "standard practice" is correct, its choice of the state of the world absent the rulemaking is completely unrealistic. The Proposed Rule assumes that "in this world, generic albuterol MDIs might remain on the market indefinitely."⁶³ By positing that generic albuterol MDIs might remain on the market indefinitely, the Proposed Rule implicitly assumes that it is certain that there will be CFCs available for all the years covered by the analysis. This assumption is directly contradicted by the statement in the Proposed Rule that "[t]he Parties will not approve U.S. essential use exemptions indefinitely."⁶⁴

As discussed in section 3.1 below, there is increasing uncertainty as to whether the U.S. essential use nominations for CFC albuterol MDIs will be approved by the Protocol Parties. In fact, "absent the rulemaking", the degree of uncertainty increases – i.e., the Protocol Parties will be even less likely to approve U.S. requests for more CFCs, as they will begin to question more publicly whether the U.S. is making efforts to adhere to the principles of the Montreal Protocol. Given these uncertainties, it would not be reasonable for FDA to assume a baseline that includes any year for which the U.S. has not been granted an essential use authorization for CFC albuterol MDIs.

At the present time, the Montreal Protocol Parties have approved essential use authorizations for the U.S. through 2005. Essential use authorizations for 2006 will be considered at the Protocol's 16th Meeting of the Parties, to be held in November 2005. As noted in section 3.1 below, a decision has been proposed that would only approve that portion of the 2006 U.S. essential use nomination that is not for single-moiety albuterol. Under the terms of Protocol Decision XV/5, the 16th Meeting of the Parties is the last Meeting of the Parties before the U.S. must submit its "plan of action" on albuterol – i.e. the final rule on albuterol non-essentiality.⁶⁵ Thus, unless the 16th Meeting of the Parties

⁶¹ Proposed Rule, 69 Fed. Reg. at 33609.

⁶² Id. at 33603-33604.

⁶³ Id. at 33609.

⁶⁴ Id. at 33608.

⁶⁵ Id. at 33609. See also Statement of Dr. Robert Meyer, 2004 PADAC Meeting Transcript at 231.

in November 2004 approves for the U.S. a 2006 essential use authorization for CFC albuterol MDIs, FDA should not include in its analysis baseline any year after 2005.

3. The Risks of Delay

3.1 Essential Use Authorizations

The Proposed Rule indicates numerous times that “[t]he [Montreal Protocol] Parties will not approve U.S. exemption requests indefinitely.”⁶⁶ At the June 10, 2004 PADAC hearing, Dr. Meyer noted that “[o]bviously, over time, there has been a ratcheting up in terms of [Protocol essential use] decisions, in terms of how closely the individual uses are looked at by the Protocol.”⁶⁷ Dr. Sullivan of FDA pointed out that

[R]ecently, the [Protocol] parties have very pointed[ly] noted the availability of two non-CFC alternatives within the U.S. and some have questioned the continued need for chlorofluorocarbons for this purpose. It is not at all clear how long the parties will continue to grant CFC requests for use in albuterol MDIs.⁶⁸

Further, in response to a question from a PADAC member as to whether the effective date could be December 2006, Dr. Meyer responded that “we cannot necessarily predict what the responses of the parties to the Montreal Protocol would be to [that] timeframe.”⁶⁹

FDA’s assessment in this regard is absolutely correct. Indeed, the frustration of the other Protocol Parties at the lack of progress in the U.S. on MDI transition was evident at the July 2004 meeting of the Protocol’s Open-Ended Working Group (OEWG). The OEWG discussed and forwarded to the November 2004 Meeting of the Parties a proposed decision on 2006 essential use authorizations that would, for the first time, withhold approval for the 70 percent of the total U.S. essential use nomination for 2006 that is for CFC albuterol MDIs.⁷⁰ Whether or not this decision is adopted by the Meeting of the Parties as drafted, it is nevertheless strong evidence that with each year of delay in phasing out CFC albuterol MDIs it will be increasingly difficult for the U.S. to obtain Protocol authorization for essential use CFCs for that purpose.

⁶⁶ Proposed Rule, 69 Fed. Reg. at 33608. See also id. at 33609, 614.

⁶⁷ Statement of Dr. Robert Meyer, 2004 PADAC Meeting Transcript at 231.

⁶⁸ Statement of Dr. Eugene Sullivan, 2004 PADAC Meeting Transcript at 56-57.

⁶⁹ Statement of Dr. Robert Meyer, 2004 PADAC Meeting Transcript at 225.

⁷⁰ United Nations Environment Programme, Report of the Open-Ended Working Group of the Parties to the Montreal Protocol on Substances that Deplete the Ozone Layer, at Annex I(A), UNEP/OzL.Pro.WG.1/24/9 (July 28, 2004).

Although FDA has appropriately pointed out the uncertainty concerning future essential use authorizations, as noted in section 2.2.4.4 above, it has neglected to factor this uncertainty into its economic analysis. This omission has led the agency to incorrectly conclude that the more that the effective date is delayed, the less the adverse effects on patients.⁷¹ In fact, the longer that FDA delays the effective date for phasing out CFC albuterol MDIs, the greater the risk that patients will be denied access to treatment due to a shortage of CFCs.

3.2 CFC Supply

GSK agrees with FDA that it should take into account the possible near-term disruption in supply of pharmaceutical-grade CFCs.⁷² The Proposed Rule notes the closing of the Honeywell's plant in Weert, Netherlands and Honeywell's plans to re-commission a plant in Baton Rouge, and expresses uncertainty that Honeywell will be able to meet its goals given that it has not produced pharmaceutical grade CFC-11 or CFC-12 since 1995.⁷³ GSK agrees that it is important for FDA to take this uncertainty into account. GSK believes that this uncertainty is heightened by the question raised by an environmental group that Honeywell's recommissioning of Baton Rouge plant may not be permitted under the Montreal Protocol and the Clean Air Act.⁷⁴

It should be noted that this uncertainty of CFC supply is separate from the uncertainty of future essential use authorizations. Put another way, even if the recommissioning of Honeywell's Baton Rouge plant is not illegal, and even if the plant is capable of producing pharmaceutical grade CFCs, the Clean Air Act would prohibit Honeywell from producing CFCs for essential uses in any year for which the Protocol Parties have not approved an essential use authorization for the United States. Section 604(d)(2) of the Clean Air Act allows production of an ozone depleting substance for an essential use only, *inter alia*, to the extent consistent with the Montreal Protocol.⁷⁵ Thus, without authorization from the Protocol, new CFC production is illegal, whether in the Netherlands or the United States.

3.3 Environmental Risks

The Proposed Rule appears to minimize the environmental risk from continued CFC emissions and resulting depletion of the stratospheric ozone layer – as well as the benefit from a near-term cessation of such emissions – simply because the incremental

⁷¹ Proposed Rule, 69 Fed. Reg. at 33607.

⁷² Id. at 33608.

⁷³ Id.

⁷⁴ Natural Resources Defense Council Letter to Docket 03P-0029 at 5-6 (May 13, 2004) (FDA Docket 03P-0029, Doc. C12).

⁷⁵ 42 U.S.C. § 7671c(d)(2).

benefit of phasing out CFC albuterol MDIs cannot be quantified.⁷⁶ However, the United States has already made the commitment under the Montreal Protocol to eliminate all uses of ozone depleting substances. FDA itself, as far back as 1978, stated that:

It is the Commissioner's goal to reduce the risks associated with chlorofluorocarbon emissions from nonessential aerosol propellant uses to the greatest extent possible and as soon as possible⁷⁷

In the past, FDA has made it very clear that it is not appropriate to consider the incremental benefit of ceasing emissions from individual sources:

[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 C.F.R. 1508.7). Significance cannot be avoided by breaking an action down into small components (40 C.F.R. 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 ODS use. If each small step were provided an exemption, the cumulative effect would be to prevent environmental improvements.⁷⁸

Having promulgated a rule based on the over-arching goal of eliminating all ozone depleting substances and which sets explicit criteria for determining when a particular use is non-essential – criteria that do not include cost/benefit analysis – FDA may not now revisit that issue.

Nevertheless, it is important to note that the Proposed Rule's estimation that only 1400 metric tonnes of CFCs are emitted annually⁷⁹ under-estimates the potential adverse effect that could result if the United States were to unduly delay phasing out CFC use in albuterol MDIs. As the Proposed Rule correctly notes, "if the United States adopts a relatively later phaseout date, other [countries] may decide to alter their own adoption of control measures. . . . Selection of a date seen to be unsuitable could have adverse

⁷⁶ Proposed Rule, 69 Fed. Reg. at 33612.

⁷⁷ Certain Fluorocarbons (Chlorofluorocarbons) in Food, Food Additive, Drug, Animal Food, Animal Drug, Cosmetic, and Medical Device Products as Propellants in Self-Pressurized Containers, 43 Fed. Reg. 11301, 11309 (March 17, 1978).

⁷⁸ Essentiality Regulation, 67 Fed. Reg. at 48380.

⁷⁹ Proposed Rule, 69 Fed. Reg. at 33610, 33614.

environmental and health consequences (e.g., if all countries interpret U.S. action as a license to consume 1,400 additional tons of CFCs per year).⁸⁰

Using FDA's own example, there are 187 countries Party to the Montreal Protocol. If each emitted an additional 1400 metric tonnes a year, as suggested by FDA's example, that would be 261,800 metric tonnes per year in additional CFC emissions. Thus, a ten year delay in phasing out CFC albuterol MDIs (i.e., from 2005 to 2010) would increase CFC emissions by a total of 2,618,000 metric tonnes; a 15 year delay (from 2005 to 2015) would increase total CFC emissions by 3,927,000 metric tonnes. To the extent that Tables 2 and 3 in the Proposed Rule will be used by FDA in its decision-making, column 6 of those tables (showing aggregate CFC emissions) should be revised accordingly.⁸¹

4. Intellectual Property Issues

The Proposed Rule states that it would welcome comments on when relevant patents will expire on HFA albuterol MDIs, given the assumption that such expirations may allow generic HFA albuterol MDIs to enter the market.⁸² The Proposed Rule indicates that the last listed patent for albuterol HFA MDIs expires in 2015 and that another listed patent expires in 2010.⁸³ GSK notes that it holds an exclusive license under U.S. Patent 6,743,413, covering certain aspects of HFA albuterol technology, which expires in 2021.

FDA acknowledges that it “[does] not have the expertise to evaluate the validity of patents” – but then adds that “it seems at least possible that key patents could be successfully challenged well before 2015 or perhaps even 2010, allowing generic drugs to enter the market much earlier than anticipated.”⁸⁴ Like FDA, GSK does not have confidence that it can evaluate with a high degree of certainty how well a patent owned by another entity will withstand potential future challenge. Therefore, GSK cannot comment on which, if any, of the relevant patents could be successfully challenged, nor on the timing of any such challenges. However, in light of the significant risks of delay discussed in section 3 above, it would be irresponsible to decide on an effective date for CFC albuterol non-essentiality based on assumptions of the status of patents that have no higher degree of certainty than “it seems at least possible”.

⁸⁰ Id. at 33614.

⁸¹ Although it could be questioned whether such a scenario is likely, it would be arbitrary and unreasonable for FDA, having suggested this scenario, to ignore it or discount it based on probability of occurrence – while at the same time basing the rest of its analysis on the equally unlikely assumption that the CFCs will be available and authorized by the Protocol Parties for any year after 2005.

⁸² Proposed Rule, 69 Fed. Reg. 33608.

⁸³ Id.

⁸⁴ Id. (emphasis added).

Moreover, other companies can enter the HFA albuterol market prior to expiration of existing device and formula patents. The active ingredient albuterol has been off-patent for over a decade.⁸⁵ Although 3M Pharmaceuticals does hold patents relevant to HFA MDIs, it has publicly stated its willingness to license its technology.⁸⁶ One company, Sepracor, apparently has taken 3M up on its offer and has just recently submitted an NDA for an HFA levalbuterol MDI.⁸⁷ Another potential entrant is IVAX, which has two approvable letters from FDA for CFC-free albuterol MDIs.⁸⁸

In both cases, these companies had to invest resources, conduct research and development, and/or enter into licensing arrangements with other companies that had already invested considerable time and resources to develop the technology. More companies may be willing to do so – unless the setting of a long-term effective date removes the incentive for companies to enter into this market.

5. Effective Date for Albuterol Non-Essentiality

The Proposed Rule states that FDA is particularly interested in receiving comments on an appropriate effective date for CFC albuterol non-essentiality.⁸⁹ At the June 10, 2004 PADAC hearing, GSK recommended an effective date of December 31, 2005.⁹⁰ GSK will have production capacity in place by December 31, 2005 to produce 30 million Ventolin HFA MDIs annually (see section 2.1.1.). Moreover, GSK will have extensive patient assistance programs (see section 2.2.1.1), as well as a comprehensive education and outreach program in place (see section 2.2.3), which should alleviate concerns about patients being adequately served. As noted in section 2.2.3 above, GSK needs only six months to fully implement its education and outreach program; thus, this is not a limiting factor.

GSK therefore continues to believe that December 31, 2005 is merited, provided that Schering Plough commits to having production capacity in place by that date to

⁸⁵ See U.S. Patents 3,644,353 and 3,705,233.

⁸⁶ See 3M Drug Delivery Systems Division, “3M Receives FDA Approval for Second HFA MDI”, available at <<http://www.3m.com/us/healthcare/manufacturers/dds/pdf/nov00newsltr.pdf>>, visited on Aug. 6, 2004.

⁸⁷ See 3M Drug Delivery Systems Division and Sepracor press release, “3M To Manufacture Xopenex HFA Metered-dose Inhaler” (Jan. 7, 2002) available at <http://www.3m.com/us/healthcare/manufacturers/dds/pdf/pr_2002_01_07_3m_to_manufacture_xopenex_hfa_metered-dose_inhaler.pdf>, visited on Aug. 6, 2004.

⁸⁸ IVAX press release, “IVAX Receives FDA Approvable Letter for Albuterol HFA in Breath-Activated Inhaler” (July 7, 2004); see also Statement of Neil Flanzraich, PADAC Hearing Transcript at 152-53.

⁸⁹ Proposed Rule, 69 Fed. Reg. at 33608.

⁹⁰ Statement of Dr. Elaine Jones, PADAC Meeting Transcript at 119.

produce at least 20 million Proventil HFA MDIs annually. Other than production capacity, GSK believes there is no reason to delay the effective date on albuterol non-essentiality. As discussed in section 2.2.4 above, there is no basis to conclude that patients will be better served with each year that an effective date is postponed. In fact, as discussed in section 3 above, there are cogent reasons to conclude that risks to asthma and COPD patients, and to the general public, will only heighten each year that the effective date is postponed.

The Proposed Rule states that it is FDA's current intention "to establish the earliest effective date that will adequately protect the public health."⁹¹ To meet that objective, GSK strongly recommends that FDA choose an effective date that is no later than the date by which both GSK and Schering Plough have committed to having production capacity ready sufficient to serve the albuterol MDI market.

6. Conclusion

GSK fully appreciates the years of effort that FDA has invested in developing a regulatory framework for addressing this unique and extremely difficult public policy issue. GSK also understands the decision facing FDA is difficult given the importance of albuterol for treatment of asthma and COPD. In view of this, GSK has also made every effort to respond to public health concerns, has made and continues to make a substantial commitment of resources in support of the transition, and strives to contribute to the process in a positive way.

GSK is a corporate steward to the US commitment under the Montreal Protocol to phase out all ozone-depleting substances, and fully supports the Protocol's objectives. Indeed, GSK has conducted a lengthy, resource-intensive, and technically difficult effort to reformulate its CFC MDIs and bring to market new chemical entities in new delivery systems such as HFA MDIs and/or dry powder inhalers (DPIs), with a total investment estimated at \$1 billion. By November 1, 2004, all MDIs manufactured by GSK in the United States will be CFC-free.

As discussed in this submission, GSK believes that FDA has the information it needs to make an informed, reasonable decision to deem CFC albuterol MDIs non-essential effective within the timeframe discussed in section 5 above. However, if FDA feels that it needs any further information, GSK stands ready to assist further in whatever way that it can.

⁹¹ Proposed Rule, 69 Fed. Reg. 33609.