Asthma Therapy Coalition

August 16, 2004

Via Hand Delivery

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
ATTN: Docket No. 2003P-0029

Re: Comments on the Proposed Rule Regarding Use of Ozone-Depleting Substances; Removal of Essential-Use Designation

To Whom It May Concern:

The Asthma Therapy Coalition ("ATC") respectfully submits these comments to the U.S. Food and Drug Administration ("FDA") in response to the Proposed Rule, 69 Fed. Reg. 33602 (June 16, 2004), which would remove albuterol-containing oral pressurized metered-dose inhalers ("MDIs") from the list of products deemed to be an "essential use" under the federal Clean Air Act. As explained further below, phasing out the use of chlorofluorocarbon ("CFC") containing albuterol MDIs before affordable generic alternatives enter the market would pose a direct threat to the needs of asthma and chronic obstructive pulmonary disease ("COPD") sufferers in the U.S. who would not otherwise have access to life-saving medications.

As an environmentally conscious organization, ATC does support the eventual transition away from ozone-depleting substances ("ODS"). However, weighing the immeasurable near-term positive effect on the environment that eliminating CFC albuterol MDIs would have in the foreseeable future and the unquestionable need of millions of patients in the U.S. for affordable rescue inhalers, ATC hopes that the Final Rule will reflect sound economic principles and ensure that Americans with asthma and COPD continue to have access to these therapies during the transition away from CFC albuterol MDIs to alternatives that are more environmentally friendly.

I. ALBUTEROL MDIs ARE EFFECTIVE AND CRITICAL TO A SIGNIFICANT POPULATION OF ASTHMA AND COPD SUFFERERS

A. Asthma

Albuterol MDIs have been proven effective in rescuing patients from asthma attacks. From 1995 (i.e., the year generic inhalers entered the market) to 2000, albuterol MDI

prescriptions climbed by more than 20% while asthma mortality declined by more than 10%.[1] According to the American Lung Association ("ALA"), close to 20 million Americans suffered from asthma in 2002 and this disease was the cause of over 1.9 million emergency department ("ED") visits in 2002 and 4,269 deaths in 2001.[2] Moreover, $2.8 *billion* dollars was spent on medication in 2002.[3] As FDA already recognizes, "[t]he proposed rule could result in increased health care expenditures of about a billion dollars for each year between the reintroduction of generic competition in this market and the selected year for removing the essential use designation."[4] Therefore, the increase in cost to the nation's health care system would be approximately 30% with no added benefit. Asthma now ranks among the most chronic conditions and one of the fastest growing diseases in the U.S. The fact that this disease is prominent and growing dramatically in the poorest segments of our country magnifies the need for FDA to maintain these affordable multi-source drug products on the market.

B. COPD

COPD is one of the leading causes of death in this country behind heart disease, certain forms of cancer, and stroke. It is believed that more than 13.5 million Americans suffer from COPD.[5] This condition affects a particularly large number of Medicare beneficiaries due to the fact that age is one of the major contributors. There is also data to suggest that living in low socioeconomic conditions also contributes to COPD.[6] The economic impact of COPD is enormous-in 2002 $18 *billion* dollars was spent in direct health care expenditures for COPD patients. MDIs are an integral part of COPD management. In fact, one of the two most common inhalation drugs prescribed is albuterol sulfate.[7]

Yet MDIs are deemed to be a type of disposable medical equipment for which no Medicare Part B benefit category exists, whereas nebulizers are considered durable medical equipment ("DME"). The new Part D benefit will cover MDIs for COPD, as of January 1, 2006. As stated by the Centers for Medicare and Medicaid Services ("CMS") stated in the Proposed Rule regarding Revisions to Payment Policies Under the Physician Fee Schedule for Calendar Year 2005:

> It would not be unlikely for many [Medicare] beneficiaries to choose the convenience of MDIs over nebulizers once the Medicare coverage imbalance is removed in 2006. Since MDIs are less expensive, very portable, and easier to use, it is likely there will be a substantial shift of Medicare beneficiaries from nebulizers to MDIs beginning in 2006, even

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[1] *Trends in Asthma Morbidity and Mortality*, American Lung Association, Epidemiology & Statistics Unit, Research and Scientific Affairs (Apr. 2004) ("ALA Report").
[2] ALA Report.
[3] *Id.*
[4] 69 Fed. Reg. at 33617.
[5] *Chronic Obstructive Pulmonary Disease,* National Institutes of Health, Publication No. 95-2020 (Nov. 1995).
[6] *Id.*
[7] The other most common inhalation drug is ipratropium bromide, which is an anticholinergic bronchodilator. 69 Fed. Reg. 47487, 47546 (Aug. 5, 2004).

> absent the Medicare payment changes for nebulizers and inhalation drugs in 2005.[8]

Note further that the Medicare program has paid a monthly $5 dispensing fee for each covered inhalation drug. In 2003 alone, Medicare spent approximately $1.6 *billion* for nebulizers and inhalation drugs alone, $1.3 billion of which was for albuterol sulfate and ipratropium bromide. The Agency has consoled itself by stating in the proposed rule that "[b]oth albuterol sulfate and ipratropium bromide are generic drugs that have multiple manufacturers" and, therefore, that pharmacies might be able to acquire them at lower-than-average prices. However, FDA's decision to prematurely remove CFC-propelled albuterol MDIs from the U.S. marketplace will turn CMS's argument on its head.

These facts raise serious concerns about increasing the cost of a critical rescue medication to the financial detriment of asthma and COPD sufferers and their families and to the federal and state governments. To the extent that sufferers would defer utilizing medications as the costs to them increase, more serious medical problems will develop. In light of the negligible environmental impact of CFCs, the reliance of millions of patients on CFC albuterol MDIs, particularly the indigent population, children, and elderly Americans on fixed incomes, and the prevalence of the disease in poorer and fixed income communities, eliminating the essential use designation without an ample transition period would be medically and socially unjustified and even irresponsible. The only alternative is one that presents a significant public health risk. ATC urges the Agency to conduct a careful and scientifically sound evaluation of the environmental, health, and economic ramifications before making a final decision regarding this major pharmaceutical transition.

II. FDA'S PHASE-OUT SCHEDULE MUST BE BASED ON SOUND ECONOMIC PRINCIPLES AND REALITIES

As the Agency is well aware, there is widespread reliance on CFC albuterol MDIs nationwide, particularly amongst pediatric patients and those with fixed incomes, such as those living in urban and rural areas. As an agency established to protect the public health, FDA's paramount obligation is to ensure that any decision made to remove albuterol from the list of ODS essential uses is based on economic realities, not theoretical platitudes. If a phase-out of CFC albuterol MDIs is inevitable, then FDA's transition must accommodate the medical needs of the U.S. asthma and COPD population.

It is undeniable that the states are having profound problems responding to escalating drug costs. In a survey[9] of state officials in the 50 states and the District of Columbia, the Kaiser Commission on Medicaid and the Uninsured found that 49 states as well as the District have implemented or planned cost containment strategies for 2004. In 2004, 43 states reported implementing pharmacy cost controls, and 39 reported reducing rate increases or freezing provider rates. Further, 21 states imposed additional or higher co-payments. Eighteen states reported instituting eligibility restrictions, and 17 restricted the availability of benefits. For many

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[8] *Id.*

[9] Kaiser Commission, *Medicaid Facts, State Fiscal Conditions and Medicaid*, Apr. 2004.

states, 2004 was the third consecutive year of Medicaid cost containment activity. Moreover, note that from the beginning of 2001 to the end of 2002, the average annual increase in prescription drug costs was 14.7%.[10] Specifically, albuterol is one of the top five most frequently prescribed drugs.[11] Driving of up the cost of this critical therapy will only serve to take money from other parts of the state Medicaid budgets.

A. Patients Will Not Be Adequately Served By Assistance Programs

According to the U.S. Census Bureau, there were over 14 million uninsured people in the U.S. in 2002 living in households with a total income below $25,000 and a total of 43.5 million Americans with no health insurance at all. GlaxoSmithKline ("GSK") has presented two drug assistance programs to the Agency: (1) Bridges to Access; and (2) a plan to provide 2 million free albuterol MDIs for physicians to dispense to asthma patients who would otherwise not have access to rescue therapies. Although these programs are examples of responsible corporate citizenship and GSK's efforts should be applauded, their scope is not near broad enough to reach sufficient numbers of uninsured and under-insured patients. We discuss these programs further below.

1. Bridges to Access Program Will Have a Limited Impact

GSK's Bridges to Access program provides free medications to qualified low-income people who pay initial co-payments. According to the figures presented at the Pulmonary-Allergy Advisory Committee Meeting held on June 10, 2004 ("Committee Meeting"), from May 2003 through May 2004, the program dispensed 100,000 MDIs to 14,000 patients so that the average patient enrolled in the program was using 7 inhalers throughout that year. Considering this number and assuming a national asthma prevalence rate of approximately 7.2%[12] among the 14 million uninsured with household incomes below $25,000, the success rate of Bridges to Access for low income and uninsured asthma sufferers is 1.4%, leaving virtually this entire group of patients having to pay out-of-pocket for their albuterol inhalers. If these individuals purchase only 7 inhalers each year at $43 per MDI, their total annual out-of-pocket expenditure amounts to approximately $300, an amount that truly does create a financial hardship to families who struggle on a daily basis to pay for food and rent.

At the Committee Meeting, the Agency raised questions regarding the pharmaceutical industry's efforts to enroll every patient who needs it in a drug assistance program. GSK explained its commitment to enroll all of those who are eligible while conceding that this is a challenge. However, it is, in fact, possible to examine the impact that continued marketing of the programs would have on enrollment in Bridges to Access. The summary below projects enrollment by 2012. In sum, if the annual enrollment rate in Bridges to Access increased 25% each year for the next eight years, then 7.9% of all uninsured with a household income less then $25,000 would be enrolled in the program.

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[10] Kaiser Family Foundation, *Medicaid Outpatient Prescription Drug Benefit: Findings from a National Survey, 2003.*
[11] *Id.*
[12] *Trends in Asthma Morbidity and Mortality*, American Lung Association, 2004.

Annual improvement in enrollment rate, %	*Enrollment rate, % **	*# enrolled (uninsured; Hh income < $25k) ***	*Increase in enrollment since 2004, %*
0	1.4	15,160	8.29
10	2.8	32,497	132.1
25	7.9	90,361	545.4
50	33.8	388,534	2675.2
72	100.0	1,149,338	8109.6

* "Enrollment Rate" can be considered the predicted success rate in 2012 based upon annual compounding of annual improvement in success rate over the 2003-2004 results given by GSK.
** Assumes population growth rate of 1%, asthma prevalence rate of 7.2% and approximately 15 million uninsured with household income < $25,000 in 2004.

These figures lead to three conclusions regarding the future success of Bridges to Access as well as other similar programs. First, without additional promotion and emphasis, Bridges to Access will provide little incremental benefit to the asthma population. Second, moderate growth in the enrollment rate from 10% to 25% will have a minimal impact on overall program enrollment. Finally, the ability to provide free MDIs to *all* of those who truly need them and who otherwise would not have access would require a 72% increase each year over the next eight years, which would obviously require a Herculean effort.

GSK has provided only its word that it is committed to this program. To the best of ATC's knowledge, there has been no communication of any action plans that lay out how the firm plans to grow the program. In the absence of tangible details as to how this program will be executed and a clear explanation of how GSK plans to provide a meaningful level of access to a significant portion of the asthma population, FDA should downplay this program as a real factor in its calculus of the final rule.

2. Free Inhaler Program Will Have A Limited Impact

The impact of GSK's program of supplying 2 million MDIs through practitioners is unknown as the company has not specified how it plans to distribute the drugs among physicians. Uninsured and under-insured patients are unlikely to see physicians in private practice and instead are often forced to go to EDs to obtain primary care.

As FDA is aware, it has long been standard practice by pharmaceutical companies to provide free samples of their products to physicians in order to encourage these doctors to write prescriptions for those products. There is no indication that the MDIs in question will be handled differently. ATC asks that FDA consider how many low-income, uninsured people seek treatment for their asthma in the physician's office rather than the emergency department. A recent Robert Wood Johnson Foundation study[13] found that almost half of the 8.5 million children who lack health insurance have not received a medical check-up in the past year. Second, the study found that one-third of the uninsured children in this country will be the recipients of routine medical care in the ED rather than from a pediatrician office visit. ATC

[13] Reuters, August 3, 2004.

doubts that it is common practice for pharmaceutical sales representatives to visit the ED to provide free samples of rescue inhalers to the patients who need them the most.

Assuming that the 2 million inhalers are distributed proportionately among patients based on the type of insurance coverage (i.e., 15.2% of MDIs dispensed among uninsured population and 7 MDIs per patient), only 1.3% of the uninsured population benefits. It would be misguided to conclude at this point that these free drugs will actually reach the patients who need them the most.

B. Price Elasticity

As FDA is well aware, the cost of health care has risen dramatically in recent years, making adequate coverage prohibitively expensive to those segments of our population who need it the most. Even with private insurance, premiums and co-payments have risen significantly because insurance companies cannot fully absorb the increasing cost of health care. According to a recent *JAMA* study, increasing the cost of asthma medications may result in significantly reduced usage of these drugs.[14]

Eliminating generic MDIs will invariably have the effect of increasing patient co-payments and third-party payor expenses. However, just as in the past, there is no guarantee that these third party payers will not *further* increase premiums and co-payments, costs that are incurred by patients and their families. In engaging in the current discourse about CFC-containing MDIs and their effects on the environment, too many commenters are narrowly focused on eliminating CFCs altogether rather than recognize that this one type of CFC product is but one minute part. This perspective also applies to a consideration of the U.S. health care system's entire expenditures. When nation-wide efforts are targeted at making healthcare more affordable and providing coverage to all Americans, how can FDA rationalize increasing the cost of life-saving medications?

The interested parties in this debate have already presented some evidence of price elasticity in albuterol MDI demand, meaning that as price increases, demand decreases. Although FDA has considered this, it has been hesitant to affirmatively state that sales of albuterol MDIs are elastic. The primary argument presented by commenters that are urging FDA to wholly eliminate CFC albuterol MDIs in an unreasonably short timeframe against an elastic effect is depicted in Exhibit 2 in the impact assessment of National Economic Research Associates ("NERA")[15], which compares unit sales for albuterol from 1992 to 2002 with selected market events.

NERA's impact assessment shows relatively flat albuterol sales since 1996, which is the year generic albuterol entered the U.S. market. In fact, unit sales dipped slightly for the two years following this market entry. This seems to lead to the obvious conclusion that a reduction in average prices attributable to generic entry had no meaningful effect on volume of the entire

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[14] Goldman et al., *Pharmacy Benefits and the Use of Drugs by the Chronically Ill, JAMA*, Vol. 291, No. 19, pp. 2344-50 (May 19, 2004)

[15] Rozek, Richard and Emily Bishko. *The Impact on Patients and Payers of Designating Albuterol a Non-essential Use of an Ozone Depleting Substance.* National Economic Research Associates, Sept. 8, 2003.

market. However, to avoid drawing a conclusion in a vacuum, it is important to consider other events occurring around that time period. Around the time that generic albuterol MDIs were launched, FDA approved several other new products. Some of these products were corticosteroids, providing a therapeutic alternative to albuterol for asthma management. These new products include: GSK's Serevent (approved February 1994), Boehringer Ingelheim's Atrovent (approved October 1995), Boehringer Ingelheim's Combivent (approved October 1996), and GSK's Flovent (approved March 1996).

As physicians began to direct patients to control their asthma by replacing beta-agonists with new alternatives, sales of albuterol may have decreased, therefore confounding any price elasticity conclusions that may be drawn. The Agency also argues that, historically, the quantity of drugs sold once generics become available does not increase in response to diminished advertising. ATC suggests that albuterol is not being highly advertised currently, nor will it be in the future. Therefore, the offsetting effect mentioned in FDA's assessment in the Proposed Rule will not actually occur. Instead, there is likely to be more of a pure price elasticity effect. ATC urges FDA to reconsider its evaluation based on this principle.

Although it is difficult to predict with any degree of certainty the change in demand in response to a price increase, even FDA agrees that fewer MDIs will be sold if the average price were to increase. At the Committee Meeting, FDA presented estimates of the number of MDIs that would be affected by an increase in price. ATC does not understand why FDA deliberately omitted the entire insured population from its analysis, when Goldman et al.[16] was specifically studying the effect on the insured population. Further, the Agency failed to include the higher price elasticity of -0.15, even though it had data from the literature indicating a range of elasticity from -0.10 to -0.20. In order for there to be a better estimation of the range of possibilities, FDA estimated 400,000 to 1 million units among the price sensitive population would not be sold. We believe that these numbers are grossly understated. Thus, ATC conducted a more thorough and conservative assessment, as there are lives at stake. In addition, the consequences for increasing price do not stop at decreased MDI consumption. Indeed, if patients forgo use of their medications, increased numbers of ED visits, hospital stays, and possibly mortalities should be expected.

ATC has evaluated the changes in annual albuterol MDI consumption, as well as the medical effects associated with decreased use. In general, increasing the amounts people spend on MDIs will:

- Decrease the total consumption of albuterol by 5.73 million units;
- Send 459,000 more people to the emergency room; and
- Place 96,000 more people in the hospital.

When a price tag is placed on these events, an *extra $1.1 billion* will be spent on medical care for asthmatics. This is *in addition to* the increased cost of MDIs. (Although ATC anticipates that a greater number of deaths that would result from decreased albuterol MDI use,

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[16] Goldman et al., *Pharmacy Benefits and the Use of Drugs by the Chronically Ill, JAMA*, Vol 291, No. 19, pp. 2344-50 (May 19, 2004)

no data in the literature is available to determine these effects). A more detailed summary of this analysis is presented in the Appendix.

III. A PREMATURE PHASE-OUT WOULD COMPROMISE THE REWARD STRUCTURE FOR INNOVATION

According to FDA, pharmaceutical companies have developed CFC-free alternative MDI products to enable the U.S. to comply with the Clean Air Act and the Montreal Protocol. Therefore, it has been a commonly held belief that the companies that have invested resources in developing alternatives be rewarded for those efforts. Many believe that the reward should be a swift transition so that they can receive the payback for developing CFC-free albuterol MDIs. By eliminating CFC-containing albuterol MDIs, drug manufacturers will increase their sales of branded products.

ATC understands that pharmaceutical companies have invested heavily to reformulate CFC-containing MDIs with propellants that are more environmentally friendly. In addition to CFC-free MDIs, dry powder inhaler ("DPI") technology has been developed. In fact, GSK has profited handsomely from its DPI product for asthma, Advair/Seretide, which was launched in 2000. In its most recent quarterly report, the company announced Advair sales of $1.1 billion, granting this product blockbuster status. Although sales of branded CFC-free MDIs have been slow due to generic competition, pharmaceutical companies have been rewarded--and no doubt will continue to be rewarded--for their innovation.

ATC recognizes the importance of eventually changing asthma management protocols so that patients are not primarily dependent on rescue inhalers. Commenters have encouraged FDA to use a transition away from CFC albuterol MDIs as a "teachable moment" to force physicians to prescribe therapeutic alternatives. However, steroids and long- acting anti-inflammatories remain prohibitively expensive to a significant portion of the asthma population. Further, it should not be necessary to raise prices in order to wean patients off of rescue medications. Physicians can and should already be doing so, and many are, at least for insured patients who can afford more costly therapies. However, there is no doubt that many insured parents are not obtaining the most appropriate medications for their dependents at this point.

Yet the parties urging FDA to effectuate a premature transition do not appear to predict a lower volume of albuterol post-transition. The bottom line is that patients and doctors should be free to choose the therapy they want or can afford. Steroids and long- acting anti-inflammatories are priced sky-high compared to albuterol, particularly for the uninsured. Not everyone can afford or wants these medications. Also, Advair, an increasingly popular drug, has been shown to cause significantly higher side effects on African American patients who comprise a significant component of the population that these physicians want to steer away from using albuterol. Moreover, it is important to note that GSK has pulled its Serevent CFC MDI off the market and is now marketing only a dry powder inhaler ("DPI") version, which helps to drive patients to its combination therapy Advair, which is also a DPI. As a result, patients are forced to take DPIs in order to obtain their long-acting drugs, and yet many have already submitted comments to this docket to express their dissatisfaction about the effectiveness of the DPI dosage form.

IV. THE MANUFACTURING CAPACITY TO PRODUCE NON-CFC INHALERS IS INSUFFICIENT TO PROVIDE AMPLE INTERIM ACCESS AND FDA's DECISION REGARDING THE TRANSITION PERIOD SHOULD BE UNAFFECTED BY THE MONTREAL PROTOCOL

The manufacturing capacity in the U.S. for the production of non-CFC inhalers is currently limited to two production facilities, one plant operated by GSK and the other by 3M for ScheringPlough ("SP"). GSK has reported to FDA that *will* have capacity to manufacture 30 million units by December 31, 2005. Although SP has not announced its capacity to produce non-CFC units, it has stated that it will take 18 months to ramp up production to an unknown amount. Although two facilities are available, it remains unclear whether one company alone has the ability to supply the entire market. This places patients at risk if one of these plants was forced to close for any reason. Although GSK's initiative to assure an adequate supply of MDIs should certainly be applauded, ATC urges FDA to not feel obligated to reward GSK for its efforts by establishing a premature transition date. Affordability and availability remain paramount. Only when the FDA has enough information to make a reliable determination of how all asthma patients who need it will have access to albuterol MDIs should FDA feel assured that that sufficient quantities can be produced to preclude a public health emergency.

One concern voiced at the Committee Meeting was future exemptions for the production of CFCs for essential uses. Paragraph 4 of Decision XV/5 from the meeting of the Parties to the Montreal Protocol states as follows:

> [N] o quantity of CFCs for essential uses shall be authorized after the commencement of the Seventeenth Meeting of the Parties if the nominating Party not operating under paragraph 1 of Article 5 has not submitted to the Ozone Secretariat, in time for consideration by the Parties at the twenty-fifth meeting of the Open-ended Working Group, *a plan of action regarding the phase-out of the domestic use of CFC-containing metered dose inhalers where the sole active ingredient is salbutamol.*

The twenty-fifth meeting of the Open-Ended Working Group is scheduled for the Summer of 2005.

ATC urges FDA to avoid being misguided by this mandate in establishing a transition date that would appease the Parties to the detriment of American public health and safety. The Parties want an action plan that takes into account the supply of products but, most importantly, accessibility for all patient populations. Other commenters to this docket have relied on the precedent of "the major developed countries," including European Union members, Japan, Canada, and Australia, in urging FDA to adopt a 2005 phase-out date. In this situation, it is irrational to compare U.S. policy to that of other Parties because our health care systems are simply not compatible. These nations have their own unique regulatory environments and market conditions. Unlike the populations of other Party nations, Americans do not benefit from price negotiations between the Federal government and the pharmaceutical companies. The high prescription drug prices that are paid in the U.S. do, in fact, subsidize research and development for new products and help keep global prices low. In responding to ATC's request, FDA can be

assured that the Parties have, in fact, acknowledged that the U.S. health care system is distinguishable and, in kind, must accept the need for the U.S. government to effectuate a plan that is commensurate with the American health care system and economy. The action plan for albuterol MDIs must be about national health and safety, rather than international political appeasement. FDA boasts a long history of independent evaluation and leadership. These issues present a prime opportunity for FDA to recognize that it is empowered to make a more rational and reasoned decision here where the alternative may create a public health emergency.

V. THE COST OF A PREMATURE FDA DECISION TO BAN CFC ALBUTEROL MDIs WOULD FAR OUTWEIGH THE ENVIRONMENTAL BENEFITS

Banning CFC albuterol MDIs in the U.S. will bring negligible benefit to the environment relative to other types of CFC and other ODS products. As is well known, CFCs are considered to be detrimental to the ozone layer because they release chlorine to the stratosphere, which then destroys stratospheric ozone. Therefore, scientists monitor the stratospheric chlorine levels (or loading) in order to track trends regarding stratospheric ozone depletion/recovery. Although the Montreal Protocol has been quite effective in reducing ODS production, stratospheric chlorine loading is not expected to reach even close to the targeted level for another half century. Even if all CFC albuterol MDI production were eliminated *this year*, it would only reduce stratospheric chlorine loading by an imperceptible amount so that the stratospheric chlorine loading will still not near the targeted level for another half century. Delaying the cessation of all CFC production for albuterol MDIs in the U.S. for another decade would add, at most, *a few days* onto the half-century it would already take for the environment to recover. Therefore, the net public health effect of removing albuterol CFC-containing MDIs in the near term would be to reduce stratospheric chlorine levels by an amount that is unlikely to be measurably perceived.[17] In other words, allowing affordable generic albuterol MDIs to remain on the U.S. market until generic alternatives of non-CFC inhalers are permitted to enter the U.S. market for a decade would cost the environment a mere few days *in addition to* the half century it will already take for the ozone layer to recover.

This imperceptible near term environmental impact would be more than countered by the detrimental medical impact in the event FDA takes the alternative course, namely removal of *all* CFC albuterol inhalers from the U.S. marketplace, which poses a significant and near immediate threat to the health of a significant population of asthma sufferers, particularly children and patients in poor communities. These products retail for approximately $20 less per inhaler than brand MDIs using non-CFC propellants.[18] Furthermore, FDA has already acknowledged in the preamble to the proposed rule that the removal of generic MDIs would raise the cost of asthma treatment by $1 billion annually until the hydrofluoroalkane ("HFA") alternatives, Ventolin® HFA and Proventil® HFA, will come off patent and companies currently marketing CFC albuterol MDIs may be able to re-enter the market with low-cost alternative products.[19] Of far

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[17] *See* United State Environmental Programme/World Meteorological Association Scientific Assessment of Ozone Depletion (July 31, 2002); Alternative Fluorocarbon Environmental Acceptability Study ("AFEAS"), Production and Sale of Fluorocarbons (2003).

[18] http://www.drugstore.com/pharmacy/prices/drugprice.asp?ndc=00173032188&trx=1Z5006

[19] *See generally* 69 Fed. Reg. at 33605.

greater concern is the unavoidable consequence that clearly this ban would dramatically increase the costs of rescue inhalers.

VI. A PREMATURE BAN ON CFC ALBUTEROL MDIs WOULD BE AN UNPRECEDENTED SWITCH FROM PRIMARY RELIANCE ON A GENERIC PRODUCT TO A BRAND PRODUCT

As ATC already urged the Agency to recognize in the comments it submitted to this docket on April 7, 2004, a decision to ban CFC albuterol MDIs without a sufficient transition period would fly in the face of the Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Amendments"). This argument bears repeating. According to FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" ("The Orange Book"), eight albuterol MDIs are marketed under approved new drug applications ("NDAs") (i.e., 4 brand products) or abbreviated NDAs ("ANDAs") (i.e., 4 generic products). A ban on CFC albuterol MDIs will leave asthma sufferers to rely on the significantly more expensive but *only* non-CFC rescue inhaler alternatives available in the U.S. market--Ventolin® HFA and Proventil® HFA. This action would present an unprecedented switch from primary reliance on a generic product to a branded product and would be inconsistent with the Agency's undeniable mandate under the Hatch-Waxman Amendments[20] to promote the affordability of drugs by increasing the availability of generic drugs.[21] In an era where this statute has wholly redefined the dynamics of the pharmaceutical marketplace to enable access to more affordable therapies, a transition towards brand reliance has become unprecedented regulatory reversal that artificially interferes with the normal life cycle of a given drug. Hindering access to lower cost asthma therapies will spur a tremendous financial ripple effect, not to mention the unquantifiable cost of human life. Alternatively, the U.S. healthcare system could spend the same billions of dollars in more impactful areas, including asthma *research and prevention.*

As the Agency has acknowledged, cost must be a significant factor in making all of its decisions.[22] Without due consideration to cost here, FDA would not be making a legally sound decision. In this situation, the negligible benefit that reducing CFC emissions from MDIs might have on the environment would not outweigh the public need to curb the cost of effective therapies that are critical to disease management, particularly for asthma sufferers in the nation's poor and minority communities, particularly where the federal, state and local governments are the payors, directly or indirectly.

It is important to understand the difference between essential use allowances and essentiality. FDA has, in the past, declared products essential without giving them essential use allowances. Therefore, the Agency could set two dates as part of the rulemaking: a date for which essential use allowances will no longer be approved and a different date of essential use designation. There is no reason why the two dates have to be the same and, in fact, it is detrimental to patients to do so, as any unused, but perfectly good CFC albuterol MDIs could no longer be marketed after a certain date. For example, the FDA could declare albuterol non-

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[20] Public Law 98-417 (1994).

[21] *See* Mark B. McClellan, M.D., Ph.D., FDA Commissioner, speech before Food and Drug Law Institute (Apr. 1, 2003).

[22] *See,* McClellan speech, *supra.*

essential in 2012, while no longer approving allowances after 2009. This would allow manufacturers, wholesalers, and retailers/hospitals to use up the supply of inventory of low-cost CFC-made products in order to maximize the benefit to patients.

Essential Use Allowances are normally approved by the Montreal Protocol two years in advance of the control period in question. A notable exception is this year, where essential use allowances approvals for albuterol have been delayed to motivate parties to finalize albuterol phase-out plans. FDA should do everything possible to minimize patient impact by declaring a phase-out date that minimizes the time to entry of generic versions. On the other hand, if the Montreal Protocol decides essential use allowances will no longer be granted, then the Agency and industry will have ample notice to respond accordingly, as they have stated that they could be operational within 18 months of a noted transition time.

Therefore, the ATC submits that albuterol should be considered essential until 2016, with the proviso that essential use allowances be allowed until either the Montreal Protocol does not approve them or the impact to patients has decreased to an acceptable level, as measured by use of patient assistance programs and competitive pricing. FDA needs this flexibility in order to fulfill its mandate to protect the public health.

VII. CONCLUSION

As FDA is aware, through the transition period, the only non-CFC alternatives available in the U.S. would be Ventolin® HFA and Proventil® HFA, which must come off patent before generic alternatives may re-enter the market. There was discussion at the Committee Meeting suggesting that there could be a third NDA approved for albuterol as IVAX obtained an approvable letter on July 6, 2004, and possibly more competition as a result. FDA should note that on June 19, 2003, Neil Flanzraich, Vice Chariman and President of IVAX, addressed shareholders about the firm's albuterol product: "We will be one of a very few number of players in a very large and important market. We think we are going to capture the largest part of what will then be a $2 billion market, and that is not too far away". Clearly, IVAX is viewing this product as a $40 per inhaler (i.e., 50 million inhalers at $40 per = $2 billion) and not a low-cost generic.

A ban on CFC albuterol MDIs should be no sooner than affordable generic alternatives enter the U.S. market. A premature phase-out would be unworkable because it would fail to provide a reasonable amount of time for manufacturers of CFC inhalers to redirect their research and development and marketing efforts towards the development of alternative products for marketing, pull products with post-2005 expiration dates, and recoup significant expenditures already spent in reliance on a supposed ability to market these MDIs for years to come.

The establishment of an unreasonably short transition period would constitute arbitrary and capricious administrative action in violation of the Administrative Procedure Act.[23] If the Agency acts prematurely, the damage will not be easily remedied.

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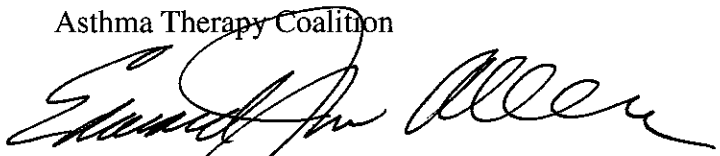
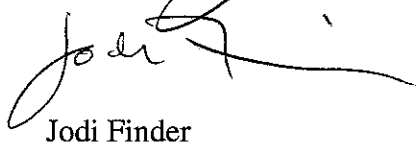
[23] 5 U.S.C. § 706(2)(A).

Respectfully submitted,

Asthma Therapy Coalition



Edward John Allera



Jodi Finder

cc: Wayne Mitchell, Regulatory Counsel, Office of Regulatory Policy
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APPENDIX

Changes in Annual MDI Usage among Asthmatics by Insurance Type

	% Population[1] (A)	# MDI Usage[2] (B)	% Decrease in MDI Usage[3] (C)	Decrease in MDI Usage[4] (D)
Uninsured	15.2%	6.8M	15.0%	1.03M
Private Insurance	69.6%	31.3M	15.0%	4.70M

Changes in Annual Emergency Department (ED) Visits among Asthmatics by Insurance Type

	# ED Visits[5] (E)	% Increase ED Visits / % Decrease in MDI Use[6] (F)	% Increase in ED visits[7] (G)	Increase in ED Visits[8] (H)	Added Cost[9]
Uninsured	288,800	5.40	81%	234,000	$94M
Private Insurance	1,322,400	1.13	17%	225,000	$90M

Changes in Annual Hospital Discharges (HD) among Asthmatics by Insurance Type

	# HD[5] (E)	% Increase HD / % Decrease in MDI Use[6] (F)	% Increase in HD[7] (G)	Increase in HD[8] (H)	Added Cost[9]
Uninsured	69,000	6.17	93%	64,000	$620M
Private Insurance	316,000	0.67	10%	32,000	$307M

[1] From *Health Insurance Coverage in the United States: 2002*. U.S. Census Bureau, September 2003

[2] Total MDI usage is approximately 45 million units

[3] From Goldman et al., *Pharmacy Benefits and the Use of Drugs by the Chronically Ill*, *JAMA*, Vol. 291, No. 19, pp. 2344-2350 (May 19, 2004).

[4] (D) = (B) x (C)

[5] 1.898M annual ED visits and 454,000 HDs (from *Trends in Asthma Morbidity and Mortality*, American Lung Association, Epidemiology & Statistics Unit, Research and Scientific Affairs (Apr. 2004) "ALA Report) x (A)

[6] Changes in MDI Use, ED visits and HDs for uninsured population from *Adverse Events Associated With Prescription Drug Cost-Sharing Among Poor and Elderly Persons*. Tamblyn, et al. JAMA January 24/31, 2001 - Vol 285, No.4 pp 421-429.

Changes in MDI Use, ED visits and HDs for private insurance population from Goldman et al.

[7] (G) = (C) x (F)

[8] (H) = (E) x (G)

[9] Average cost per ED visit is $402. Average cost per HD is $9,708 (ALA Report)