

COMMENTS OF THE
US STAKEHOLDERS GROUP ON MDI TRANSITION

TO THE NOTICE OF PROPOSED RULEMAKING
ON THE NON-ESSENTIALITY OF CFC-CONTAINING
SINGLE MOEITY ALBUTEROL MDIs

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About the US STAKEHOLDERS GROUP ON MDI TRANSITION

In 1996, at the request of the U.S. Environmental Protection Agency, the American Lung Association (ALA) invited patient and medical professional organizations to convene a process for advising the international effort to eliminate ozone-depleting chemicals in metered dose inhalers (MDIs). Over the past eight years, these nine organizations, collectively known as the US STAKEHOLDERS GROUP ON MDI TRANSITION, have met regularly with the goal of ensuring that transition to CFC-free MDIs properly balances the threat to public health posed by stratospheric ozone depletion with the needs of patients who rely on inhaled therapies.

Members of the US STAKEHOLDERS include the following organizations:

Allergy & Asthma Network Mothers of Asthma (AANMA), founded in 1985, is a nationwide community-based nonprofit health organization dedicated to eliminating suffering and death due to asthma and allergies through education, advocacy, community outreach, and research. AANMA provides information and services to the public on asthma through its publications (*Allergy & Asthma Today* and *The MA Report*), e-news updates, a toll-free help line, community awareness programs, and an interactive website, *Breatherville, USA*.™ AANMA advocates for patient access to specialty care and appropriate treatments, promotes the importance of a school nurse in every school, and has been a leading proponent of students' rights to carry and self-administer asthma and anaphylaxis medications while at school.

The **American Academy of Allergy, Asthma and Immunology (AAAAI)** has more than 6,000 members who are practicing allergist/immunologists and allied health professionals. AAAAI publishes the peer-reviewed journal *The Journal of Allergy and Clinical Immunology*, which helps the Academy achieve its mission in the advancement of the knowledge and practice of allergy, asthma, and immunology for optimal patient care.

The **American Academy of Pediatrics (AAP)** represents 60,000 pediatricians, pediatric medical subspecialists, and pediatric surgical specialists dedicated to the health, safety and well-being of infants, children, adolescents and young adults. The **Section on Allergy and Immunology** is one of many medical subspecialty sections at the AAP with a membership of approximately 400 board-certified allergist-immunologists whose mission it is to ensure pediatric-aged patients receive the highest quality of care in allergy, asthma, and immunology. To accomplish its mission, the Section provides a number of educational, training and research programs, and continually advocates for improved allergy and immunology care and services. The Section's educational endeavors include a Speaker's Bureau, Pediatric Speaker's Kit on Asthma, Visiting Professor Program, Pediatrics Supplement on asthma, allergy, and immunology, and an electronic quality improvement in practice program. The Section authors brochures and other publications for parents and families such as the *Guide to Managing Allergies and Asthma*.

The **American Association for Respiratory Care (AARC)** is a not-for-profit professional organization consisting of 35,000 respiratory therapists, physicians and other healthcare professionals. Established in 1947, the AARC is dedicated to ensuring that persons with respiratory diseases receive safe and effective respiratory care. The AARC encourages and promotes professional excellence, advances in the science and practice of respiratory care, and serves as an advocate for patients, their families, the public, and the profession on health issues impacting respiratory care. The AARC produces *Respiratory Care Journal*, a peer-reviewed, scientific journal, in addition to a monthly magazine and various publications.

The **American College of Allergy, Asthma and Immunology** (ACAAI) is dedicated to the clinical practice of allergy, asthma, and immunology through education and research. The College is comprised of 4,000 qualified allergists-immunologists and related health care professionals. The College publishes the peer-reviewed journal *The Annals of Allergy, Asthma & Immunology* and provides information and news for patients, parents of patients, the news media, and purchasers of group health care programs.

The **American College of Chest Physicians** (ACCP), founded in 1935, currently has over 16,000 members, including physicians, surgeons, allied health professionals, and individuals with Ph.D. degrees who specialize in diseases of the chest: pulmonology, cardiology, cardiovascular and cardiothoracic surgery, hypertension, critical care medicine, and related disciplines. Medical professionals must meet stringent requirements to be granted admission into the College, and are recognized leaders in their respective disciplines. The ACCP publishes the peer-reviewed journal *CHEST: The Cardiopulmonary and Critical Care Journal*, reaching nearly 23,000 people worldwide.

The **American Lung Association** (ALA) was founded in 1904 to fight tuberculosis, making it the oldest voluntary health organization in the United States. ALA continues to fight lung diseases, with special emphasis on asthma, tobacco control, and environmental health. ALA reaches the general public through a wide variety of published materials, grants and awards, communications, outreach and training programs, and advocacy to promote clean air and the development and enforcement of laws and regulations related to lung health.

The **American Thoracic Society** (ATS) is an independently incorporated, international, educational, and scientific society that focuses on respiratory and critical care medicine. Founded in 1905, the approximately 13,500 ATS members help prevent and fight respiratory disease around the globe through research, education, patient care, and advocacy. The American Thoracic Society produces the annual International Conference for over 14,000 attendees, which serves as an international forum for physicians and scientists who work in pulmonary and critical care medicine. The Society also publishes two peer-reviewed journals, the *American Journal of Respiratory and Critical Care Medicine* and the *American Journal of Respiratory Cell and Molecular Biology*, and sponsors annual courses in respiratory epidemiology in Central and South America.

The **Asthma and Allergy Foundation of America** (AAFA), founded in 1953, is a not-for-profit national network of 12 chapters that work with volunteers, health care providers, government agencies, and local leaders to improve the quality of life for people with asthma and allergies and their caregivers through education, advocacy, and research. AAFA sponsors research grants and educational support groups, and advocates for the development and implementation of public policies that improve the quality of life for people with asthma and allergies. AAFA national toll free information line offers support and referrals to more than 7,000 people each year.

Collectively, the member organizations of the US STAKEHOLDERS GROUP represent and reach more than 25 million Americans who suffer from asthma and other respiratory diseases. These nine organizations, many with local chapters and affiliates, are relied on by individual patients and their families for education, advocacy and care. The physicians, respiratory therapists and other healthcare professionals represented by member organizations are recognized as leaders in their fields. The STAKEHOLDERS GROUP, and its individual members, collaborates with various organizations in the U.S. and around the world, including for

instance, the National Medical Association, the COPD Coalition and the European Asthma Federation. Two member organization representatives to the GROUP, Dr. Adam Wanner of the American Thoracic Society (ATS) and Dr. Albert Sheffer of the American Academy of Allergy, Asthma and Immunology (AAAAI), serve on the United Nations Aerosols Technical Option Committee (ATOC).

In the eight years since the GROUP has acted formally, neither its membership nor its procedures have changed. American Lung Association convened the group, and Fran Du Melle, previously with American Lung Association, now with the American Thoracic Society, coordinates STAKEHOLDERS communications. The member organizations select representatives to the STAKEHOLDERS process, and these individuals meet once or twice a year in person, and communicate regularly. In addition, representatives from government and industry often are invited to make presentations to the GROUP, and other leadership of member organizations periodically attend information sessions and/or participate in deliberations. Formal positions taken under the STAKEHOLDERS signature are approved by member organizations.

Activities and Positions of the US STAKEHOLDERS GROUP

Over the past eight years, the STAKEHOLDERS have provided expertise to international and domestic U.S. decisionmaking bodies, including the following statements and positions¹:

Criteria for a Smooth Transition (June 1996)
Comments to TEAP (August 1996)
Comments on FDA's NPRM (May 1997)
Letter to Open-Ended Working Group (September 1999)
Comments on FDA's NPR (November 1999)
Letter to Open-Ended Working Group (July 2000)
Statement to Twelfth Meeting of the Parties (September 2000)
Comments to Open-Ended Working Group (July 2002)
Statement to Fourteenth Meeting of the Parties (November 2002)
Citizen's Petition to Consider Albuterol Non-Essentiality (January 2003)
Comments to Open-Ended Working Group (July 2003)
Statement to Fifteenth Meeting of the Parties (November 2003)
Comments to ATOC (March 2004)

Taken together, these statements demonstrate the STAKEHOLDERS' long-standing commitment to achieving transition. Over the past eight years, STAKEHOLDERS have supported the development of national transition strategies, enhanced collection of data to support decisionmaking, and measures to guard against unauthorized use of CFCs obtained through the essential use exemption process. We repeatedly have called for a "clearly defined timeframe" because we believe that transparency is the proper mechanism for protecting patients, ensuring fairness to both CFC and HFA manufacturers, and rewarding manufacturers who have demonstrated commitment to reformulation and transition in advance of formal requirements to do so. From inception, we have called for: transition to be accomplished between the patient and physician, not at the pharmacy level; patients, physicians, providers

¹ Each of these documents is available for download at www.inhalertransition.org ("About the US STAKEHOLDERS GROUP").

and payers to be properly educated about transition before it begins; and FDA to monitor implementation.

It is true that when the STAKEHOLDERS GROUP formed in 1996, we regarded stratospheric ozone depletion primarily as an environmental problem. Although we recognized the positive health benefits associated with reduced ozone layer destruction², our interest was in ensuring patient access to needed MDI therapies. We chose to embrace -- not challenge -- the eventuality of CFC elimination, but our support for ozone layer recovery did not mean that the environmental imperative could or should be pitted against the right to life-saving drugs. Over the past decades, as alternative propellants were identified and later, as safe and effective CFC-free alternatives were commercialized in both developed and developing countries, our interest in achieving transition became more pressing. CFC manufacture cannot be relied on indefinitely and we see unmistakable agreement on ozone layer recovery.

The STAKEHOLDERS embraced the December 31, 2005 end date for the essential use exemption process when first proposed by the Montreal Protocol Parties. Information we received from manufacturers, physicians and patients in the U.S. and other countries confirmed the Protocol's Technical and Economic Assessment Panel (TEAP) 1994 conclusion that there could be a major reduction in the use of CFCs in MDIs by 2000, with an absolute end by 2005. As we learned more about the costs of implementing transition in the U.S. and elsewhere, we came to understand that transition might not happen in the U.S. without further regulatory action and/or Protocol level measures. More recently, as developed countries began to meet the voluntary goals first outlined in 1994 and as the issue of CFC supply heightened, we became increasingly concerned about U.S. patients' continuing reliance on chemicals that were slated for elimination. It is in that spirit we petitioned the U.S. FDA to publicly consider the risks to U.S. patients if transition was not properly planned and launched.

The STAKEHOLDERS' January 2003 Petition to Consider Albuterol Non-Essentiality

Pursuant to FDA's issuance in June 2002 of a Final Rule outlining the criteria for removing specific drug moieties from the list of those eligible to use CFCs, the STAKEHOLDERS GROUP in January 2003 petitioned the Agency to consider albuterol MDIs. The STAKEHOLDERS' Petition asserted that with respect to albuterol, FDA's essentiality criteria already had been met, or could be met, such that it was time for FDA to initiate rulemaking to consider removing the essential use designation.

The STAKEHOLDERS had three primary motivations for initiating the Petition. First, we were and remain concerned about reliable, uninterrupted future supply of pharmaceutical-grade CFCs, not just for albuterol but for every drug product, some of which may never be reformulated to HFA. Second, we support the environmental goal of ozone layer repair, and understand that the Montreal Protocol Parties will not indefinitely authorize the use of CFCs in MDIs. Finally, we believe that transition presents a specific opportunity to improve patient outcomes, if managed by the patients' physician and not at the pharmacy level. Fundamentally, the STAKEHOLDERS' interest is in a transparent and orderly transition, with a timeline set by

² Abundant evidence points to the public health risks associated with CFCs. See, e.g., de Gruijl, Longstreth, et. al., "Health effects from stratospheric ozone depletion and interactions with climate change." *Photochemical and Photobiological Sciences*, Vol. 2, No.1 (January 2003).

FDA not the Parties to the Montreal Protocol, and in achieving transition before availability of or access to CFCs has an impact on the supply or price of any MDI product.

Future CFC Supply

The STAKEHOLDERS' concern over future CFC supply is well-founded. Almost three years have passed since the Dutch ordered the 2005 closure of Honeywell's CFC manufacturing plant in Weert – the last remaining source of pharma-grade CFCs in the world. Until April 24, 2004, when Honeywell submitted a letter into the FDA docket, there had been no publicly announced commitments regarding a new source of pharma-grade CFCs after December 31, 2005. Despite Honeywell's stated intent to recommission the Baton Rouge facility, as FDA indicates in the NPR³, there is no conclusive evidence that the company can reliably produce adequate quantities of pharmaceutical grade CFC-11 and CFC-12.⁴

In addition to the technical uncertainty noted by FDA in the NPR, legal questions also have been raised. On May 13, the Natural Resources Defense Council, a nongovernmental environmental advocacy organization, charged in a letter to EPA Administrator Leavitt that recommissioning the Baton Rouge site would violate the Montreal Protocol and the U.S. Clean Air Act. At a July meeting of the Montreal Protocol's Open Ended Working Group, the issue was raised for the first time as to whether the reported re-opening of CFC production in the U.S. was in line with previous Protocol decisions.⁵

Like FDA, the STAKEHOLDERS do not know whether Honeywell will ultimately prevail. We add though, that the issue of whether new CFCs will be available after December 31, 2005 is of critical importance for *all drugs*, not just albuterol. If no pharma-grade CFCs can be produced after December 31, 2005, quantities obtained from Weert plus remaining stockpiles must suffice

³ "Use of Ozone Depleting Substances: Removal of Essential Use Designations, 69 Fed. Reg. at 33602, 33614 (Jun 16, 2004) ("NPR").

⁴ FDA does not detail in the NPR all of the questions that have been raised about the Honeywell facility. For example, the STAKEHOLDERS have been made aware that there is doubt even about whether pharma-grade CFC-11 has ever been produced at the site. For some time, we have understood also that there are industry-wide concerns about stability issues in MDIs manufactured via the "liquid-phase" process, used in Baton Rouge but all but abandoned elsewhere. This is of particular concern to us if patients are to rely on Baton Rouge as the *sole source* of pharma-grade CFCs after December 31, 2005. Additionally, we understand that production of pharma-grade CFCs in Baton Rouge would be "periodic" (also known as "swing" production), which calls for extensive cleaning of the equipment to make sure that all traces of previous production – feedstock, products and by-products – are completely removed. Our understanding is that only one of the traditional sources of medical grade CFCs has been a swing plant, so we would expect that as part of the certification process, FDA would seek proof of adequate cleaning/switch-over procedures. Finally, we refer to the several serious safety violations that have occurred at this site in the past eighteen months, including a worker fatality which led to temporary closure of the plant. Again, the STAKEHOLDERS have neither full information nor the expertise to assign a level of confidence to Honeywell's stated intent. But taken together, we believe the evidence warrants carefully scrutiny by FDA of the Baton Rouge facility and the likelihood that CFCs will be available from there after December 2005.

⁵ The Protocol Parties never have been asked to interpret their Decision VII/9 regarding the prohibition against commissioning or installing new production capacity. As per above, we do note however, that questions have been raised as to whether pharma-grade CFC 11 has *ever been produced* at the site, at least raising the possibility that the Parties would interpret its production in Baton Rouge to be new capacity.

for albuterol until transition is completed, and, for 14 other CFC-containing moieties until suitable alternatives are available. Given the critical importance of CFCs to patients who rely on all MDI therapies, we believe it is incumbent upon FDA, if setting the effective albuterol phaseout date after December 31, 2005, to have reasonable evidence that Honeywell can technically meet pharma-grade specifications and prevail legally.⁶

Future Access to CFCs

Even if Honeywell is able to recommission the Baton Rouge facility, there is still the matter of how long the Montreal Protocol Parties will authorize the U.S. to produce new CFCs for albuterol. As FDA points out in the NPR, the temporary exemption for MDIs has been of particular interest to the Parties and the subject of repeated decisions promoting its closure. The Parties have considered but not adopted decisions limiting the use of CFCs for albuterol after 2005 and in MDIs generally after 2007. As we know, the U.S. nomination for 2006 currently under consideration will be reviewed again next year pending the outcome of this rulemaking.

The STAKEHOLDERS for many years have tracked the international commitment to eliminate ozone-depleting substances. Repeatedly, we have voiced our concern over dependence on chemicals whose future use and access carries so many uncertainties. Twelve years have passed since the Parties to the Montreal Protocol established the essential use exemption process, and developed countries are meeting or exceeding voluntary timetables to eliminate CFC MDIs. CFCs for MDIs is the *last remaining private sector essential use*. With safe and effective alternatives in use around the world, it is reasonable for FDA to assume that there is sufficient political will to close the essential use exemption for MDIs, even if we cannot pinpoint the exact date the Parties will act. Therefore, the STAKEHOLDERS believe that when assessing the risk that future Protocol decisions will impact the sale of specific MDI products in the U.S., it is prudent for FDA to assume that the Parties will take decisions to limit, and eventually deny, essential use nominations for albuterol, beginning next year when they reexamine the 2006 nomination.

Valuing the Environmental and Health Aspects of Transition

FDA in the NPR requests comments on how to further analyze the environmental benefits of its proposed action, and how to compare the health benefits of reduced UVB radiation with possible negative impacts of reduced access to inexpensive generic albuterol.⁷ As an initial matter, the STAKEHOLDERS GROUP would like to reiterate its longtime support for the environmental objective of ozone layer repair. Despite MDIs' seemingly small contribution to the overall problem, we understand the cumulative nature of ozone destruction, and the indivisibility of all CFC uses. On this point, we refer to the discussion in FDA's 2002 Final Rule,

⁶ At a minimum, the STAKEHOLDERS would hope that FDA will seek formal written responses to NRDC's charges from both EPA and Honeywell. Given the importance of CFC supply to users of all CFC-containing therapies, perhaps it also would be appropriate for the U.S. to request the treaty's legal advisor to issue an opinion on whether the reported recommissioning of production in the U.S. is in line with previous Protocol decisions.

⁷ NPR at 33614.

explaining why the environmental impact of individual essential uses cannot be evaluated independently.⁸

With that discussion in mind, we respectfully question the extent to which further analysis of the incremental environmental benefit is relevant to choosing a date for albuterol transition. If as FDA's 2002 Rule states "significance cannot be avoided by breaking an action into small components," we cannot understand how significance could be found by seeking to quantify impacts from one specific moiety, albuterol, or the minute difference in impacts of two different dates, one or two years apart.

We would ascribe the same pointlessness to comparing the health benefits of reduced UVB radiation with possible negative impacts of reduced access to inexpensive generic albuterol, as if it were possible to tradeoff mortalities between asthma and melanoma. This is not to suggest possible negative health impacts of transition are unimportant – they are, and steps must be taken to moderate patient impact. But we believe the matter is resolved as to whether or not CFC albuterol and other MDIs will be phased out. We also point out that FDA has not included in the NPR any discussion about the possible health benefits of eliminating CFC-containing inhalers.⁹ Regardless, at this point in time, the issue of picking the optimum date has little to do with virtually impossible-to-quantify health and environmental benefits, and much to do with political considerations about CFC supply and availability, and with practical questions about when manufacturers will have sufficient HFAs available.

The five year FDA rulemaking process to establish essentiality criteria considered whether, why, and under what conditions CFC-containing MDIs would be removed from the market. With the 2002 Final Rule in place, the setting of a precise effective date is less an environmental or health matter as it is an administrative one, albeit with significant political and economic implications. In the matter at hand, FDA foremost must make judgments about how long CFCs will be reliably manufactured and available, and how the continued use of CFCs in albuterol might affect other drug products. Thereafter, FDA must determine when there will be adequate manufacturing capacity of HFA albuterol MDIs, what period of time after issuance of the Final Rule is sufficient to develop and deploy an educational campaign, and what safeguards are adequate to ensure patients can access and afford albuterol.

Transition as an Opportunity to Improve Patient Outcomes

In our earliest meetings, we identified transition to HFA albuterol as a unique opportunity for patient and physician education. First, albuterol is the only moiety used by patients with different types of asthma -- mild, moderate or severe – so any outreach associated with transition has the potential to reach the vast majority of people with asthma and COPD. Second,

⁸ Use of Ozone-Depleting Substances: Essential Use Determinations, 67 Fed. Reg. 48370, 48380 (Jul. 24, 2002) ("Final Rule").

⁹ For instance, STAKEHOLDERS for many years have heard anecdotally that FDA has collected evidence about possible links between CFCs in inhalers and paradoxical bronchospasm. While we understand no clear link has been established, we also understand that FDA has used the occasion of reformulation to significantly tighten the specifications on the various compounds found in the device, especially extractibles from the elastimers. We are not claiming that CFC-containing MDIs is a bad technology, only that HFA technology potentially will be an improvement for patients, many of whom use MDIs over their lifetime.

we feel strongly that transition needs to occur at the physician level so that the switch from CFC to HFA albuterol can provide a specific occasion for doctors to review and improve asthma care plans for their patients. Given our sense that education more than anything improves patient adherence with treatment plans, transition offers the opportunity for doctors to educate patients about adhering to their disease treatment plan, including taking simple steps for minimizing exposure to their asthma triggers and the importance of utilizing their maintenance medications, and to evaluate over-reliance on rescue medications. Finally, we saw that transition could provide an opportunity to increase usage and familiarity with treatment guidelines, especially among non-specialty physicians. There have been significant advancements in asthma therapy since the National Asthma Education and Prevention Program first published treatment guidelines in 1991. The STAKEHOLDERS are committed to working with the NAEPP and the range of organizations that educate physicians so that they are well-equipped to maximize the opportunity afforded by the switch to HFA.¹⁰

The Incremental Costs of Eliminating CFC Albuterol MDIs

Like FDA, the STAKEHOLDERS have struggled with the fact that HFA albuterol will cost more than the CFC albuterol it replaces. Early on, we had hoped that momentum to phase out all CFC MDIs would result in HFA alternatives being priced only modestly higher. In our Comments to FDA's Notice of Proposed Rulemaking, we called for FDA to make "comparable" pricing a consideration for removing the essentiality designation. As HFA alternatives came into use around the world and the future of CFCs became more questionable, the STAKEHOLDERS petitioned in part to gain a better appreciation of the costs associated with Montreal Protocol compliance. We appreciate FDA's thoughtful discussion in the NPR as to how the increased price of HFA inhalers might potentially impact insurers, providers, purchasers and consumers. Together with the report submitted into the docket by National Economic Research Associates (NERA),¹¹ we believe FDA's analysis is sufficient to inform the choice of a precise effective date for albuterol non-essentiality.

We understand from FDA's analysis in the NPR that transition in the albuterol market will result in significant transfers to branded pharmaceutical manufacturers from third-party payers, patients and others in the chain-of-distribution. Despite increased costs to the healthcare system generally, we agree with FDA that the price difference between HFA and CFC MDIs would not be so large as to deny large numbers of people access to therapy. Our reading of FDA's analysis suggests that because demand for prescription medicines is generally inelastic, only a small fraction of the total annual albuterol purchases may be foregone, perhaps 1 million out of a 50 million canister market.¹² That implies that on the individual patient level, the cost of HFA albuterol, like the costs of countless other branded products, will be distributed among

¹⁰ For example, through the American Lung Association, the STAKEHOLDERS developed a brochure, "Stepwise Approach to CFC-Free Management of Asthma." Available for download at www.inhalertransition.com (What Physicians Need to Know), the *CFC-Free Stepwise* brochure helps physicians and other caregivers identify specific CFC-free products for treating disease according to the NAEPP guidelines.

¹¹ See National Economic Research Associates, Inc. "The Impact on Patients and Payers of Designating Albuterol a Non-Essential Use of an Ozone-Depleting Substance" at 11-12 (September 6, 2003) (FDA Docket No. 03P-0029) (including a concise description of the vertical market for albuterol MDIs.)

¹² NPR at 33616: "This research suggests that any effect on consumption by the removal of generic albuterol MDIs may be quite small."

various intermediate points in the chain of distribution.¹³ As FDA's analysis finds, for the majority of patients -- close to two-thirds of albuterol users have prescription drug coverage -- the price increase will be moderate, less than \$50 per year, and mostly due to increased co-pays.¹⁴ An additional 15 percent of albuterol users who currently receive their medication free of charge will not be affected at all by transition. For these reasons, we believe FDA reasonably could have reached no conclusion other than that patients will be adequately served by HFA alternatives.

Despite this, the STAKEHOLDERS still have concerns about how transition might impact public health. First, we point out that there may be patients for whom paying higher costs, even in the form of increased co-pays, may result in reduced use of medication.¹⁵ Second, we are uneasy about how cost increases for albuterol might affect purchases of other needed medications. Finally, we note that there may be unintended consequences as a result of additional stress on the U.S. healthcare system generally. Unfortunately, while we would like to provide FDA with particular data on how the expected price increase will affect the public health, at this point we can only speculate how individual patients and the system overall may react to increased costs.

Since transition must proceed, we believe that the best course is to address potential financial impact through appropriate education and targeted programs to assist patients and physicians manage transition. We agree with FDA that generous sampling and enhanced patient assistance programs, if suitably targeted and administered, have the potential to significantly ameliorate negative public health impacts of foregone purchases by uninsured and underinsured patients. One idea under consideration would ameliorate negative health impacts from increased co-pays by providing retail-level rebates or coupons for HFA albuterol. With various organizations, NAEPP, and manufacturers, the STAKEHOLDERS currently are discussing this and a range of other ideas, as well as outreach and communication strategies, to ensure access and minimize financial impact. We intend to file supplemental comments to this rulemaking outlining a more detailed plan for educating patients, physicians, and other healthcare providers.

¹³ As an aside, we note that the current average price of HFA albuterol, \$35, is less than half the average price of all branded products, \$83.66. See Statement of Richard Rozek, Transcript of the Meeting of the Pulmonary and Allergy Drugs Advisory Committee to discuss FDA proposed rule on essential use determinations, at 162 (Jun.10, 2004).

¹⁴ This figure is based on FDA's average of three prescriptions per user per year and assumes the average co-pay will increase from \$10 to \$22. Note, however, that the number of insured patients who will face an increase in co-pay may be smaller because as FDA explains, many plans do not charge the higher, branded co-pay if there is no generic substitute. On the other hand, some percentage of insured patients are "co-insured" for prescription drugs and *would* face higher out of pocket costs because of the loss of the CFC generic.

¹⁵ On this point though, we would remind FDA of its own finding -- that before the albuterol market was genericized a decade ago, large segments of the population were *not* denied access to needed therapies. And as far as we are aware, there are no studies demonstrating a link between inexpensive generic albuterol inhalers and decreased morbidity. In fact, decreases in deaths from asthma in the United States since 1997 have followed stabilization of asthma mortality rates since 1988, although changes in a single year cannot establish a trend. Improved management is the most likely explanation of the reversal of previous increases in asthma mortality. For more on asthma mortality rates, see, e.g., R.M. Sly, "Continuing decreases in asthma mortality in the United States," ANN. ALLERGY 92(3):313-18 (2004).

Setting an Effective End Date for CFC Albuterol MDIs

As FDA aptly points out in the proposed rule, only the albuterol market carries such an exceptional opportunity for significant return on investment because of the price difference between branded and generic products. Transition has the potential to double the value of the 50 million unit albuterol market.

The member organizations of the STAKEHOLDERS understand the difficult dilemma facing FDA. Internally, our member groups have had different reactions to where on the calendar between December 2005 and December 2009 to place the "x". Each has ascribed different weights to various legal, technical and political uncertainties. Some members, placing heavy emphasis on system costs, favored delaying the effective date for as long as possible. Others favored setting the date as soon as feasible, believing FDA's cost analysis did not provide adequate justification for choosing a later effective date. Some suggested FDA look simply at HFA manufacturing capacity and how long after issuing the rule it would take to put that, and an adequate education program, into place. We are confident that FDA and other government agencies have struggled with these same issues.

Despite much discussion, the STAKEHOLDERS as a group reached no consensus on a specific date for albuterol transition. There are simply too many items on which we lack sufficient information to presume we are equipped to select the optimum effective date. Members of the STAKEHOLDERS GROUP agreed to join in the submission of these comments, leaving open the possibility that individual organizations could comment further, including the recommendation of a specific date. Regardless of what date FDA chooses ultimately, the members of the STAKEHOLDERS GROUP remain committed to their original principles for a smooth transition: the HFA marketplace must be able to adequately serve patient; transition must be well-planned and transparent and include adequate education and monitoring; and transition should be completed before scarcity or unavailability of CFCs negatively impacts patient health.

Likewise, the GROUP is not able to offer one collective suggestion about how much time should elapse between issuance of the Final Rule and the albuterol end date. We understand that some manufacturers with product removal experience have suggested transition could be completed as soon as 9-12 months, whereas others have suggested a longer, gradual phase-in of 12-18 months that parallels the ramping up of manufacturing capacity. As mentioned above, the STAKEHOLDERS currently are discussing the character and contents of an education and outreach plan for transition and our recommendations for what period of time is sufficient for deploying adequate education will be included in supplemental comments. Like FDA, we hope over the next few months to gain more certainty about the future of CFC supply, available CFC stockpiles, and the timeframe for having adequate HFA manufacturing capacity. At this time, we are in agreement that whatever length transition period is chosen, it must: take into account CFC supply after December 31, 2005; consider the timeline for HFA manufacturing; provide reasonable notice to both CFC and HFA manufacturers; and minimize the potential that patients will face unnecessary price increases, either of HFA MDIs or of to-be discontinued CFC MDIs.

Conclusion

The STAKEHOLDERS are in considerable agreement about most aspects of transition, despite being unable to recommend an optimal effective date. We know that transition must proceed in order to protect patients and physicians from the uncertain future of CFCs.

Before FDA sets an end date for CFC albuterol, we urge the Agency to carefully scrutinize the viability of Honeywell's stated intent to produce pharma-grade CFCs in Baton Rouge. If doubt remains as to whether new CFCs will be manufactured after December 31, 2005, we believe FDA must consider how the continued use of CFCs in albuterol might affect other drug products. Whether or not new CFCs can be manufactured, FDA still must establish when there will be adequate manufacturing capacity of HFA albuterol MDIs.

Regarding the inevitable cost implications of transition, we call for FDA to ameliorate negative impacts, specifically at the patient level, by insisting on adequate patient assistance and education programs, including appropriate innovative measures that reflect the importance of the albuterol moiety. FDA also must judge what period of time after issuance of the Final Rule is sufficient to develop and deploy these programs and measures, as well as what safeguards are required to monitor transition so as to ensure patients can access and afford albuterol. As we have indicated, the STAKEHOLDERS GROUP and individual members intend to file supplemental information on these points.

The US STAKEHOLDERS GROUP ON MDI TRANSITION is committed to working with manufacturers and FDA to provide expertise and our individual institutional strengths to assist in this effort. We thank FDA for its careful consideration of the matter.

SUBMITTED ON BEHALF OF THE US STAKEHOLDERS GROUP ON MDI TRANSITION

Allergy & Asthma Network Mothers of Asthma (AANMA)
American Academy of Allergy, Asthma and Immunology (AAAAI)
American Academy of Pediatrics (AAP)
American Association for Respiratory Care (AARC)
American College of Allergy, Asthma and Immunology (ACAAI)
American College of Chest Physicians (ACCP)
American Lung Association (ALA)
American Thoracic Society (ATS)
Asthma and Allergy Foundation of America (AAFA)

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