Tab 1	May 21, 2009 Letter from Graceway Pharmaceuticals to Acting Commissioner Sharfstein, enclosing physician letters
Tab 2	June 24, 2009 Letter from Association of Asthma Educators to Commissioner Hamburg
Tab 3	August 28, 2008 Letter from Senator Kennedy and Senator Alexander to Commissioner von Eschenbach
Tab 4	June 30, 2008 Addendum to Graceway Pharmaceuticals Comment (regarding availability of stockpiled CFCs for supply of Maxair Autohaler throughout transition to CFC-free pirbuterol MDI)
Tab 5	September 10, 2007 Comment from Graceway Pharmaceuticals on RIN 09-AF93 Use of Ozone-Depleting Substances; Removal of Essential Use Designations Proposed Rule (including index of exhibits)

Tab 1

GRACEWAY™
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Corporate Headquarters
Bristol, Tennessee

May 21, 2009

Joshua M. Sharfstein, MD
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
5600 Fishers Lane (HF-1)
Rockville, MD 20857

Re: The Breath-Actuated Pirbuterol MDI

Dear Commissioner Sharfstein:

As the Chief Medical Officer of Graceway Pharmaceuticals, LLC, I am writing to reaffirm Graceway's request to extend the effective date of FDA's proposed rule titled "Use of Ozone-Depleting Substances; Removal of Essential Use Designation," as applied to pirbuterol.

Since entering the market in 1992, Maxair® Autohaler® (pirbuterol acetate inhalation aerosol) has maintained a strong record of safe and effective use. The drug (pirbuterol) and the delivery device (the breath-actuated Autohaler) are both unique to patients. Under a rule proposed by the Food and Drug Administration, the Maxair Autohaler would be banned at the end of 2009 because the product contains small amounts of chlorofluorocarbons (CFCs). However, more than a quarter million US patients currently depend on the Maxair Autohaler for treatment of their asthma and chronic obstructive pulmonary disorder (COPD).

With publication of the final rule targeted for June 2009 in the Unified Agenda of Regulatory and Deregulatory Actions, and given the passage of time since the close of the comment period in 2007, Graceway is concerned that the new leadership of the agency may not have had the opportunity to give full consideration to the public health issues associated with the rule. If the rule is finalized with the proposed December 31, 2009 effective date, pirbuterol will soon be unavailable to patients in any form, and patients who depend on Maxair's breath-actuated system will be left without a proven alternative. As we requested in our formal comment on the proposed rule submitted on September 10, 2007 (Docket No. 2006N-0454, Comment No. 4122), an extension of the effective date of the rule to December 31, 2015 would enable Graceway to continue to supply the market while we transition to a non-CFC pirbuterol system.

While a relatively small percentage of the millions of Americans who suffer with asthma and COPD rely on the Maxair Autohaler, many of those patients turned to the Maxair Autohaler only after failing on albuterol MDIs because of bad side effects or non-response. Others, particularly those in vulnerable populations, depend on the breath-actuated delivery device. These patients, as well as their physicians and caregivers, believe strongly in the Maxair Autohaler and attest to its critical importance as a treatment alternative, as evidenced by the more than 200 detailed letters and more than 7,000 short-form comments that were sent to FDA during the formal

comment period, as well as the testimony from clinicians, researchers and patients at FDA's August 2, 2007 public meeting on the proposed rule.

As the sponsor of the product, we are regularly in contact with leading clinicians and researchers, many of whom submitted formal comments or provided testimony regarding the proposed rule in 2007. Several of these clinicians and researchers likewise wished to express their ongoing concern about the proposed rule, and enclosed are several recent letters with respect thereto.

We want to reiterate our respect for the important environmental goals promoted by the Montreal Protocol, and we again laud FDA for its leadership in managing down the use of CFCs. To that end, Graceway is working diligently toward development of a CFC-free product, and has already invested millions of dollars in reformulation with its development partner, 3M. Given progress to date, Graceway is confident that it can complete the reformulation, approval and transition process to a CFC-free pirbuterol MDI by 2015. Furthermore, with other CFC products departing the market, stockpiles of existing CFCs have become more readily available. Last year, Graceway made arrangements to obtain from existing stockpiles all the CFCs it needs to supply patients with Maxair Autohaler through 2015. Graceway informed both FDA and the Environmental Protection Agency of this development, and has since rescinded its request for an allocation of CFCs from the US nomination to the Montreal Protocol for 2010 and informed EPA that it does not anticipate submitting any further request for allocation of new CFCs.

In closing, we understand that this issue is the subject of a rule-making process, and we are not writing to suggest FDA act outside of that process. Rather, we want to ensure that new leadership is aware that FDA has received extensive public comments indicating that, for many patients, press-and-breathe albuterol MDIs are not acceptable replacements for the Maxair Autohaler, and that the Maxair Autohaler can be manufactured throughout the transition to a CFC-free product with use of existing stockpiles of CFCs. Given this record, and before acting to take a unique, safe and effective product off the market, we urge the agency to give our prior request to extend the effective date of the rule as applied to pirbuterol careful consideration.

We appreciate your attention, and welcome the opportunity for further dialogue with FDA.

Sincerely,

James H. Lee, MD, PhD
Chief Medical Officer

Enclosures

cc:

David Dorsey
Randall W. Lutter, PhD
Janet Woodcock, MD
Division of Dockets Management
Food and Drug Administration (FDA)

Ross Brennan
Drusilla J. Hufford
Environmental Protection Agency (EPA)

Honorable Edward M. Kennedy
Honorable Lamar Alexander
United States Senate

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Michael Wechsler, M.D.
Assistant Professor of Medicine
Associate Director, Asthma Research Center

Joshua M. Sharfstein, M.D.
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

May 15, 2009.

Re: Breath-Actuated Pirbuterol MDI

Dear Dr. Sharfstein:

I am writing to reiterate the comments I made at the FDA's August 2, 2007 public meeting, and in my written submission to the agency on September 6, 2007 (a copy of my letter is enclosed), regarding the proposed rule to ban breath-actuated pirbuterol as of December 31, 2009.

I am an Assistant Professor of Medicine at Harvard Medical School and Brigham and Women's Hospital (BWH) in Boston, Massachusetts. I am also the Associate Director of the BWH Asthma Research Center, and I serve on the Steering Committee of the National Institutes of Health Asthma Clinical Research Network (ACRN). My research remains focused on the underlying pathogenesis of asthma, with emphasis on the genetic and pharmacogenetic associations of the asthma phenotype. In addition to my academic work, I maintain a clinical practice in the Partners Asthma Center at the BWH Center for Chest Diseases and in the BWH Medical Intensive Care Unit.

As an asthma researcher, and given the well-established data on the heterogeneity of response to asthma therapies (including short-acting beta agonists, long-acting beta agonists, inhaled corticosteroids, and leukotriene modifiers), both across and within populations and across and within these classes of drugs, I remain concerned about any agency action that would remove a proven product with a unique molecule and a unique delivery device from our treatment armamentarium.

As a clinician, I remain concerned because I have patients who do not respond to press-and-breathe albuterol MDIs, many of whom respond well to breath-actuated pirbuterol. While breath-actuated pirbuterol is not necessarily my first-line treatment, for many of my patients who do not respond to press-and-breathe albuterol MDIs, breath-actuated pirbuterol remains an important alternative rescue therapy.

Thus, both as a researcher and a clinician, I urge FDA not to take this unique and important product away from physicians and their patients.

Sincerely,

Michael E. Wechsler, M.D., M.M.Sc.

cc: Division of Dockets Management

BRIGHAM AND WOMEN'S HOSPITAL

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Michael Wechsler, M.D.
Assistant Professor of Medicine
Associate Director, Asthma Research Center

September 6, 2007

Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Subject: Docket No. 2006N-0454
Use of Ozone-Depleting Substances;
Removal of Essential Use Designations Proposed Rule (June 11, 2007)
Regulatory Information No. 0910-AF93

Dear Commissioner von Eschenbach:

I am writing to follow up on my remarks at the Food and Drug Administration's August 2, 2007, public meeting on the use of ozone-depleting substances in metered-dose inhalers. I spoke at the meeting on behalf of Graceway Pharmaceuticals and expressed my opinion that the FDA should not remove the essential-use designation for pirbuterol acetate, the active ingredient in Graceway's product Maxair Autohaler. I also described the literature and current research on the heterogeneity of patients' responses to short acting beta-2 agonists, and how a significant number of patients do not appear to respond to albuterol. After my comments, the FDA panel expressed interest in the potential pharmacogenomic basis for this observation.

To summarize my background, I am an Assistant Professor of Medicine at Harvard Medical School and Brigham and Women's Hospital (BWH) in Boston, Massachusetts. I am also the Associate Director of the BWH Asthma Research Center, and I serve on the Steering Committee of the National Institutes of Health Asthma Clinical Research Network (ACRN). My research interests are focused primarily on the underlying pathogenesis of asthma, with emphasis on the genetic and pharmacogenetic associations of the asthma phenotype. In addition to my academic work, I maintain a clinical practice in the Partners Asthma Center at the BWH Center for Chest Diseases and in the BWH Medical Intensive Care Unit.

Pharmacogenomics is the study of the ways in which genetic variability between individuals may impact those individuals' responses (both positive and negative) to drugs. Although most studies conducted to date are more strictly *pharmacogenetic* in nature – concerning the impact of individual, rather than multiple, genes – the broader term is more common. Both fields are expanding rapidly, providing new insights into the patterns of response that clinicians have long

seen in their patients. Research now suggests that a substantial portion of inter-individual variability in the response to drug treatment – as much as 70% – may be genetic in nature.[1]

Specifically in the context of asthma, the largest pharmacogenetic efforts to date have focused on the beta-2 agonists. This is because the site of action of the short and long acting beta-2 agonists, the beta-2 adrenergic receptor, has been sequenced, and because the effect of single nucleotide polymorphisms (SNPs) in the beta-2 adrenergic receptor gene have been investigated. As I alluded to during my remarks at the FDA meeting, many studies have demonstrated that an SNP at the 16th amino acid position on the beta-2 adrenergic receptor gene may have a significant impact on the patient's response to albuterol.

One retrospective analysis in more than 250 subjects with mild asthma showed that individuals with homozygosity for arginine (Arg/Arg) at this position, when randomized to regular albuterol use versus as-needed use, suffered a *decline* in peak expiratory flow of 24L/minute.[2] Another retrospective study of the same SNP found that subjects had more asthma exacerbations during treatment with albuterol than during treatment with placebo.[3] This amino acid position has also been found to be associated with airway hyper-responsiveness, particularly among non-smokers.[4]

The same result has recently been documented in a prospective study.[5] In this well-controlled study, subjects with mild asthma were enrolled in pairs matched for forced expiratory volume in one second (FEV-1) according to whether they were homozygous for arginine (Arg/Arg) or glycine (Gly/Gly) at the 16th amino acid position. The groups were provided regular treatment with either albuterol or placebo in a masked, crossover design, for 16 weeks. The study began with a six-week, single-blind run-in period, during which subjects were instructed to minimize their use of albuterol and to rely instead on twice-daily use of a placebo inhaler, with open-label ipratroprium bromide for rescue.

During the run-in period, subjects with the Arg/Arg genotype had a 23L/minute increase in their morning peak expiratory flow rate (PEFR) by the end of week six, while relying on placebo and non-albuterol rescue. By contrast, the Gly/Gly subjects had only a 2L/minute improvement. During the double-blind phase of the study, the Arg/Arg subjects demonstrated no significant change in their morning PEFR over the 16 weeks on albuterol, while demonstrating a significant increase in PEFR on placebo. The Gly/Gly subjects, again, showed just the opposite – no change while on placebo, but a significant increase in PEFR while on albuterol. Significant genotype-related differences were also seen in this study in FEV-1, forced vital capacity, patient-recorded evening PEFR, rescue inhaler use, and asthma symptoms.

---

1 Drazen JM, Silverman EK, Lee TH. Heterogeneity of therapeutic responses in asthma. *Br Med Bull.* 2000;56(4):1054-1070.

2 Israel E, Drazen JM, Liggett SB, *et al.* The effect of polymorphisms of the beta2-adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med.* 2000;162:75-80.

3 Taylor DR, Drazen JM, Herbison GP, *et al.* Asthma exacerbations during long term beta-agonist use: influence of beta2 adrenoceptor polymorphism. *Thorax.* 2000;55:762-767.

4 Litonjua AA, Silverman EK, Tantisira KG, *et al.* Beta 2-adrenergic receptor polymorphisms and haplotypes are associated with airways hyperresponsiveness among nonsmoking men. *Chest.* 2004;126(1):66-74.

5 Israel E, Chinchilli VM, Ford JG, *et al.* Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet.* 2004;364:1505-1512.

Furthermore, colleagues and I recently published a retrospective analysis of two ACRN studies that demonstrated similar findings with the long acting beta-2 agonist salmeterol. Both in the presence and absence of inhaled corticosteroids, airway function and indices of asthma control in Arg/Arg individuals either declined or failed to improve with this beta-2 agonist therapy.[6]

The fact that such consistent results have now been documented in both retrospective and prospective studies, with different subject populations, having different ages and degrees of asthma, and with different types of beta-2 agonists, strongly supports the reliability of the association between Arg/Arg homozygosity and an inadequate response to beta-2 agonists such as albuterol. As discussed during the FDA meeting, this type of controlled research has not yet been conducted on pirbuterol. However, clinical experience and patient reports certainly suggest that at least some non-responders to albuterol respond well to Maxair Autohaler, and thus this hypothesis is worthy of investigation. We learn more each day about the role genetic variability plays in patients' responses to drugs.[7]

In this light, and in light of the fact that approximately *one-sixth* of all asthma patients in the United States express the Arg/Arg genotype,[8] it is essential that physicians have at their disposal many different drugs for the treatment of patients with asthma and related conditions. Please do not hesitate to contact me if I can provide the FDA with any additional information.

Sincerely,

Michael E. Wechsler, M.D., M.M.Sc.

---

6 Wechsler ME, Lehman E, Lazarus SC, *et al.* Beta-agonist genotype and response to salmeterol. *Am J Respir Crit Care Med.* 2006;173(5):519-26.

7 For example, another recent study suggests that pharmacogenetic differences in patients' responses to albuterol may exist within individual ethnic groups. Choudhry S, Ung N, Avila PC, *et al.* Pharmacogenetic differences in response to albuterol between Puerto Ricans and Mexicans with asthma. *Am J Respir Crit Care Med.* 2005;171:563-570.

8 Weir TD, Mallek N, Sandford AJ, *et al.* Beta 2-adrenergic receptor haplotypes in mild, moderate and fatal/near fatal asthma. *Am J Respir Crit Care Med.* 1998;158:787-791.

GEORGETOWN UNIVERSITY MEDICAL CENTER

International Center for Interdisciplinary Studies of Immunology
Office of the Director

May 6, 2009

Joshua M. Sharfstein, MD
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20903

Re: Breath-Actuated Pirbuterol

Dear Dr. Sharfstein:

I am Professor of Pediatrics and Microbiology-Immunology and Director of the International Center for the Interdisciplinary Study of Immunology at Georgetown University Medical Center. Over the course of my more than 40-year career in medicine, I have been privileged to serve in many national positions, including President of the Society for Pediatric Research (SPR), President of the American College of Allergy and Immunology (ACAAI), and President of the American Board of Allergy and Immunology (ABAI), as well as President of the international asthma organization INTERASMA.

When FDA first proposed to declare breath-actuated pirbuterol a non-essential product and remove it from physician and their patient usage, I provided testimony, at the FDA's public meeting on August 2, 2007. I have no financial or consulting relationships with the sponsor of breath-actuated pirbuterol and I appeared on my own.

At the public meeting, I addressed the unique molecular structure of pirbuterol hydrochloride – a Beta 2 agonist with a structure similar to that of albuterol, except for the molecular substitution of a pyridine ring instead of a benzene ring – resulting in unique pharmacologic action in patients. I explained that the pirbuterol molecule was an important treatment alternative for my patients who have had adverse side effects with albuterol and its active isomer, levalbuterol. Because of differences in pharmacologic action, many of my patients who have had

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untoward side effects with albuterol and levalbuterol successfully use pirbuterol. That was true in 2007 and remains true today. The unique pirbuterol molecule provides many of my patients with important health benefits they simply do not obtain from albuterol MDIs.

I also testified as to the value of breath-actuation, explaining how patients who fail to properly coordinate inspiration with actuation of their MDI fail to receive the proper dose of the medicine they need. These short-acting Beta-agonist MDIs provide rescue therapy, so a suboptimal dose is potentially life-threatening. Proper coordination is challenging and requires training for even my most able patients. For many of my patients who struggle with coordination, whether because of age or disability, breath-actuated pirbuterol is essential.

Once again I would strongly urge the FDA to consider the testimony provided by the many clinicians, researchers, patients and caregivers who commented on the proposed rule and to approve this unique breath-actuated pirbuterol as an essential treatment alternative.

Sincerely,

Joseph A. Bellanti, MD
Director

cc: Division of Dockets Management

Michael Blaiss, M.D. ▪Jerald Duncan, M.D. ▪Fred Grogan, M.D. ▪Tammy Heinly McCulley, M.D. ▪Brandon D. Hill, M.D.
Phil Lieberman, M.D. ▪George Treadwell, M.D. ▪Marcia Johnston, A.P.N. ▪Regina Seaton, A.P.N. ▪Ingrid Cantrell, P.A.

April 30, 2009

Joshua M. Sharfstein, M.D.
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

Re: Proposed Rule to Remove Breath-Actuated Pirbuterol MDI from the Market

Dear Dr. Sharfstein:

I write regarding FDA's proposed rule to remove from the market certain non-albuterol asthma medications that contain small amounts of chlorofluorocarbons (CFCs). *See* 72 Fed. Reg. 32030 (June 11, 2007) (proposed rule outlining planned phaseout for inhalers using seven non-albuterol compounds as active ingredients). When the proposed rule was announced in 2007, I formally submitted to FDA's docket a public comment on behalf of the American College of Allergy, Asthma & Immunology (ACAAI). Given that nearly two years have passed since the proposed rule was released, I would like to take this opportunity to reemphasize the need for alternative medications in the treatment of asthma and other serious respiratory diseases.

As stated in the previous letter, some of the medications subject to the proposed rule are unique, and there is presently no direct HFA substitute for patients who depend on them. Maxair Autohaler, for example, is the only medication that has pirbuterol as its active ingredient, as well as a unique breath-actuated delivery device. In that case, FDA's proposed rule is accordingly premised on the untested assumption that press-and-breathe HFA albuterol products will be adequate therapeutic alternatives for those patients who now depend on breath-actuated pirbuterol. This premise, however, is contrary to the extensive comments from top clinicians and scores of patients who wrote into FDA's docket to report that they turn to breath-actuated pirbuterol after failing on press-and-breathe albuterol. Although Maxair is just one example, the situation exemplifies the risk of removing unique medications from the marketplace.

At a time when asthma and other severe respiratory diseases are on the rise, FDA should be working to expand – not restrict – the treatment alternatives available to physicians. Patients' lives are literally at stake, and I am hopeful that FDA carefully considers the implications of this important decision.

Sincerely,

Michael S. Blaiss, MD
Clinical Professor of Pediatrics in Medicine
Division of Clinical Immunology and Allergy
University of Tennessee Health Science Center – Memphis

cc: Division of Dockets Management

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Nora Lin, M.D.

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May 21, 2009

Joshua M. Sharfstein, MD
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

Re: Breath-Actuated Pirbuterol MDI

Dear Dr. Sharfstein:

I am a pediatric allergist and immunologist, specializing in the treatment of asthma, and a fellow of the AAAAI and the ACAAI. I have a private practice, with several locations in the Philadelphia area, and I have also served has the Clinical Assistant Professor, Department of Allergy, Division of Pediatrics, for the University of Pennsylvania School of Medicine.

I am very concerned about the proposed ban on the Maxair Autohaler breath-actuated pirbuterol MDI. This is an important therapeutic alternative, both because of the molecule and the breath-actuated delivery device. As I stated in my prior recorded testimony to the FDA, I have patients who are clearly intolerant of albuterol, experiencing tachycardia, sleeplessness and irritability. Many of my patients who experience this intolerance to albuterol do not have the same side effects with pirbuterol. I also routinely switch patients who have trouble with press-and-breathe albuterol devices to breath-actuated pirbuterol, with great success.

There is unquestionably a need for this unique medication. Indeed, as I testified, when there was a temporary shortage of breath-actuated pirbuterol in our area a few years ago, my offices fielded hundreds of phone calls from families who were upset, asking "What happened to Maxair? What am I going to use? I don't want to go back to albuterol. What am I going to do for my child?" If FDA has any doubt about the continued need for Maxair, I'd like to reiterate the offer I made in August 2007 for FDA representatives to spend a day in my office to witness first-hand the essential nature of Maxair Autohaler.

Speaking for those who treat asthma patients every day, we need breath-actuated pirbuterol, and I urge FDA to take appropriate action to ensure that this product remains available.

Sincerely,

Robert Anolik, MD

cc: Division of Dockets Management

CAPITAL ALLERGY & RESPIRATORY DISEASE CENTER
A MEDICAL CORPORATION

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Acute Care Nurse Practitioner

April 29, 2009

Joshua M. Sharfstein, M.D.
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

Dear Dr. Sharfstein:

I am writing you regarding my strong support for the continuation of Maxair Autohaler in its current form. Since this is the only breath actuated delivery system, it allows me to treat patients who are not able to use either an albuterol or Xopenex PMDI on an effective basis. Maxair also has distinct advantages of having less tachycardia. With 400 inhalations in each inhaler, it is very cost effective for my patients. I use Maxair routinely in my practice. It would be a significant negative effect Maxair is removed from the market. I am hopefully the FDA will agree and allow Maxair to stay on the market.

Yours truly,

Bradley E. Chipps, M.D.

BEC:js

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May 20, 2009

Joshua M. Sharfstein, M.D.
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

RE: Breath-Actuated Pirbuterol MDI

Dear Dr. Sharfstein:

I am Santiago Reyes de la Rocha, M.D., a pediatric pulmonologist.
I am very concerned about the public health implications of the proposed ban on the Maxair Autohaler breath-actuated pirbuterol MDI. This product is the only MDI with pirbuterol as its active ingredient and the only rescue MDI with a breath-actuated delivery device, and is thus an essential treatment alternative for many of my asthma patients.

While I prescribe albuterol MDIs for most of my asthma patients, there is a significant subset of my patients who fail on albuterol because of side effects or subtherapeutic response. Man of these patients who fail on albuterol find the relief they need during asthma attacks from pirbuterol.

Many of my patients also depend on the breath-actuated device, which delivers the puff of rescue medication when triggered by the patient's own inhalation. To use a conventional press-and-breathe inhaler, the patient has to carefully coordinate pressing the inhaler with inhalation, and a failure of technique results in delivery of most of the medicine to the back of the throat, not the lungs where it is needed. This challenge of coordination is compounded by the stress felt by patients who cannot breathe during an asthma attack. I have many patients who, because of age or disability, cannot effectively use press-and-breathe MDIs. Breath-actuated pirbuterol provides these patients with potentially life-saving rescue therapy that they cannot obtain from any other MDI.

In sum, we need breath-actuated pirbuterol as an essential treatment alternative, and I urge FDA to take appropriate action to ensure that this product remains available.

Sincerely,

Santiago Reyes de la Rocha, M.D./sdg

ALLERGY & ASTHMA
CARE OF NEW YORK

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Assistant Clinical Professor, SUNY HSCB

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Faculty, New York University School of Medicine

UJWALA KAZA, M.D.
Diplomate, American Board of Allergy and Immunology
Faculty, New York University School of Medicine

May 12, 2009

Joshua M. Sharfstein, M.D.
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

Re: Breath-Actuated Pirbuterol MDI

Dear Dr. Sharfstein:

As a practicing allergist I am concerned about the public health implications of the proposed ban on the Maxair Autohaler breath-actuated pirbuterol MDI. This product is the only MDI with pirbuterol as its active ingredient and the only rescue MDI with a breath-actuated delivery device.

I feel that some of our patients will benefit from an easier, simplier breath actuated inhaler. It is also a good option for some of our patients who have trouble with using a MDI properly.

I request the FDA to take appropriate action to ensure that this product will continue to be available.

Sincerely,

Clifford W. Bassett, MD

cc: Division of Dockets Management

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Joshua M. Sharfstein, M.D.
Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

Re: Breath-Actuated Pirbuterol MDI

Dear Dr. Sharfstein:

My name is Myron Zitt, MD and I am a practicing physician with the Mid Island Allergy Group, Director of the Adult Allergy Clinic at the Nassau University Medical Center and Associate Clinical Professor of Medicine at the State University of New York at Stony Brook.

While I am familiar with the environmental need to eliminate CFC containing metered dose inhalers (MDIs) for the treatment of asthma, I am quite concerned about the public health implications of the proposed ban on Maxair Autohaler MDI. This product is the only MDI with pirbuterol as its active ingredient and the only rescue MDI with a breath-actuated delivery device, and is thus an essential treatment alternative for many of my patients with asthma.

While I prescribe albuterol MDIs for most of my asthma patients, there is a significant subset that fails albuterol MDI therapy because of side effects or subtherapeutic response. Many of these patients find the asthma symptom relief they require from pirbuterol autohaler. A significant number depend on the breath-actuated device, which delivers rescue medication when triggered by the patient's own inhalation. To use a conventional "press-and-breathe" inhaler, patients must coordinate pressing their device with inhalation. A failure of technique would result in delivery of most of the medicine to the back of the throat, instead of to the bronchial airways where it is needed. This challenge of coordination is compounded by the stress felt by patients who have difficulty breathing during an asthma attack. For my patients who, because of age or disability, cannot effectively use press-and-breathe MDIs, breath-actuated pirbuterol provides potentially life-saving rescue therapy that they cannot obtain from any other MDI.

In sum, I believe that breath-actuated pirbuterol is an essential treatment alternative for my patients with asthma. Hopefully, in time, the manufacturer will be able to reformulate this product to create a CFC free, ozone layer friendly, HFA containing pirbuterol autohaler. In the interim, I would strongly urge the FDA to take appropriate action to ensure that Maxair Autohaler remains available.

Sincerely,

Myron Zitt, MD, FACAAI, FAAAAI
cc: Division of Dockets Management

Tab 2

June 24, 2009

Margaret Hamburg, MD
Commissioner of Food and Drugs
U.S. Food and Drug Administration
5600 Fishers Lane (HF-1)
Rockville, MD 20857

Re: The Breath-Actuated Pirbuterol MDI

Dear Dr. Hamburg:

The Association of Asthma Educators wants to bring an important public health issue to your attention. On June 11, 2007, FDA proposed a rule – now pending for nearly two years – to ban the breath-actuated pirbuterol metered dose inhaler (MDI) because the current product (Maxair Autohaler) contains small amounts of chlorofluorocarbons (CFCs). Under the proposed rule, the ban would take effect on December 31, 2009.

As the premier inter-professional organization of diverse individuals who educate patients and families living with asthma, we are concerned that this proposed rule could take an important and unique rescue medication away from patients and healthcare providers.

The Maxair Autohaler is the only breath-actuated rescue MDI, and thus fills an important niche. The breath-actuated delivery system benefits those who have difficulty coordinating actuation with inhalation when using conventional press-and-breathe MDIs, including patients who are young, old or disabled. The unique delivery system also eliminates the need for a cumbersome spacer device, which many patients, particularly children and teenagers, find inconvenient to carry. This breath-actuated product thus reliably delivers rescue medication to many patients who would otherwise struggle to effectively use a press-and-breathe MDI, particularly during the stress of an asthma attack.

Association of Asthma Educators
AAE
Who's teaching YOU about asthma?

1215 Anthony Avenue
Columbia, SC 29201-1701
Toll Free: 1.888.988.7747
Fax: 803.254.3773
www.asthmaeducators.org

We have encouraged the sponsor of Maxair Autohaler, Graceway Pharmaceuticals, to develop a non-CFC MDI as soon as possible, and we urge FDA to work with Graceway to ensure that this unique product remains available during the transition.

Sincerely,

Tim Op't Holt, EdD, RRT, AE-C, FAARC
President

cc:

David Dorsey
Randall W. Lutter, PhD
Janet Woodcock, MD
Division of Dockets Management
Food and Drug Administration (FDA)

Ross Brennan
Drusilla J. Hufford
Environmental Protection Agency (EPA)

Honorable Edward M. Kennedy
Honorable Lamar Alexander
United States Senate

Tab 3

United States Senate

WASHINGTON, DC 20510

August 28, 2008

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner of Food and Drugs
Parklawn Building (HF-1)
5600 Fishers Lane, Room 14-71
Rockville, MD 20857

Dear Commissioner von Eschenbach:

We are writing to urge you to consider asthmatic patients' needs when acting on the Food and Drug Administration's proposed rule (Docket No. 2006N-0454; RIN 0910-AF93) to remove the essential-use designations from certain chloroflorocarbon (CFC) metered-dose inhalers on December 31, 2009.

This proposed date—as an across-the-board deadline for the transition to CFC-free formulations of these inhalers—does not adequately consider the needs of patients for alternatives to albuterol-only inhalers. We understand that the agency has received hundreds of detailed letters, thousands of shorter comments, as well as testimony at the August 2, 2007, public meeting about the value to patients of asthma inhalers that do not contain albuterol or that contain albuterol in combination with another drug. For patients who fail to obtain satisfactory relief with albuterol-only inhalers or who have unwelcome side effects from albuterol, alternatives to albuterol-only inhalers are essential.

We therefore urge you, when establishing timetables for the withdrawal of these alternatives, to give due consideration to the needs of patients who use these products, and to develop a timetable for the transition to a CFC-free formulation of any of these alternatives that is both reasonable and appropriate to preserve access to the treatment option, as well as mindful of our obligation to reduce and ultimately eliminate the production and use of CFCs.

With respect and appreciation, and thank you for your consideration of this request.

Sincerely,

Ted Kennedy

Lamar Alexander

Tab 4

GRACEWAY™
PHARMACEUTICALS

June 30, 2008 0669 8 JUN 30 P4 :33

Commissioner Andrew von Eschenbach, M.D.
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2006N-0454 (June 11, 2007); RIN 0910-AF93
Use of Ozone-Depleting Substances; Removal of Essential Use Designations Proposed Rule

ADDENDUM TO COMMENT NO. 004122

Dear Commissioner von Eschenbach:

Graceway Pharmaceuticals, LLC (Graceway) submits the following addendum to its comment on the above-referenced proposed rule. The purpose of this addendum is to include in the record of this proceeding, for consideration by the agency, new information regarding Graceway's effort to obtain sufficient quantities of pre-existing pharmaceutical-grade chlorofluorocarbons (CFCs) to allow for the continued availability of Maxair® Autohaler® (pirbuterol acetate inhalational aerosol) at existing levels throughout the development of and transition to a CFC-free formulation.

This new information is provided in response to specific questions raised by agency officials at the August 2, 2007, public meeting on the proposed rule, as well as similar questions raised by agency officials during meetings with Graceway on the company's CFC-free development program. As outlined below, we are pleased to report that Graceway has taken steps to ensure that all patients who presently rely on Maxair® Autohaler® can expect, absent unforeseen circumstances, to continue to have access to the product during the period needed to complete the development of and transition to a new formulation.

Graceway is the sponsor of the new drug application for Maxair® Autohaler®, one of the products directly impacted by the proposed rule. Maxair® Autohaler® contains CFC 11 and CFC 12 as propellants. During the August 2, 2007, public meeting, the panel asked whether companies had sufficient CFCs to complete the development of and transition to a CFC-free formulation, or whether they would expect to request production of additional CFCs to complete the transition. Transcript of August 2, 2007, Public Meeting at 118-19, 174-76. The panel also noted the possibility that new CFCs may not be available after 2010 and the concern that patients on existing CFC-based products may experience a precipitous interruption in the supply of their product if the products were permitted to remain on the market in and beyond 2010. *Id.*

In comments 20 and 21 of our comment, we addressed issues regarding CFC allocations and supplies, and are now pleased to update these comments with important new information. Graceway

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Pharmaceuticals, LLC, Comment to Docket No. 2006N-0454, 37-39 (Sept. 10, 2007). Based on information submitted to and on file with CDER's Division of Pulmonary and Allergy Drug Products, in the context of our planned investigational new drug application for a CFC-free pirbuterol acetate inhalational product (pIND 76,395), we expect to rely on already existing stockpiles of CFC 11 and CFC 12 to maintain the supply of Maxair® Autohaler® at current levels throughout the transition to a CFC-free formulation. These stockpiles have become available as other sponsors have opted to discontinue the marketing of their CFC-based products, thereby allowing for continued availability of products such as Maxair® Autohaler® without the need for new CFC production.

To ensure that this information is given full consideration in this rulemaking proceeding, we are submitting to the record this addendum to our previously submitted comment after consulting with the Division of Pulmonary and Allergy Drug Products and the Office of Regulatory Policy regarding the process for doing so. This information bears directly on the issue of the choice of an appropriate effective date for an essential use determination under the proposed rule with respect to the pirbuterol moiety.

Thus, in response to the concern that limits on the availability of CFCs might result in shortages of Maxair® Autohaler®, or even the precipitous unavailability of the product, Graceway has obtained a commitment from a third-party manufacturer to use existing stockpiles of CFCs to maintain the supply of Maxair® Autohaler® throughout the expected transition to a CFC-free formulation in or about 2015. With this commitment, and based on the information provided to the agency, Graceway has made adequate provision to ensure that patients who rely on Maxair® Autohaler® will continue to have access to the product throughout the expected development and transition period.

Please do not hesitate to contact me if you have any questions, or if you need additional information on this or any other issue. Thank you for your attention.

Respectfully submitted,

Sean Brennan

Sean Brennan, Vice President, Regulatory Affairs
Graceway Pharmaceuticals, LLC

cc:

Michelle D. D. Bernstein
Badrul A. Chowdhury
Wayne Mitchell
Martha Nguyen
Food and Drug Administration (FDA)

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Tab 5

GRACEWAY PHARMACEUTICALS

Graceway Pharmaceuticals, LLC
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Jefferson J. Gregory, J.D.
Chairman and Chief Executive Officer

10 September 2007

Commissioner Andrew von Eschenbach, M.D.
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2006N-0454 (June 11, 2007); RIN 0910-AF93
Use of Ozone-Depleting Substances; Removal of Essential-Use Designations Proposed Rule

Dear Commissioner von Eschenbach:

Graceway Pharmaceuticals, LLC (Graceway), is pleased to submit the following comments on the Food and Drug Administration's (FDA) proposed rule titled "Use of Ozone-Depleting Substances; Removal of Essential-Use Designations" (the Proposed Rule). 72 FR 32030 (June 11, 2007).

INTRODUCTION

Graceway is the sponsor of Maxair® Autohaler® (pirbuterol acetate inhalation aerosol), a metered dose inhaler (MDI) that would lose its long-standing essential-use designation under the Proposed Rule. More than a quarter of a million patients rely on Maxair Autohaler for the prevention and reversal of bronchospasm associated with asthma and chronic obstructive pulmonary disease (COPD). It is the only FDA-approved product that offers patients the distinct active moiety, pirbuterol, and it is the only rescue inhaler that offers patients a breath-actuated delivery system. Since entering the United States market in 1992, Maxair Autohaler has maintained a strong record of safe and effective use.

As demonstrated by the comments submitted by patients, caregivers, physicians, and pharmacists, Maxair Autohaler is an essential product in the treatment of asthma and COPD. First, many Maxair Autohaler users are patients who previously failed on albuterol therapy. That is, Maxair Autohaler is essential for those who require a short-acting rescue medication but cannot tolerate or do not respond to albuterol or its active isomer, levalbuterol. Maxair Autohaler is the only product that offers asthma and COPD patients an alternative and distinct chemical moiety – pirbuterol. If the Proposed Rule is finalized without amendment, pirbuterol will be unavailable in any form to patients.

Second, Maxair Autohaler is the only currently marketed rescue inhaler with a breath-actuated delivery system. Many Maxair Autohaler patients are completely dependent upon the breath-actuated system. These include pediatric patients, patients with movement disorders,

severely arthritic patients, and an array of others who simply lack the strength, dexterity, or capacity to use a press-and-breathe apparatus.

For these reasons, Maxair Autohaler fills an essential need among asthma and COPD patients. The comments submitted by patients and caregivers in this rulemaking – including more than 7,000 short-form comments and more than 200 detailed letters – speak volumes. Patients across the country have offered first-hand accounts of adverse experiences with albuterol products, and many individuals have commented that they, or a loved one, cannot find relief with the alternative products recommended by the agency.

The reports from patients have been thoroughly validated by detailed comments from physicians, who have observed that a subset of patients simply cannot tolerate albuterol. These statements include letters submitted to the docket, testimony at the August 2, 2007, open public meeting, as well as taped interviews with allergists and pulmonologists. These clinicians report that many patients who experience tachycardia, nervousness, and hypersensitivity with albuterol are able to tolerate pirbuterol. They also report that a subset of their patients do not show an adequate response to albuterol, but do respond when using Maxair Autohaler. And, without fail, they praise Maxair Autohaler's breath-actuated delivery system, its ease of use, and its crucial role among pediatric, geriatric, and impaired populations.

Should there be any doubt, the administrative record for this proceeding also includes authoritative statements and literature from experts at leading academic medical centers on both albuterol intolerance and non-therapeutic response. Among other points, experts advise that the asthma patient population is notably diverse, with demonstrated genetic variations in beta-2 adrenergic receptors among individuals and ethnic subgroups. This diversity argues strongly in favor of keeping at least one additional, chemically distinct short-acting beta-2 agonist available to patients.

Overall, in 2005, approximately 7.7% of the United States population – 22.5 million people – suffered from asthma. The prevalence of the disease is escalating at an alarming rate, with greater than a 10% increase from 2002-2005,[1] and the disease is surging in urban centers. The attendant costs, including emergency room visits (nearly 2 million in 2004), primary care visits (13.6 million in 2004), and missed days of school and work (valued in the billions of dollars) speak for themselves.[2] In this context, every possible step should be taken to avoid removing from the market a safe and effective drug, delivered in a breath-actuated system that many find indispensable.

As discussed at the open public meeting, Graceway is deeply committed to the long-term availability of Maxair Autohaler. In or about June 2006, 3M Pharmaceuticals (3M) offered to qualified bidders the opportunity to purchase its branded pharmaceutical business, including Maxair Autohaler. Graceway vigorously pursued this opportunity and, in December 2006,

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1 Tab 1, L. Akinbami, *Asthma Prevalence, Health Care Use and Mortality: United States, 2003-05*; *see also* 72 FR at 32042.

2 Tab 2, American Lung Association, *Trends in Asthma Morbidity and Mortality* (July 2006).

completed the purchase of 3M's product lines in the Americas. Graceway is a small enterprise headquartered in Bristol, Tennessee. We provide jobs to approximately 400 full-time employees, primarily in Bristol and in Exton, Pennsylvania. We are continuing to grow as a business and are working to establish the company as a leader in the specialty pharmaceutical sector.

Graceway purchased Maxair Autohaler because we recognized the unique and important health benefits the product offers to patients. We also understood the environmental issues associated with a product that continues to use chlorofluorocarbons (CFCs). We carefully analyzed the issue, including efforts by 3M to develop an alternative formulation. We concluded that we could build on 3M's efforts and successfully offer patients a non-CFC product in a reasonable amount of time. We also concluded that sound science and good medical judgment would support a finding that the product is essential, even with the availability of non-CFC albuterol and levalbuterol products.

Graceway supports the important public policy goal of terminating all uses of CFCs and transitioning to an array of non-CFC inhalation products. Graceway lauds the leadership provided by FDA and the Environmental Protection Agency (EPA) in meeting the challenge of managing down the use of CFCs. We share in this goal and, thus, we are committed to reformulating Maxair Autohaler. Graceway is fully prepared to invest significantly in overcoming the remaining technical barriers, and we look forward to meeting with the agency to present our confidential development program.

Maxair Autohaler continues to offer patients a unique and otherwise unavailable set of benefits, including a unique active moiety and a proven breath-actuated delivery system. Because it occupies a small niche (behind albuterol), Maxair Autohaler also requires relatively modest amounts of CFCs to meet patient needs. In short, the continued essential-use listing of pirbuterol represents a rational and prudent use of the limited amount of CFCs that will remain available in the years ahead.

As discussed in detail in the comments that follow, the Proposed Rule should be amended to provide for the continued listing of pirbuterol as an essential-use moiety under 21 CFR 2.125(e)(2). We also recognize the need to continue to assess the essential-use status of the product. Thus, consistent with the goals of the Montreal Protocol and the measured approach that has been followed to date, the agency should revisit the essential-use designation for pirbuterol in or after December 2012 (*i.e.*, 3 years beyond the recommended effective date in the Proposed Rule). At that time, we expect that Graceway and FDA will have a clear view of the remaining stages of the Maxair Autohaler reformulation program, and can plan accordingly for the transition to a non-CFC pirbuterol product.

REGULATORY FRAMEWORK

Under the Montreal Protocol on Substances that Deplete the Ozone Layer (the Montreal Protocol), S. Treaty Doc. No. 10, 100th Cong., 1st Sess., 26 I.L.M. 1541 (Sept. 1987), the production and consumption of ozone-depleting substances (ODSs) is being phased out

worldwide. In the United States, the Montreal Protocol is codified into law in Title VI of the Clean Air Act, which bans the production and consumption of ODSs in the United States as of January 1, 1996, unless an essential-use exemption is recognized. *See* 42 USC 7671i; Montreal Protocol Article 2A(4).

The Parties to the Protocol have agreed that use of an ODS is essential if:

(i) It is necessary for the health, safety, or is critical for the functioning of society (encompassing cultural and intellectual aspects); and

(ii) there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health.

Montreal Protocol, Decision IV/25.

Consistent with national policy and the obligations of the United States under the Montreal Protocol and the Clean Air Act, FDA and EPA have codified a regulatory framework for the listing, and de-listing, of essential-use products. 21 CFR 2.125(f) and (g); *see* 40 CFR 82.64 and 82.66. Medical products found to be essential are listed based on the active moiety in the product. The active moiety in Maxair Autohaler, pirbuterol, is currently listed as essential. 21 CFR 2.125(e)(2).

Under the framework, a determination on whether to continue an essential-use listing is made on a product-specific basis. *Id.* at (g). An FDA-regulated drug product includes the active drug substance, any inactive ingredients included in the finished product, and the dosage form (*e.g.*, "aerosol, metered"). *See* 21 CFR 314.3. Thus, an essential-use determination considers the product as a whole, the active moiety, and the formulation of active and inactive ingredients.

The framework includes a process for de-listing a product where one (or more) non-ODS product(s) with the same active moiety, the same route of administration, the same indication, "and with approximately the same level of convenience of use" becomes available on the market. 21 CFR 2.125(g)(3)(i) and (4)(i). The framework also includes a process – effective January 1, 2005 – for de-listing a product that contains an essential-use moiety, but for which there is no marketed non-ODS product with the same moiety. *Id.* at (g)(2). Under the former procedure, patients are able to continue therapy on the same active moiety. Under the latter, if a product is de-listed, patients must transition to a different moiety from the one on which they are currently treated. Thus, the latter procedure can raise a much more difficult set of public health and patient care issues than the former.

To de-list a product (and moiety) for which there is no non-ODS substitute, FDA must make a determination that the product no longer meets the criteria that previously supported the listing of the product. *See id.* This determination is based on comments solicited through notice-and-comment rulemaking, as well as consultation with an appropriate advisory committee and evidence gathered during an open public meeting. *Id.*

The three substantive criteria the agency must consider are:

(1) Whether substantial technical barriers exist to reformulating the product,

(2) Whether the product provides an otherwise unavailable important public health benefit, and

(3) Whether use of the product does not release cumulatively significant amounts of ODSs into the atmosphere or the release is warranted in view of the unavailable important public health benefit.

Id. (incorporating by reference 21 CFR 2.125(f)(1)).

Where there are approved non-ODS products available to patients, the central issue in a 2.125(g)(2) proceeding is whether a given ODS product continues to provide an important and essential public health benefit. 72 FR at 32024. In making this determination, the agency must consider whether removal of the ODS product would cause an increase in mortality or a significant increase in an important morbidity, or would significantly impact the quality of life of patients who rely on the ODS product. *See id.* at 32033. If the agency believes that other products may be used in place of an ODS product, the agency must determine whether patients will in fact use the alternatives and will in fact obtain relief with the alternatives. Here, FDA will consider stated factors such as cost, convenience, portability, physical and mental barriers to use, adequacy of supply, as well as evidence that some patients may uniquely require the ODS product in place of a non-ODS substitute. *See id.* at 32034.

As shown below, Maxair Autohaler clearly meets the criteria for listing as an essential-use product. The administrative record – which includes numerous first-hand comments from patients, physicians, and experts – demonstrates that breath-actuated pirbuterol provides an otherwise unavailable public health benefit to patients suffering from asthma and COPD. The additional factors of cost, convenience, and ease of use serve to underscore the critical niche filled by the product. In addition, the use of Maxair Autohaler does not release cumulatively significant amounts of ODSs, and the amounts that are released are warranted by the public health benefits of the product. Finally, substantial technical barriers exist to reformulating a product that consists of a unique active moiety in a complex delivery system.

COMMENTS

Graceway submits the following specific Comments on the Proposed Rule and supporting data, analyses, and references.

I. Maxair Autohaler is an Essential-Use Product

To remove Maxair Autohaler from the essential-use list, FDA must determine that the product no longer meets the criteria in 21 CFR 2.125(f)(1). FDA has failed to present sufficient evidence to support its tentative determination that Maxair Autohaler no longer meets these criteria. To the contrary, the administrative record establishes that:

- Maxair Autohaler provides important public health benefits that would otherwise be unavailable to substantial numbers of patients (*see* Comments 1-14),

- The use of Maxair Autohaler does not release cumulatively significant amounts of ODSs into the atmosphere, and its *de minimis* release is warranted in view of the essential health benefits provided by the product (*see* Comments 15-17), and
- There are substantial barriers to reformulating Maxair Autohaler without CFCs, including chemistry, manufacturing, and engineering barriers, magnified by economic constraints associated with investing in a small market product (*see* Comments 18-19).

For these reasons, Maxair Autohaler continues to be an essential medical product, and its active moiety, pirbuterol, should be excluded from the final rule and continue to be designated as essential under 21 CFR 2.125(e)(2).

A. Maxair Autohaler Provides an Otherwise Unavailable Important Public Health Benefit

Comment No. 1

Maxair Autohaler provides an otherwise unavailable important public health benefit to patients in the heterogeneous asthma and COPD populations. All of the alternative products addressed in the Proposed Rule contain albuterol or its active isomer, levalbuterol, and all are conventional press-and-breathe MDIs. The active moiety in Maxair Autohaler, pirbuterol, is essential for those patients who do not tolerate albuterol and levalbuterol. Pirbuterol is likewise essential for those patients who do not respond to, or respond inadequately to, albuterol and levalbuterol. In addition, the breath-actuated Autohaler device provides an important, proven, and otherwise unavailable benefit to the many patients who cannot successfully operate press-and-breathe MDIs, particularly during episodes of bronchospasm. Finally, for many patients, the proposed alternative products are substantially more difficult to use, less convenient and portable, and would impose significant new costs. For these reasons, Maxair Autohaler is an essential product and must remain on the essential-use list.

The dominant criterion in determining whether a moiety should be removed from the essential-use list is whether the use of the moiety provides an otherwise unavailable important public health benefit. 21 CFR 2.125(f)(1)(ii). As the agency explained in the Proposed Rule:

> In determining if a drug product provides an otherwise unavailable important public health benefit, our primary focus is on the availability of non-ODS products that provide *equivalent* therapeutic benefits for patients who are currently using the CFC MDIs. If therapeutic alternatives exist for *all patients* using the CFC MDI, we would then determine that the CFC MDI does not provide an otherwise unavailable public health benefit.

72 FR at 32033 (emphasis added). Thus, if there are patients who cannot use or cannot succeed on the alternative products, and would be put at risk, the ODS product must remain available. *See* 64 FR 47719, 47726 (Sept. 1, 1999) (proposed rulemaking setting standard for removal of essential-use designations). Furthermore, proposed alternative products and moieties cannot displace a product from the essential-use list if the alternatives are difficult for some patients to use, lack convenience and portability for some patients, or would impose costs that may be a barrier to use.

In the Proposed Rule, FDA failed to present evidence that the proposed alternatives are acceptable for all patients who currently rely on Maxair Autohaler. As shown in the Comments below and in the emerging administrative record for this proceeding, the alternative products are not acceptable for patients who (1) do not respond adequately to albuterol or its active isomer, levalbuterol, (2) cannot tolerate albuterol or levalbuterol, or (3) require breath-actuated drug delivery. Without Maxair Autohaler, these patients face significantly increased risks and a significantly reduced quality of life. As a result, the use of ODSs in Maxair Autohaler remains essential.

1. Non-Response to Albuterol

In the course of developing the essential-use framework, FDA emphasized that it would "take into account the needs of the entire asthma population" as well as "the medical needs of demographic subgroups, including racial and ethnic groups, economic groups, or other socioeconomic or medical groups." *Id.* at 47727. If patients cannot use proposed alternative products, then those products are not acceptable alternatives to an essential-use product. *See id.* at 47726. With respect to the Proposed Rule, the administrative record establishes that there are patients who do not respond to, or respond inadequately to, albuterol and levalbuterol, either initially or over time. For this reason, it is imperative not to limit the patient population only to albuterol and its active isomer, levalbuterol.[3]

Comment No. 2

A significant number of patients requiring treatment with short-acting beta-adrenergic bronchodilators do not respond adequately to albuterol and levalbuterol. This is confirmed in the literature and by the data submitted in support of FDA's approval of the albuterol and levalbuterol products. Patients failing to achieve therapeutic responses to albuterol and levalbuterol

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[3] Albuterol and levalbuterol products share the same active isomer, (R)-albuterol. Albuterol is a 50-50 racemic mixture of (S)-albuterol and (R)-albuterol. It is the (R)-isomer of the racemic mixture, and not the (S)-isomer, which is responsible for reversal of bronchoconstriction when the racemic mixture is used for the treatment of asthma. Thus, albuterol and levalbuterol products both derive their effect from the identical moiety, (R)-albuterol. For this reason, levalbuterol is generally dosed at one-half the dose of racemic albuterol. For example, Xopenex HFA (levalbuterol tartrate) is approved in a 0.045mg base/inhalation strength, while each of the three albuterol HFA products are approved in 0.09mg base/inhalation strengths. In short, albuterol and levalbuterol share the same active moiety. *See also* Comment 10, *infra*.

are likely to have poor clinical outcomes. For this reason alone, it is essential from a public health perspective that FDA continue to offer patients at least one alternative active moiety, pirbuterol.

Many patients with reversible bronchospasm do not respond to albuterol and levalbuterol, or they demonstrate a non-therapeutic response that results in poor clinical outcomes. This effect (or lack thereof) is widely reported in the literature and confirmed by data from numerous clinical trials.

Most notably, the clinical trial data submitted to FDA to support approval of the proposed alternative albuterol and levalbuterol products show that significant numbers of patients demonstrate an inadequate response to the product over the course of the study. Ventolin HFA, for instance, was approved on the basis of three placebo-controlled clinical trials in adults, adolescents, and children with asthma. These trials were known as SALA3002, SALA3005, and SALA3006. In SALA3002, the percentage of patients achieving a 15% or greater increase above baseline in forced expiratory volume (FEV-1) declined steadily during the 12-week study. Depending on the study arm and visit, between 19 and 40% of patients in the study who received albuterol CFC or HFA failed to exhibit this increase in FEV-1. In SALA3005, the percentage of patients achieving a 15% or greater increase in FEV-1 likewise declined throughout the course of the study; overall, the percentage of patients who demonstrated non-therapeutic response to albuterol was between 11 and 37%, depending on the study arm and visit. In SALA3006, the percentage of patients demonstrating non-therapeutic response was between 12 and 37%. Tab 3, FDA Medical Review for Ventolin HFA at 41, 69, 98.

The rates of non-therapeutic response seen in the clinical trials for the three other albuterol and levalbuterol products were consistent with these results, further confirming that there are weak or inadequate non-therapeutic responders to albuterol and levalbuterol in the population. As shown in FDA's review documents:

- Proventil HFA was approved largely on the basis two pivotal trials, Trial 1031 and Trial 1012. The percentage of patients in Trial 1031 receiving albuterol CFC or HFA who failed to achieve a 15% or greater increase in FEV-1 by 30 minutes was between 20 and 36%, depending on the study arm. For Trial 1012, non-therapeutic response rates were similar. Tab 4, FDA Summary Basis of Approval for Proventil HFA at 79-80, 259.
- Xopenex HFA was shown to be safe and effective primarily on the basis of three large, randomized, placebo-controlled clinical trials – two in adults and adolescents (known as trials 051-353 and 051-355) and one in children (known as trial 051-354). The percentage of patients in trials 051-353, -355, and -354 who failed to achieve the minimum therapeutic response of a 15% or greater increase in FEV-1 above baseline on levalbuterol HFA or albuterol HFA increased over time, and was between 13 and 40%, 17 and 43%, and 18 and 47%, respectively, depending on the study, arm, and visit. Tab 5, FDA Medical Review for Xopenex HFA at 119, 138, 154.

- Proair HFA pivotal trial BNP-301-4-167 showed that between 34 and 51% of patients failed to achieve a 15% or greater increase in FEV-1 over baseline during the course of the six-week trial, depending on the study, arm, and visit. Tab 6, FDA Medical Review for Proair HFA at 98.[4]

The entry criteria for these trials also may have excluded other patients who would not have responded adequately to albuterol or levalbuterol over the course of the full study. That is, patients were screened for their responsiveness to albuterol, and those who did not appear to show an initial response were excluded from participation. For example, in Ventolin HFA trials SALA3002, SALA3005, and SALA3006, patients were required to demonstrate "airway reversibility." The reversibility of each patient's condition was documented by the response to two puffs of albuterol inhalation aerosol. If a patient's FEV-1 increased by 15% or more, then the patient's airway condition was considered to be reversible and he or she was permitted entry into the trial. If the patient did not respond to this degree, he or she was excluded. Patients with "poorly controlled asthma" were likewise excluded (including, for instance, those whose asthma may have been poorly controlled due to their non-therapeutic response to albuterol). Tab 3, Ventolin Review at 28, 53, 81.

The same or similar selection criteria were used in the trials supporting approval of the other proposed alternative products. *See* Tab 4, FDA Summary Basis of Approval for Proventil HFA at 74, 90; Tab 6, Proair Review at 36, 72, 115; and Tab 5, Xopenex Review at 5, 38, 104-05, 129, 145. The fact that such high and consistent rates of non-therapeutic response were seen in clinical trials designed to *exclude* such patients underscores the importance of not limiting patients who require short-acting beta-2 agonist therapy to a single active moiety.[5]

In addition to the clinical study experience, studies reported in the literature show compelling examples of albuterol non-response in various contexts. For example, one prospective study involved 116 emergency room patients with acute asthma exacerbations who were treated with albuterol. To ensure full delivery of the drug, patients were administered albuterol *via* an MDI and a spacer device. The study showed that 30% of the patients failed to have an adequate therapeutic response to the drug and had to be admitted to the hospital for further care. Tab 9, C. Rodrigo & G. Rodrigo, *Therapeutic Response Patterns to High and*

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[4] The clinical trials supporting FDA approval of the original Maxair MDI also showed instances of non-therapeutic response to pirbuterol. As with albuterol and levalbuterol, there are many possible explanations for the diversity of patient responses to these drugs, including tachyphylaxis and genetic factors. The consistency of these non-therapeutic response rates underscores that no one moiety can be considered effective for all asthma patients.

[5] The exclusion from clinical trials of patients who fail to demonstrate a positive bronchodilator response to albuterol may be leading to selection bias with regard to the primary endpoints in the trials. For this reason, some investigators have chosen to study patients with "doctor-diagnosed" asthma, rather than patients with drug-specific spirometrically-defined "reversible airway obstruction." *See* Tab 7, D. Taylor, *et al.*, *Bronchodilator Response in Relation to β2-Adrenoreceptor Haplotype in Patients with Asthma*, 172 AM. J. RESPIR. CRIT. CARE MED. at 700-03 (2005). As noted below, Charles A. Martin, P.A., testified at FDA's August 2, 2007, public meeting regarding the Proposed Rule that he personally has been invited to participate in several asthma trials, only to be excluded because of his non-therapeutic response to albuterol: "[A]t Wake Forest I've been asked to participate in a number of trials. And in participating in those trials, many of them for entrance, you have to be able to respond to Albuterol, and I still do not respond to Albuterol." Tab 8, Transcript of August 2, 2007, Public Meeting at 131.

Cumulative Doses of Salbutamol in Acute Severe Asthma, 113 CHEST at 593-98 (1998); *see also* Tab 10, L. Strauss, *et al.*, *Observations on the Effects of Aerosolized Albuterol in Acute Asthma*, 155 AM. J. RESPIR. CRIT. CARE MED. at 454-58 (1997) (finding 34% of patients non-responsive to albuterol).

Comment No. 3

At the Public Meeting, FDA heard evidence that some patients do not respond adequately to albuterol, but nevertheless succeed on pirbuterol. Comments submitted to the docket for this proceeding offer additional reports of patients who have failed on albuterol therapy but succeeded on pirbuterol. Prescribing data likewise show that many patients who begin on albuterol subsequently switch to pirbuterol. While some switches may be prompted by allergies, intolerance, or other side effects, or the need for breath-actuated delivery, experience suggests that many switches are the result of non-therapeutic response to albuterol and levalbuterol.

Testimony from distinguished physicians at FDA's August 2, 2007, public meeting (the Public Meeting) reinforces the prevalence of non-therapeutic response to albuterol. The substantial clinical experience of these physicians also shows that many patients who fail to show an adequate response to albuterol can be treated successfully with pirbuterol.

At the Public Meeting, FDA was presented with the comments of Hassan M. Makhzoumi, M.D., the Chief of Pulmonary Medicine of St. Joseph Medical Center in Maryland. In addition to his role at St. Joseph's and his extensive private practice, Dr. Makhzoumi has also served as an Instructor in the Division of Respiratory Medicine at the Johns Hopkins University School of Medicine. As Dr. Makhzoumi explained (in audio-recorded comments):

> First of all, as you know, the chemical agent in Maxair is Pirbuterol. It's a rapid acting beta-agonist . . . . importantly, it seems that that particular subtype of beta-agonist seems to work very well with a subset of my asthmatics in which Albuterol does not seem to produce the same effects. To be very honest with you, Maxair or Pirbuterol is not my first choice. My first choice is Albuterol. And I'd have to say six, maybe seven out of ten asthmatics do well with that. Pirbuterol is what I turn to when asthmatics do not do well with Albuterol, when asthmatics on Albuterol seem to end up frequently in the emergency room and be admitted. Do not ask me why, I am not a scientist, I'm the clinician, I'm the practitioner, I'm the front lines here. What I can tell you is that about 30% of my asthmatics, particularly the young and the professional, seem to do far better with Pirbuterol rescue therapy and lead much more of a controlled asthma life than those who use Albuterol.

Tab 11, Graceway Presentation at Aug. 2, 2007, Public Meeting.

At the Public Meeting, FDA also heard testimony from Mark Boguniewicz, M.D., a Professor in the Division of Pediatric Allergy and Immunology in the Department of Pediatrics at National Jewish Medical and Research Center in Colorado, one of the most respected respiratory

hospitals in the country. Dr. Boguniewicz stated that he uses Maxair Autohaler to treat patients "who either don't tolerate or have sub-optimal responses to Albuterol, or other short-acting beta agonists," and that Maxair Autohaler is "effective for that subgroup of patients." Tab 8, Aug. 2, 2007, Transcript at 159.

Another expert who testified at the Public Meeting was Michael E. Wechsler, M.D., M.M.Sc., an Assistant Professor of Medicine at Harvard Medical School and Brigham and Women's Hospital in Massachusetts. He is also the Assistant Director of the BWH Asthma Research Center, and also serves on the Steering Committee of the National Institutes of Health Asthma Clinical Research Network. Dr. Wechsler described for the FDA panel both his own clinical experience with albuterol non-response, as well as his research into characterizing a genetic basis:

> I generally prescribe generic Albuterol to most of my patients. It works in most people, but it doesn't work in everybody. And I used to think when I was early on in my career that when a patient said he wasn't responding to Albuterol, that they were crazy, or didn't have asthma. And they would say, you know, I just don't get better. And then as we've done more work in this area, we've come to understand that there's a fair amount of heterogeneity in terms of response to these therapies, not just short-acting beta agonists, but long-acting beta agonists, inhaled corticosteroids, leukotriene modifiers. For each of these therapies in asthma, there are responders and non-responders with each of these classes, and also, across classes, as well as within each of these classes. And we've demonstrated that there are responders and non-responders to each of these therapies . . . . And we've published data demonstrating both prospectively, as well as retrospectively, that there is a differential response to beta agonists in individuals who harbor different genotypes.

Id. at 160-62.

In addition, FDA heard testimony from patients who report that they do not respond to albuterol, but respond well to Maxair Autohaler. According to Charles A. Martin, P.A., a physicians' assistant and an Instructor of Surgical Sciences in Ophthalmology at Wake Forest University:

> When I first had a test done for my pulmonary function study, it was noted on that occasion that my pulmonary function study looked like an asthmatic, but when challenged with Albuterol, I showed no response. And since that time, I still show no response. And that's been repeated a number of times, and at Wake Forest I've been asked to participate in a number of trials. And in participating in those trials, many of them for entrance, you have to be able to respond to Albuterol, and I still do not respond to Albuterol. I do respond to Maxair.

Id. at 131.

Further, Meg Griffiths, an asthmatic for 17 years who first developed the condition after a series of respiratory infections at the age of 10, testified:

> [F]rom 1991 to 1997, I worked with my asthma doctor to find a medicine that worked, basically went through like a mix of asthma medicine cocktails. It was like, okay, is this one going to work? No. Is this one going to work? I went through Ventolin, Vanceril, Tilade, Theophylline, and later Advair, and various other colorful pumps, pills, and powders that made [me] shaky, [but] they didn't make me – the wheeziness go away . . . . Finally, after seven years, my asthma doctor, who is also a fellow asthmatic, said to me, 'Meg, we've got one that'll work.' And it was Maxair.

Id. at 135-36.

Numerous written comments have also been submitted by patients and caregivers who report that they or a family member do not respond sufficiently to albuterol products, but do respond to pirbuterol. Among these are the following:

- I have been using the Maxair Autohaler for over a year now to control my activity-induced asthma. After struggling with asthma and allergies for over a decade, I have finally found something that allows me to exercise without instant chest pain and wheezing . . . . I have tried a dozen other inhalers and medicines, but Maxair is the only one that has ever worked for me. (S. Costanza.)
- I've recently heard from my doctor that Maxair autohaler will not be on the market after 2009. This has me worried as other medications do not work nearly as well as Maxair. Without Maxair, I'm worried asthma attacks may force a change in lifestyle. This is because the medicine that would be available won't work as nearly as well and [I] must take greater care to avoid any activities that may lead to even a remote chance of attacks. (B. Shaw.)
- Maxair has saved me from many asthma attacks, and has saved me from going to the hospital. No other medication has worked for me so fast. PLEASE DON'T TAKE IT OFF THE MARKET. (V. Van Artsdalen.)
- My Granddaughter needs this medication. She is immune compromised and this stuff works for her as others have not. (F. Stowman.)
- Without Maxair [my daughter] may not be able to continue with her normal day to day activities. She has tried other inhalers and doesn't respond to those medications as well as Maxair. (T. Swier.)

Tab 12 (emphases in originals).

Finally, prescription data show that significant numbers of patients are prescribed Maxair Autohaler only *after* having been prescribed an albuterol product. According to Verispan data, between June 1, 2006, and May 31, 2007, more than 14,000 patients were switched from albuterol to Maxair Autohaler. Of these, more than 4,000 patients moved from an albuterol HFA product to pirbuterol, indicating that they were not switched as part of the market's general transition away from CFC products. Tab 13. Even if only a

fraction of these patients switched from albuterol to pirbuterol due to non-response, it is a substantial number over a relatively brief period of time.

In making its tentative conclusion that the four albuterol/levalbuterol products are "adequate therapeutic alternatives" to Maxair Autohaler, the agency has improperly failed to consider (a) the fact that many patients do not respond adequately to the albuterol moiety, and (b) the significant clinical evidence that many of these patients do respond well to pirbuterol, and thus depend on Maxair Autohaler for their rescue therapy.

Comment No. 4

Academic research and expert opinion are focusing on a specific biological mechanism to explain non-therapeutic responses to albuterol and levalbuterol, *i.e.*, heterogeneity at a critical site on the beta-2 adrenergic receptor gene. Clinical studies have not been conducted to establish whether these patients may respond differently to pirbuterol. Nevertheless, empirical reports from patients and clinicians strongly suggest that many patients experience such a differential response.

There are several potential reasons why patients may not respond adequately to albuterol or levalbuterol. For example, with respect to non-therapeutic response rates in clinical trials, the frequent dosing of patients may result in an acquired resistance to the drugs. However, a growing body of evidence suggests that much of the observed variability in patient response has a genetic basis.

The current state of knowledge about the pharmacogenomics of asthma is summarized in a follow-up letter prepared for the docket by Dr. Wechsler, supplementing his testimony at the public meeting. His letter states

> One retrospective analysis in more than 250 subjects with mild asthma showed that individuals with homozygosity for arginine (Arg/Arg) at [the 16th amino acid position on the beta-2 adrenergic receptor gene], when randomized to regular albuterol use versus as-needed use, suffered a *decline* in peak expiratory flow of 24L/minute. Another retrospective study of the same [single nucleotide polymorphism, or] SNP found that subjects had more asthma exacerbations during treatment with albuterol than during treatment with placebo. This amino acid position has also been found to be associated with airway hyper-responsiveness, particularly among non-smokers.
>
> The same result has recently been documented in a prospective study. In this well-controlled study, subjects with mild asthma were enrolled in pairs matched for forced expiratory volume in one second (FEV-1) according to whether they were homozygous for arginine (Arg/Arg) or glycine (Gly/Gly) at the 16th amino acid position. The groups were provided regular treatment with either albuterol or placebo in a masked, crossover design, for 16 weeks. The study began with a six-week, single-blind, run-in period, during which subjects were instructed to

> minimize their use of albuterol and to rely instead on twice-daily use of a placebo inhaler, with open-label ipratroprium bromide for rescue.
>
> During the run-in period, subjects with the Arg/Arg genotype had a 23L/minute increase in their morning peak expiratory flow rate (PEFR) by the end of week six, while relying on placebo and non-albuterol rescue. By contrast, the Gly/Gly subjects had only a 2L/minute improvement. *During the double-blind phase of the study, the Arg/Arg subjects demonstrated no significant change in their morning PEFR over the 16 weeks on albuterol, while demonstrating a significant increase in PEFR on placebo. The Gly/Gly subjects, again, showed just the opposite – no change while on placebo, but a significant increase in PEFR while on albuterol.* Significant genotype-related differences were also seen in this study in FEV-1, forced vital capacity, patient-recorded evening PEFR, rescue inhaler use, and asthma symptoms.

Tab 14 (references omitted) (emphasis added).

Another recent study suggests that pharmacogenetic differences in patient response to albuterol may exist within individual ethnic groups. Tab 15, S. Choudhry, *et al.*, *Pharmacogenetic Differences in Response to Albuterol between Puerto Ricans and Mexicans with Asthma*, 171 AM. J. RESPIR. CRIT. CARE MED. at 563-70 (2005); *see also* 64 FR at 47727 (emphasizing the need to consider "the medical needs of demographic subgroups, including racial and ethnic groups" when determining whether to remove an essential use).

Dr. Wechsler acknowledges in his letter, as he did in his testimony at the public meeting, that studies have not been conducted to establish whether and how many of these patients may respond to pirbuterol. That said, the quantity and quality of clinician and patient reports indicate that at least some albuterol non-therapeutic responders do respond to pirbuterol. Moreover, as Dr. Wechsler writes, the fact that approximately *one-sixth* of asthma patients in the United States express the Arg/Arg genotype makes it essential that physicians continue to have access to different drugs for the treatment of patients with asthma and related conditions.

Comment No. 5

> **FDA tentatively concluded that the four albuterol/levalbuterol products would collectively provide adequate therapeutic alternatives for all patients currently using Maxair Autohaler. In light of the available data, the testimony at the Public Meeting, and the many submissions to the docket, the agency cannot reach a final determination that albuterol/levalbuterol will be effective for all patients who require short-acting therapy. The evidence points strongly to the conclusion that at least one additional, distinct moiety should continue to be available for this group.**

The agency's tentative conclusion that all Maxair Autohaler patients may switch to the four proposed alternative products was based primarily on the fact that all five products bear nearly the same labeled indication. 72 FR at 32036-37. The "Indications and Usage" section of the labeling is, however, a poor proxy for assessing whether one product is an adequate

substitute for another, particularly when the products contain chemically distinct active ingredients.

For example, the scientific literature and clinical data show that a significant number of patients with reversible bronchospasm do not respond adequately to albuterol or its active isomer, levalbuterol. *See* Comments 2-4, above. Further, as discussed in Comments 6-9, below, even patients who may respond to the drug for its intended use may not be able to tolerate its side effects. The fact that albuterol and levalbuterol are indicated for treating bronchospasm certainly does not establish that all patients in the class will respond favorably to these chemically synonymous drugs. As discussed at the Public Meeting:

> [W]e've just really started to recognize that asthma is much more complex, and has unique phenotypes or subtypes, and that individual patients will respond or fail to respond, or have problems with specific medications. Tab 8, Aug. 2, 2007, Transcript at 158-59 (Dr. M. Boguniewicz).
>
> [F]or people who are non-responders, [pirbuterol] does provide an additional agent in the armamentarium against asthma. *Id.* at 164 (Dr. M. Wechsler).
>
> Asthma is on the rise . . . [a]nd we should be increasing our options to our physicians rather than taking away from them substances that seem to work, and work well. Tab 11 (Dr. H. Makhzoumi).

In short, given the well-established – but not completely understood – heterogeneity in the asthma population, there is no rational basis for concluding that all Maxair Autohaler patients will find albuterol and levalbuterol to be adequate therapeutic alternatives. To the contrary, the evidence strongly supports retaining at least one additional unique moiety. *See generally* 62 FR 1889, 1891 (Jan. 14, 1997) (recognizing "that responses to drugs are not uniform among individuals and, for reasons that are often unclear and difficult to discover, some patients may respond better, with respect to therapeutic effectiveness or tolerance, to one drug than to another."); Tab 16, *CDER Offices Go Public with "Fundamental Disagreement" Over Avandia*, THE PINK SHEET (Aug. 6, 2007) (quoting a senior FDA official as stating that "[s]imply having drug choices is worthwhile for a disease where multiple drug treatment is common and patients do not uniformly either respond to or tolerate any given agent").

2. Intolerance to Albuterol

For purposes of an essential-use rulemaking, if patients cannot use the available alternative products, because of intolerance or allergic reaction, then the alternatives are not acceptable. 64 FR at 47726. The administrative record establishes that there are patients who cannot tolerate, or who are allergic to, albuterol and levalbuterol. The four proposed alternative products – all of which depend on either racemic or isomeric albuterol – are not acceptable alternatives. As a result, pirbuterol must remain an essential-use under the regulatory framework.

Comment No. 6

Many patients with reversible bronchospasm experience intolerance or an allergic reaction to albuterol and its active isomer, levalbuterol. This is illustrated in, among other sources, the scientific literature, the clinical data supporting approval of each of the four alternative products, and each product's approved labeling. For patients who experience side effects or allergic reactions to albuterol or its active isomer, levalbuterol, pirbuterol is an essential product.

The selectivity of beta-agonists for beta-2 receptors (which are found primarily in pulmonary tissue), as opposed to beta-1 receptors (found primarily in cardiac tissue), is known to affect the risk of cardiac side effects in this class of drugs. As FDA acknowledged in the Proposed Rule, beta-agonists that are less selective tend to present a greater risk of cardiac side effects.[6]

With regard to pirbuterol, early *in vitro* animal studies demonstrated that the selectivity of pirbuterol for beta-2 receptors, as opposed to beta-1 receptors, is nine times greater than that for albuterol (and, by extension, levalbuterol). Tab 17, P. Moore, *et al.*, *Pirbuterol, a Selective Beta$_2$ Adrenergic Bronchodilator*, 207 J. PHARMACOL. EXP. THER. at 410-18 (1978). In the same study, *in vivo* tests on dogs showed that albuterol caused more pronounced tachycardia than pirbuterol: "The present results suggest that pirbuterol has a more favorable dose-cardiac effect ratio than [albuterol] . . . and it thus is expected to have less propensity to cause cardiovascular side-effects in man." *Id.; see* Tab 18, H. Windom, *et al.*, *A Comparison of the Haemodynamic and Hypokalaemic Effects of Inhaled Pirbuterol and Salbutamol*, 103 N. Z. MED. J. at 259-61 (1990) (finding that albuterol caused greater cardiovascular effects than equal doses of pirbuterol in a double-blind study in eight healthy human subjects).

As recounted in numerous comments submitted to the docket (including several highlighted below), the experience of patients and physicians confirms this. *See, e.g.*, Tab 19 (Dr. H. Makhzoumi) ("First of all, as you know, the chemical agent in Maxair is pirbuterol. It's a rapid acting beta-agonist. It is rather specific for beta 2 as opposed to beta 1, which I like, doesn't affect the cardiovascular system a whole lot."). The approved labeling for the proposed alternative products also provides clear clinical evidence of the cardiac-related side effects for the products in the class. The labeling for Proventil HFA, for example, reports that 7% of patients in the pivotal clinical trial suffered from tachycardia, and that an equal number of patients suffered from nervousness. In addition, the labeling for each of the alternative products contains a prominent Warning on "immediate hypersensitivity reactions," including urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. Tab 20, Approved Labeling for Proair HFA, Proventil HFA, Ventolin HFA, Xopenex HFA, and Maxair Autohaler. The risk of allergic reaction is also noted in the Adverse Reactions section of the products' approved labeling. *Id.*

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[6] 72 FR at 32036 n.15 ("Metaproterenol, because it is less selective than pirbuterol, albuterol, levalbuterol and some other beta$_2$-agonists, may present greater potential for excessive cardiac stimulation") (references omitted).

On the other hand, the approved labeling for Maxair Autohaler shows only a 1.2% rate of tachycardia. *Id.* Maxair Autohaler has also not been required by FDA to carry a hypersensitivity warning, and Graceway is not aware of clinical data or published literature that indicate a similar hypersensitivity risk for pirbuterol. *Id.* Again, no one product and, most of all, no single moiety, is sufficient to adequately treat the asthma and COPD population, given the known side-effect profiles of these drugs.

Comment No. 7

As recognized in the class labeling adopted by FDA, patients may experience paradoxical bronchospasm after using albuterol, levalbuterol, pirbuterol, or other inhaled medicines. The scientific literature shows that these reactions may be specific to the active moiety. FDA, through labeling, instructs patients to use an alternative drug if they experience paradoxical bronchospasm. By eliminating pirbuterol, the agency is proposing to remove a critical therapeutic alternative.

Paradoxical bronchospasm is a potentially life-threatening reaction that can occur with the use of any inhaled medicine, including the albuterol/levalbuterol products proposed as alternatives by the agency. The reaction is characterized by a sudden contraction of the smooth muscle in the walls of the bronchi soon after the administration of the drug. It is "paradoxical" because it is contrary to the response expected – bronchodilation. When a patient experiences paradoxical bronchospasm on one drug, such as albuterol, it is critical that he or she have available another short-acting beta-agonist. By eliminating pirbuterol – without the benefit of data or analysis – FDA is proposing to remove an important alternative for patients who face this life-threatening event.

The causes of paradoxical bronchospasm are poorly understood. Data are difficult to interpret because of the close relationship between the reaction and the underlying condition the drugs are intended to treat. For certain patients, paradoxical bronchospasm may be formulation-specific or may be caused by impurities that leach from device components. For other patients, however, the cause appears to be moiety-specific.

Numerous case reports in the scientific literature describe instances of paradoxical bronchospasm where the only possible cause is the individual active moiety. For example, in November 2005, professors from Rutgers University reported the case of a 92-year-old man with COPD. Within 30 minutes of his first inhalation from an albuterol MDI, he experienced shortness of breath and difficulty speaking. After being treated with oxygen, the man recovered but experienced another episode two hours later, after receiving nebulized albuterol. In this case, formulation issues could not be responsible because the metered-dose and nebulized albuterol had no excipients in common. Tab 21, L. Spooner & J. Olin, *Paradoxical Bronchoconstriction with Albuterol Administered by Metered-Dose Inhaler and Nebulizer Solution*, 39 ANN. PHARMACOTHER. at 1924-27 (2005).

In another case, a 40-year-old woman with severe chronic asthma presented in the emergency department complaining that her nebulized albuterol exacerbated her symptoms. Her

condition improved when she was switched from nebulized albuterol to nebulized terbutaline. The patient agreed to later undergo a double-blind challenge study. On two later occasions one week apart, the woman took either 2.5 mg nebulized albuterol or 5 mg nebulized terbutaline over 10 minutes. Five minutes after receiving albuterol, her FEV-1 fell 15.5% and her peak flow fell by 7.1% in 15 minutes. Five minutes after receiving terbutaline, her FEV-1 increased 18.9% and her peak flow rose by 12.8% in 15 minutes. Again, formulation was ruled out as a factor through skin prick testing of the nebulized albuterol solution. The authors concluded:

> The apparent gradual improvement in lung function when our patient was changed from nebulized albuterol to terbutaline, and the results of our challenge tests strongly indicate, however, that paradoxical bronchoconstriction to β_2-agonists is not inevitably a class-effect *but can be related to exposure to a specific β_2-agonist and not to others.*

Tab 22, J. Finnerty & P. Howarth, *Paradoxical Bronchoconstriction with Nebulized Albuterol but Not with Terbutaline*, 148 AM. REV. RESPIR. DIS. at 512-13 (1993) (emphasis added).

Nor is levalbuterol, given its identical chemical structure, likely to be an acceptable alternative for patients who experience paradoxical bronchospasm with albuterol. Indeed, a recent scientific report indicates that patients who experience paradoxical bronchospasm with albuterol may also experience it with levalbuterol. In March 2006, two physicians reported the case of an 80-year-old man with COPD suffering from worsening symptoms. He was given nebulized albuterol and ipratropium, which resulted in increased shortness of breath. He was then given levalbuterol, and within several minutes he experienced a significant increase in his dyspnea and a decrease in air entry and oxygen saturation. The patient was taken off of levalbuterol and stabilized with salmeterol and other drugs.[7] Here, as above, excipients were ruled out as a contributing factor. Tab 23, K. Raghunathan & N. Nagajothi, *Paradoxical Bronchospasm: A Potentially Life Threatening Adverse Effect of Albuterol*, 99 SOUTH. MED. J. at 288-89 (2006).

Given the serious nature of paradoxical bronchospasm, the class labeling adopted by FDA prudently states that, "[i]f paradoxical bronchospasm occurs, [use of the inhaler] should be discontinued immediately and alternative therapy instituted." Tab 20, Approved Labeling. As shown by several comments to the docket (*see, e.g.*, N. Sabak Pope, L. Mazepink, L. Taylor, in Comment 8, below), patients who have experienced paradoxical bronchospasm in response to albuterol have found safe and effective relief with Maxair Autohaler. In short, FDA must consider the twin problems of forcing pirbuterol patients to switch to albuterol or levalbuterol, as well as the absence of alternatives should pirbuterol be removed from the market. In either case, where instances of paradoxical bronchospasm arise – as predicted in the labeling – there will be no viable MDI option for those who fail on albuterol/levalbuterol.

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[7] Because this patient experienced paradoxical bronchospasm on albuterol and levalbuterol, but was then stabilized on salmeterol, another (albeit long-acting) beta-2 agonist, this represents further evidence that this reaction can be moiety-specific.

Comment No. 8

The administrative record is replete with comments from patients who have experienced intolerance (including paradoxical bronchospasm) or allergic reaction to albuterol, but have succeeded on pirbuterol. Many report a complete inability to tolerate the side effects associated with albuterol. The record also strongly suggests that many Maxair Autohaler patients would not use the alternative products, given their previous adverse experiences. These patients would be at serious risk of increased morbidity or mortality and decreased quality of life, were the agency to finalize the rule and remove pirbuterol as a therapeutic alternative.

Patients and caregivers have submitted compelling and detailed statements regarding specific experiences with pirbuterol therapy and the proposed alternatives. Following are several examples:

- Three years ago, my doctor and I discovered that I am allergic to albuterol, which is a key component in all other rescue inhalers. After suffering a near-fatal allergic reaction to an albuterol inhaler, I switched to Maxair, which has successfully controlled my asthma ever since . . . . I am sincerely worried about what I will do if Maxair is removed from the market, as I will be left with no other options to treat my asthma in rescue situations! (K. Ryzewski.)
- I am an asthma sufferer who also has Wolf Parkinson White's Syndrome, a birth defect that allows my heart to beat irregularly, sometimes over 200 beats per minute. Because of this condition I cannot use albuterol inhalers because they cause my heart to race, an understandably dangerous event. Maxair autohaler is the only inhaler I can use during asthma attacks or allergy season . . . . (A. Fussell.)
- I use [Maxair] . . . . It is the only product that does not cause problems with my heart. (N. Lloyd.)
- Due to the reactions I get from all other rescue inhalers, Maxair is the only one that really works for me. The other brands cause me to start shaking enough to stop me from typing or driving. (D. Leister.)
- I have been using Maxair for about two years now . . . . it was prescribed to me since it does not contain albuterol since I have some [arrhythmia] and the [albuterol] is harder on my heart according to the doctor. (C. Cron.)
- I personally use the maxair autohaler . . . I have tried multiple inhalers, and this is the only one which works on me, and doesn't make me shake. (T. Nikolitis.)

- I have tried others they do not work[.] Maxair is the only one that works for me and keeps me out of the hospital. The albuterol inhalers make me sick, they do not work for me. (S. Torimino.)
- I discovered that Albuterol and Salmeterol [cause] me severe bronchospasm. So the loss of Pirbuterol would leave me with ABSOLUTELY NO ALTERNATIVES as a rescue medication. I have never tried epinephrine but since I am also allergic to Bisulfites, that is not an option either . . . . Pirbuterol is the only one that works for me. (Dr. N. Sabak Pope.)
- I've used maxair as my rescue inhaler since 1996 and I'd be in big trouble with out it. I'm not able to use provental/albuterol. It actually, tightens me up and I literally can not breathe and exhale on this medicine!! I've been in a panic worrying that maxair will be taken off the market!! (L. Mazepink.)
- Maxair improved the quality of my life. I am grateful for Maxair. I had been using another product which caused jitters, high blood pressure, and irritability. (S. Leeapman.)
- My stepson uses Maxair because Albuterol causes him to have bronchospasm. Assuming that everyone can switch to Albuterol for a rescue inhaler is not being responsible. (L. Taylor.)
- I am almost 73 and have been on maxair for 18 or 19 years. I have a bad reaction to albuterol and many other inhalers. (M. St.Sauveur.)
- I have many allergies & this is the *one* that I can take – after trying others. (S. Herman.)
- I am 70 yrs old other inhalers cause my heart to speed up and make me very 'jumpy' for several hours. (J. Chapman.)
- This is the one inhaler my daughter can use for breakthroughs without allergic reactions. (P. Lukas.)
- I can't use any other emergency inhaler EXCEPT MAXA[IR] . . . . I was hospitalized once for the side effects of inhaled albuterol. I accidentally overdosed and passed out in front of a class of 20 kids. The side effects of albuterol are famously bad. Both of my parents have been ho[sp]italized due to known drug interactions from taking albuterol! I used to get such a case of the shakes and my heart pounding that I told the doctor I would rather have asthma than use that albuterol inhaler. (J. Jennings.)
- I am allergic to so many other medicines. No one medicine is right for everyone but Maxair is right for me. (E. Bush.)

Tab 24 (emphasis in originals).

Comment No. 9

The administrative record contains numerous and detailed comments from physicians regarding patients who experience intolerance or allergic reaction to albuterol and levalbuterol, including the testimony of leading clinicians provided at the Public Meeting. These physicians explain that pirbuterol is generally used as a second-line therapy, behind albuterol, for patients who react adversely or respond poorly to albuterol. The comments from physicians, including several comments from physicians at major academic medical centers, strongly support the continued listing of Maxair Autohaler as an essential-use product.

FDA has received comments from leading academic researchers, as well as practicing physicians, who consider Maxair Autohaler an essential second-line therapy. While they generally treat most of their patients with albuterol, they rely on Maxair Autohaler for patients who have adverse reactions or respond poorly to albuterol therapy. For example:

- Dr. Robert Anolik, an asthma and allergy specialist in the Philadelphia area: "[T]here are some patients who clearly are intolerant of Albuterol. They have behavior side effects. They have difficulty sleeping. They get tachycardia. Parents will occasionally describe children as getting cranky and irritable, and it appears to occur much less commonly with Pirbuterol, with Maxair, and we often switch patients from Albuterol to Maxair to avoid those side effects." Tab 19.
- Dr. Mark Boguniewicz: "I treat patients with Pirbuterol Maxair, who either don't tolerate, or have sub-optimal responses to Albuterol, or other short-acting beta agonists." Tab 8, Aug. 2, 2007, Transcript at 159.
- Dr. Michael Kaliner, an allergist in Wheaton, Maryland: "As a busy clinician I see asthmatic patients every day and always make certain they have a rescue inhaler for emergency use . . . . [T]here are a few patients who cannot tolerate albuterol because of adrenergic symptoms . . . . For my patients who cannot tolerate albuterol, Maxair provides the only alternative they have . . . . While we are only speaking of a relatively small percentage of my patients, their needs are important to me." Tab 25.
- Dr. Thomas Puchner, an allergist in Madison, Wisconsin: "I would estimate 30-40% of my asthma patients have Maxair as their rescue inhaler. The primary reason is most do not tolerate albuterol because of side effects such as tremors, palpitations, feeling jittery, etc. In my experience, I would estimate 75-80% of patients who do not tolerate albuterol tolerate Maxair. This is critical for patients to have a rescue inhaler that they can tolerate for acute symptoms. Many of the patients experiencing side effects with albuterol would avoid using albuterol because of side effects, even though they were having problems breathing!" Tab 26.

- Dr. Richard Greene, an allergist and immunologist in Pennsylvania: "I am an allergist and have been in practice for 30+ years . . . . There are clearly patients who don't tolerate albuterol and do better with metaproterenol or pirbuterol." Tab 27.
- Dr. Joseph Bellanti, professor at Georgetown University Medical Center: Patients who have "adverse effects of the albuterol products with jitteryness and hypersensitivity can successfully use pirbuterol because of this molecular difference that effects pharmacologic action." Tab 8, Aug. 2, 2007, Transcript at 41-42.

Again, as discussed in Comment 3, the experience of these clinicians is confirmed by Verispan prescribing data, which show that significant numbers of patients are prescribed pirbuterol only *after* taking an albuterol product. Between June 1, 2006, and May 31, 2007, more than 14,000 patients were switched from an albuterol product to pirbuterol. Of these, more than 4,000 patients moved from an albuterol HFA product to pirbuterol. Tab 13. This snapshot further shows the key role for Maxair Autohaler as an alternative for those patients who have previously tried an albuterol therapy, including the proposed HFA alternatives identified by FDA.

3. For Patients Who Do Not Respond to, or are Intolerant of, Albuterol, Pirbuterol Provides a Distinct Chemical Moiety

Comment No. 10

If the Proposed Rule is finalized, asthma and COPD patients who require treatment with a short-acting adrenergic bronchodilator will be limited to albuterol or its active isomer, levalbuterol. Given the size and diversity of the patient population, and the increasing numbers of patients being diagnosed with asthma and COPD, the population should not be limited to a single chemical structure, *i.e.*, (R)-albuterol.

Asthma and COPD are rapidly growing health problems in the United States. In 2005, asthma affected approximately 7.7% of the United States population and increased at a rate greater than 10% from 2002 to 2005. Tab 1, Akinbami. The disease is currently estimated to affect approximately 22.2 million Americans. *Id.* Approximately 16 million Americans suffer from COPD. Over the last three decades, COPD has increased as a cause of death and now claims over 120,000 lives annually in the United States. Tab 28, T. Croxon, *et al.*, *Future Research Directions in Chronic Obstructive Pulmonary Disease*, 165 AM. J. RESPIR. CRIT. CARE MED. at 838-44 (2002); Tab 29, American Lung Association, *COPD Fact Sheet* (2007).

Short-acting adrenergic bronchodilators, including albuterol, levalbuterol, and pirbuterol, are critically important treatments that ease the symptoms of asthma and COPD by activating the beta-2 adrenergic receptor on the muscles surrounding the airways and causing the muscles to relax. *See* Tab 30, NIH *Guidelines for the Diagnosis and Management of Asthma* at 214 (2007).

Relaxing the surrounding muscles enables the airways to dilate, relieving the breathlessness common to these conditions.

In the Proposed Rule, FDA asserts that four products – Proair HFA (albuterol sulfate), Proventil HFA (albuterol sulfate), Ventolin HFA (albuterol sulfate), and Xopenex HFA (levalbuterol tartrate) – will provide "adequate therapeutic alternatives" for every patient currently using Maxair Autohaler to treat their asthma and COPD. 72 FR at 32036. The products with albuterol sulfate contain a 50-50 mixture of the (S)- and (R)- isomers of albuterol; the product with levalbuterol tartrate contains only the active, (R)-isomer of albuterol.

As demonstrated in the Contraindications, Warnings, and Precautions sections of Xopenex's FDA-approved, levalbuterol does not offer an improved side-effect profile relative to albuterol. Tab 20, Approved Labeling. Randomized, double-blind, placebo-controlled clinical trials have found no meaningful differences in the safety profiles of albuterol and levalbuterol. *See, e.g.*, Tab 31, F. Qureshi, *et al.*, *Clinical Efficacy of Racemic Albuterol Versus Levalbuterol for the Treatment of Acute Pediatric Asthma*, 46 ANN. EMERG. MED. at 29-36 (2005); Tab 32, J. Lötvall, *et al.*, *The Therapeutic Ratio of R-Albuterol Is Comparable With That of RS-Albuterol in Asthmatic Patients*, J. ALLERGY CLIN. IMMUNOL. at 726-31 (2001). Finally, clinicians have also noted that levalbuterol is not a distinct therapeutic alternative to albuterol. As succinctly stated in the comments of Dr. Linda Rogers, Assistant Professor of Clinical Medicine, New York University School of Medicine, "Levalbuterol is not sufficiently different from albuterol to be an alternative for patients who cannot tolerate albuterol or an albuterol HFA product." Tab 33.

Thus, in proposing to remove pirbuterol from the market, FDA is proposing to limit asthma and COPD patients to only a single active moiety, (R)-albuterol. Pirbuterol, unlike albuterol or its active isomer, levalbuterol, is a unique beta-2 agonist with a distinct chemical structure. As Dr. Joseph Bellanti testified during the Public Meeting, "all of the products except pirbuterol have the same molecular structure . . . . the basic difference between the albuterol compounds is that they all have a benzene ring here and the pirbuterol has a pyridine ring which is a ring with a nitrogen atom at one of the interstices." Tab 8, Aug. 2, 2007, Transcript at 41.

As discussed above in Sections 2 and 3, the patient populations are too diverse to rely on only a single molecule, particularly when significant numbers of patients may fail to respond adequately to, or may suffer serious side effects when using, the alternative moiety. Numerous physician and patient comments document that many of these patients appear to succeed on Maxair Autohaler. In short, the size and diversity of the patient population strongly argues in favor of retaining pirbuterol, a *distinct* chemical structure.

4. The Proposed Alternatives Do Not Provide Breath-Actuated Delivery

Comment No. 11

Breath-actuated pirbuterol provides an otherwise unavailable important public health benefit to a significant number of patients. The administrative record, including hundreds of first-hand physician and patient reports,

shows that many patients cannot successfully operate press-and-breathe MDIs. For these individuals, who include children, elderly patients, and patients who are movement impaired or otherwise disabled, Maxair Autohaler is an essential product.

Unlike breath-actuated Maxair Autohaler, FDA's proposed alternative products are conventional press-and-breathe MDIs, which require a patient to have the strength, dexterity, and coordination to do three things simultaneously: press down on the actuator, hold the inhaler to the mouth, and inhale deeply and slowly.

Numerous studies have documented that patients have poor technique with conventional MDIs. According to published estimates, between 28% and 68% of patients, even those without physical limitations, do not use their inhalers well enough to benefit from them. Compounding this problem, between 39% and 67% of nurses, physicians, and respiratory therapists are themselves unable to teach the steps needed for effective inhaler use. Tab 34, J. Fink & B. Rubin, *Problems With Inhaler Use: A Call for Improved Clinician and Patient Education*, 50 RESP. CARE at 1360-75 (2005); *see also* Tab 35, T. Hartert, *et al., Inadequate Outpatient Medical Therapy for Patients With Asthma Admitted to Two Urban Hospitals*, 100 AM. J. MED. at 386-94 (1996).

A survey of 1,173 patients, which included patients who had received training in the proper use of MDIs, documented numerous errors in technique: actuation during expiration; actuation before inspiration; actuation at the end of respiration; actuation after inspiration was completed; actuation which caused inspiration to stop; actuation into the mouth, with inspiration through the nose; and multiple actuations during the same inspiration. Tab 36, G. Crompton, *Problems Patients Have Using Pressurized Aerosol Inhalers*, 119 EUR. J. RESP. DIS. SUPPL. at 101-04 (1982). Failure to use an MDI properly will vary the amount of drug a patient receives, which can negatively impact patient outcomes. For example, actuation only one second prior to inhalation can reduce the inhaled mass of drug by 90%. Tab 34, Fink and Rubin.

Physician reports confirm that Maxair Autohaler provides patients who are unable to use a conventional MDI with an important and otherwise unavailable therapy:

- Some of our patients are not able to use a regular metered-dose inhaler as they can't coordinate actuating and breathing. This device allows them to receive optimal dosage of their rescue medications without worrying about using the device correctly. *In a life-threatening asthma attack, this could make a great difference.* Tab 37, Comment of the American College of Allergy, Asthma, and Immunology (ACAAI) (emphasis in original).
- All of the MDIs require an active process of inhalation and . . . good coordination where a patient actuates the metered inhaler device with a good breath holding and a good change in volume. In contrast, patients who lack the hand-mouth coordination cannot activate this properly and . . . very little of the drug [is] delivered to where it should be going. Tab 8, Aug. 2, 2007, Transcript at 42 (Dr. J. Bellanti).

- For [my patients] who have hand deformities from rheumatoid arthritis, [the Autohaler] is uniquely effective. Tab 38 (Dr. K. Cooper).
- Maxair Autohaler: . . . this product has distinct advantages over the other beta-agonists because it is breath-actuated. I have had years of experience with this and I know that my patients and my nurses LOVE IT. Tab 39 (Dr. W. Storms).
- I am a health care provider and . . . . My arthritic patients are unable to press the canister in the regular HFA inhalers. Tab 40 (K. McGill).

Likewise, numerous patients have described the Autohaler as indispensable to managing their health:

- THIS IS THE ONLY INHALER THAT MY 9 YEAR OLD CHILD CAN TAKE CORRECTLY BY HIMSELF WHEN HAVING AN ASTHMA ATTACK. (E. Leonard.)
- My niece, who is mentally disable[d], was put on Maxair Autohaler by her doctor several years ago. She was having problems knowing when to inhale and exhale whenever she would have an attack. This has been a blessing for her. Whatever she does the Autohaler works for her. I don't know of another inhaler available like it. I request that Maxair remain available for her use. (M. King.)
- I use Maxair Autohaler because I am UNABLE to both push a spray bottle and breathe in at the same time. I've tried and it has resulted in spraying of my tongue, face, and nose – but never into my lungs. (B. Chambers.)
- [W]ith the other inhalers, I was unable to properly time the squeeze with the inhale, and I would either not get the proper dosage because I did it incorrectly, or I wouldn't get any of the dosage at all. (T. Nikolitis.)
- I've used Maxair as my rescue inhaler since 1996 and I'd be in big trouble with out it . . . . I can't co-ordinate the press the top of the [canister] thing and breathe in your meds, [it] never worked for me. (L. Mazepink.)
- The [A]utohaler feature allows me to easily use my rescue inhaler during an attack without stress or fumbling with [various] parts. (J. James.)
- Maxair is the only kind of puffer I can use because the others I lose the medication because of the way I breathe it in. (B. Kanefsky.)
- After a car accident, I was left with fine motor control difficulties. When in the middle of an asthma crisis, Maxair allows me to use my rescue inhaler without needing to focus on trying to maneuver around my coordination problems. (B. Lowery.)

Tab 41 (emphases in originals).

Comment No. 12

According to the Proposed Rule, "there are no data to adequately document that this [breath-actuated] feature leads to improvements in therapy." 72 FR at 32037. The agency also suggested that patients who use Maxair Autohaler because they have difficulty coordinating inhalation with actuation when using a press-and-breathe MDI can, instead, use a spacer device or chamber. Under the essential-use framework, however, FDA must consider whether proposed alternatives provide the same level of "convenience," including portability and the dexterity and mental ability required for use, as well as whether the removal of the ODS product would result in increased morbidity or decreased quality of life. Many patients who lack the coordination, dexterity, or strength to use a press-and-breathe MDI likewise lack the ability to use a press-and-breathe MDI with a spacer. For some, using an MDI plus a spacer device is an even greater challenge than using the MDI alone.

FDA must consider whether the proposed alternatives have the same level of convenience and portability, and whether they require patients to have comparable physical dexterity and mental ability. *See* 21 CFR 2.125(g)(3)(i) and (4)(i); 67 FR 48370, 48377 (July 24, 2002) (final rulemaking setting standard for removal of essential-use designations). The essential-use criteria also require FDA to ensure that removal of an essential product will not result in increased morbidity and mortality or significantly decreased quality of life. *See* 67 FR at 48373.

Studies indicate that Maxair Autohaler is more convenient than using an MDI with a spacer device. In one study, after completing a multi-center, randomized, open-label crossover trial comparing Maxair Autohaler and an albuterol MDI with a spacer, over 40 patients were asked to complete a questionnaire regarding their experiences with the two products. Maxair Autohaler was reported to be significantly ($p < 0.001$) easier and more convenient to use and more convenient to carry. Significantly ($p < 0.0008$) more patients reported consistent use of Maxair Autohaler on each occasion when treatment was needed. Tab 42, J. Grossman, *et al., Pirbuterol Acetate Administered via Breath-Actuated Inhaler Compared with Albuterol Administered via MDI with a Spacing Device*, MEDSCAPE GEN. MED. (1999).

Additionally, as discussed above in Comment 11, the evidence in the record shows that many patients use the Autohaler out of necessity. The record is replete with evidence that for patients with physical or mental disabilities, and patients who cannot coordinate inhalation and actuation, none of the proposed alternative products approximate the convenience, portability, and ease of use of Maxair Autohaler. Moreover, many patients who cannot use a press-and-breathe MDI alone – including children, the elderly and the disabled – will not be able to use one with a spacer. As explained by Dr. Rogers:

> To use a spacer, a patient must insert the metered dose inhaler into a spacer device, hold up both attached items and place them in a position to take an inhalation, actuate the inhaler into the spacer while holding the 2 items together, and coordinate these motions with a breath. This is a difficult or impossible

> proposition for some patients. People with deformities of their hands from arthritis, for example, often cannot press the inhaler into the spacer, and certainly cannot hold the spacer and inhaler while actuating the inhaler.

Tab 33. These obstacles are only intensified during an acute asthma attack.

In addition, because spacers are bulky and less portable, patients are unlikely to carry them and, thus, have a spacer available in the event of an attack. As one clinician put it, "patients are totally non-compliant regarding using unattached spacers." Tab 39 (Dr. W. Storms). According to another experienced clinician, "spacers just don't get utilized." Tab 8, Aug. 2, 2007, Transcript at 167 (Dr. C. Bassett). According to Dr. Santiago Reyes, a pediatric pulmonologist and asthma expert, noncompliance appears to be most prevalent among younger patients:

> It happens that when you go to the pre-teenagers and the teenagers they of course do not like to take medications and a chamber is impractical for them, right, [it] is big, [it] is bulky, they don't like to keep them in the pockets, so they are not going to use it. The result of that is that perhaps they don't get enough medication down to the airways to accomplish the therapeutic purpose of the medications. So for me, when I started using the Maxair Autohaler it was like a prayer to be answered because these patients were now able to use the inhaler, the proper amount of medications, without having to carry around a chamber, so compliance improved tremendously.

Tab 19 (Dr. S. Reyes). Parents and caregivers confirm compliance issues with younger patients using conventional MDIs with spacers:

> I have two daughters who are athletes and suffer from asthma. Both use the Maxair Autohaler as it is compact enough [to] keep with them at all times. In the past they often waited until they were having a full asthma attack because they would have to get their chamber and inhaler out.

Tab 43 (D. Worley).

Spacers also require additional maintenance, as the devices can develop an electrostatic charge that can cause the medication to stick to the tubing, and must therefore be cleaned regularly with a household detergent. Tab 44, L. Hendeles, *et al.*, *Withdrawal of Albuterol Inhalers Containing Chloroflourocarbon Propellants*, 356 N. ENGL. J. MED. at 1344-52, 1346 (2007).

When a patient is suffering an acute asthma attack, the importance of the proven breath-actuated technology of the Autohaler becomes even more apparent. As noted by clinicians and patients, for a rescue product like an asthma MDI, obstacles to compliance and lack of "convenience" will likely lead to increased morbidity and can even be life-threatening. *See* Tab 37 (ACAAI); Tab 41 (B. Lowery, J. James).[8]

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[8] At the Public Meeting, FDA asked whether the possible future approval of an HFA albuterol product with an autohaler device would negate the need to continue to offer patients the breath-actuated system in Maxair Autohaler. Tab 8, Aug. 2, 2007, Transcript at 170. Even if FDA were to approve another breath-actuated product

5. Additional Compelling Factors

When comparing potential therapeutic alternatives under 2.125(g)(2), FDA noted that it must also "borrow concepts from the more specific provisions of § 2.125(g)(3) and (g)(4) to give more structure to [its] analysis." 72 FR at 32034. Such concepts include (a) the relative "convenience" of the ODS-containing product and alternative products, (b) whether there will be supplies and production capacity of the alternative products sufficient to meet patient need, and (c) whether patients would be "adequately served" by the alternative products. 21 CFR 2.125(g)(3). These relevant factors add considerable weight to a finding that Maxair Autohaler continues to play an essential therapeutic role.

Comment No. 13

Maxair Autohaler is more convenient than the alternative products, particularly for patients who may have physical or mental disabilities and those who may have difficulty coordinating inhalation with actuation. In addition, Maxair Autohaler's 400 inhalations per MDI is double the number of inhalations offered by FDA's suggested alternatives, resulting in fewer refills.

The relevant factors in assessing the relative "convenience" of an ODS-containing MDI, compared to an ODS-free alternative, include (a) the amount of physical effort, dexterity and mental ability required for use, taking into account patient education, (b) portability, including the type, size, and shape of the product, (c) the amount of preparation require before use, and (d) the number of refills per month. 64 FR at 47726; 67 FR at 48377. As discussed above in Comment 12, using any of the alternative press-and-breathe MDIs with a spacer is unquestionably less "convenient" than using the breath-actuated Maxair Autohaler.

Moreover, with respect to patient education, studies show that Maxair Autohaler is easier to use and learn than conventional press-and-breathe MDIs, even without spacers. In one multi-center, international, open-label study, patients already using MDIs were asked to use Maxair Autohaler for four weeks. Virtually all (98%) rated Maxair Autohaler as easy or very easy to learn to use, and 88% rated it as easy or very easy to breathe in a puff of medication using the device. Nearly as many (86%) believed that Maxair Autohaler would help a person who has trouble using an MDI, and 76% found Maxair Autohaler to be easier or much easier to use than an MDI. Tab 45, E. Bronsky, *et al., Ease-of-Use Study of Pirbuterol Acetate in the Autohaler™ Actuator in Three Countries: The United States, Germany, and France*, 30 J. ASTHMA at 439-43 (1993); *see also* Tab 46, P. Marshik, *et al., Abstract: A Novel Breath Actuated Device (Autohaler™) Consistently Actuates During the Early Phase of Inspiration*, 8 J. AEROSOL MED.

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between now and the effective date of the Proposed Rule, there is no postmarketing use data or other basis on which to conclude that the new product would work as easily or reliably as Maxair Autohaler, particularly for vulnerable populations. Maxair Autohaler has 15 years of post-market experience. Finally, should the agency intend to rely on the approval of another breath-actuated product as justification for removing Maxair Autohaler from the essential-use list, FDA would need to provide the public with an opportunity to be heard, through notice-and-comment rulemaking, on whether the new product in fact provides equivalent public health benefits.

at 187-195 (1995); Tab 47, M. Schecker, *et al., A Device for Overcoming Discoordination with Metered-Dose Inhalers*, 92 J. ALLERGY CLIN. IMMUNOL. at 783-89 (1993); Tab 48, S. Newman, *et al., Improvement of Drug Delivery With a Breath Actuated Pressurized Aerosol for Patients with Poor Inhaler Technique*, 46 THORAX at 712-16 (1991).

As discussed in Comments 11-12, for those patients that may struggle to coordinate inhalation with actuation, Maxair Autohaler is significantly more portable and convenient than FDA's suggested alternative of a conventional press-and-breathe MDI and a spacer. 72 FR at 32037. As one asthma educator put it, "[m]any times children and teens do not like how cumbersome . . . besides not cool . . . spacers are. Maxair is the only . . . device that teens and adults willingly use. It fits in a jeans pocket, a purse, and other smaller places." Tab 50 (J. Bedore, R.N.).

In terms of preparation before use, the Autohaler requires only minimal preparation – especially for patients who would otherwise need to use a spacer with a press-and-breathe MDI. To use the Autohaler, a patient need only flip the lever at the top of the canister, shake the device and, when ready, inhale to receive a dose of medication. The patient can take as much time as needed between flipping the lever and inhaling the medication. This is in stark contrast to the amount of preparation required to use a spacer with a conventional press-and-breathe inhaler, where the patient must shake the press-and-breath MDI, prepare the spacer, fit the spacer to the MDI, actuate the MDI into the spacer, and maneuver the entire spacer-MDI unit into a position enabling inhalation in order to receive a dose of medication. Tab 33 (Dr. L. Rogers). When an asthmatic is suffering from an acute attack, the relative simplicity of preparing and using Maxair Autohaler as compared to a press-and-breathe MDI is evident and may be the difference between a managed attack and a trip to the emergency room. Tab 37 (ACAAI).

A final advantage of Maxair Autohaler as compared to FDA's suggested alternative products includes the number of inhalations per canister. Maxair Autohaler contains 400 inhalations compared to the 200 inhalations in Proair HFA, Proventil HFA, Ventolin HFA, and Xopenex HFA. By offering twice as many inhalations, Maxair Autohaler requires materially fewer refills. *See* 64 FR at 47726.

Comment No. 14

The Proposed Rule failed to consider the total healthcare costs for Maxair Autohaler patients who attempt a switch to the proposed alternatives. For many, the overall costs are yet another reason why Maxair Autohaler patients will not be adequately served by the proposed alternatives.

In addition to considerations such as portability and convenience, cost is an important consideration in determining whether patients will be "adequately served" by the alternative products. *See* 67 FR at 48374, 48377. As part of its aggregate economic analysis, FDA asserts that Maxair Autohaler patients may pay less in switching to a branded HFA inhaler. 72 FR at 32042. FDA's analysis, however, is confined to product acquisition costs. Even on that limited basis, FDA's analysis is questionable and fails adequately to take into account pricing dynamics once generic albuterol CFC products are removed from the market. Overall, the agency failed to

consider the array of other substantial costs Maxair Autohaler patients will face if forced to switch to another drug, formulation, and delivery system. If the Proposed Rule is finalized, these patients will be forced to absorb the costs of higher co-payments, extra visits to their health care providers, the purchase of spacers and, for many, the costs of failing to adequately manage their asthma or COPD.

As an initial matter, Maxair Autohaler is often more favorably positioned in insurance company formularies than the branded HFA MDIs. More favorable positioning or tiering generally results in lower out-of-pocket costs for the patient. Tab 51, Health Advances, *Clinical and Economic Consequences of Elimination of Maxair* (Sept. 6, 2007). If Maxair Autohaler patients are forced to switch to a higher tiered product, they certainly face greater out-of-pocket costs. Even more troubling, however, is the research showing that with higher co-payments comes lower compliance rates and, in turn, increased emergency department visits and hospital admissions. 72 FR at 32045 (citing D. Goldman, *et al., Pharmacy Benefits and the use of Drugs by the Chronically Ill*, 291 J. AM. MED. ASSN (2004)).

Second, based on extensive physician interviews, our research shows that more than two-thirds of patients would require at least one extra visit to their physician to initiate a switch from Maxair Autohaler to a branded HFA product, imposing yet another set of costs on insurers and patients. Tab 51, Health Advances. For many patients, additional visits will also be required to adjust their treatment to overcome the differences in moiety, excipients, and delivery devices between Maxair Autohaler and branded HFA MDIs. *Id.*; *see* also Tab 8, Aug. 2, 2007, Transcript at 135 (M. Griffiths) (noting that "from 1991 to 1997, I worked with my asthma doctor to find a medicine that worked . . . .").

The Proposed Rule also contends that for patients who require breath-actuation, "the use of spacer devices with other alternative products may provide options . . . allowing them to more satisfactorily use MDIs that do not have a breath-actuated mechanism." 72 FR at 32037. But the Proposed Rule fails to consider the costs of obtaining and replacing spacers. The majority of insurance companies refuse to cover the cost of spacers, and the average lifespan of a spacer is between six months and one year. Accordingly, each patient would need to purchase at least one spacer a year. Tab 51, Health Advances. Moreover, while spacers are approved for general use, the effect of spray differences between HFA and CFC formulations have not been adequately studied, which suggests that patients may need to try more than one HFA MDI-spacer combination before settling on a combination that meets their needs. Tab 44, Hendeles at 1346 (also discussing a potential $1.2 billion annual increase in costs to patients forced to switch to branded HFA products, as well as a potential step-up in co-payments).

Finally, for the reasons discussed in the Comments 2-9 above, it is likely that a significant number of Maxair Autohaler patients will fail, or will face significant challenges switching to the proposed HFA alternatives, leading to an increase in missed school and work days, and an increase in physician, hospital, and emergency department visits:

> Many of the patients experiencing side effects with albuterol would avoid using albuterol because of side effects, even though they were having problems breathing! . . . [I]f Maxair is removed from the market, I would predict an

increase in ER visits, Urgent care, and MD office visits of patients who don't tolerate albuterol – when they get acute symptoms, they are going to go to ERs if they don't have Maxair and they avoid using albuterol.

Tab 26 (Dr. T. Puchner); *see also* Tab 19 (Dr. H. Makhzoumi) ("Pirbuterol is what I turn to when asthmatics do not do well with albuterol, when asthmatics seem to end up frequently in the emergency room and be admitted.").

B. The Release of CFCs from Maxair Autohaler is Insignificant and Outweighed by the Public Health Benefits of the Product

Comment No. 15

FDA has not shown that the use of Maxair Autohaler releases cumulatively significant amounts of CFCs into the atmosphere. The agency made no attempt to quantify the release of CFCs from the product. Rather, FDA argued that any release of CFCs from an essential-use product, no matter the quantity, is "cumulatively significant" when added to the release of all seven products at issue in this proceeding. This approach fails to follow the plain language of the rule.

When deciding whether to remove a product from the essential-use list, FDA must weigh whether "use of the product does not release cumulatively significant amounts of ODSs into the atmosphere or the release is warranted in view of the unavailable important public health benefit" provided by the product. 21 CFR 2.125(f)(1)(iii); *see* 72 FR at 32034. The agency tentatively concluded in the Proposed Rule that the release of CFCs from "pirbuterol MDIs" is cumulatively significant. 72 FR at 32037. There is, however, no finding regarding the quantity of the release of CFCs from Maxair Autohaler; nor is there a finding that the incremental release of CFCs from Maxair Autohaler – even when added to the aggregate of the other six products at issue – has a "cumulatively significant" impact on the environment.[9]

Instead, the agency proposed that were it to examine the release of CFCs independently for each of the seven products at issue, it might be compelled to find that each product releases a "minor" rather than a "significant" amount of CFCs. *Id.* at 32034. In addition, the agency argued that the rule must be read in the context of the phase-out of CFC usage envisioned by the Clean Air Act and the Montreal Protocol. *Id.* In essence, in FDA's view, as the United States

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[9] According to FDA, the aggregate amount of CFCs released from all seven products at issue in the Proposed Rule is approximately 310 to 365 tonnes of CFCs per year. 72 FR at 32044. The agency, however, was unable to demonstrate that this release, taken in the aggregate, has a significant impact on the human environment. Indeed, as FDA concedes: "[W]e are unable to quantify the environmental and human health benefits of reduced emissions from this regulation." *Id.* FDA speculates that "the reduced exposure to UV-B radiation that will result from these reduced emissions will help protect public health," but offers no tangible support for this statement and admits that "we are unable to assess or quantify specific reductions in future skin cancers and cataracts associated with these reduced emissions." *Id.*

approaches the end of the phase out, any release of CFCs by an essential-use product must be considered a "significant" release. *See id.*

The rule, however, is structured to require a product-specific finding. *See* 21 CFR 2.125(f)(1)(iii) and (g)(2) (referring specifically to "the product" under consideration). While it allows FDA to consider a release from "the product" on a "cumulative" basis (*i.e.,* additive to the release from other products), it nevertheless requires a finding that the cumulative release is "significant." *See* 21 CFR 2.125(f)(1)(iii). Put another way, the rule accepts that there can be both significant *and* insignificant releases of CFCs, and that a product that releases only minor amounts of CFCs need not be removed from the essential-use list. *See* 72 FR at 32034. The rule does not set a zero-release or "zero-tolerance" standard.

Finally, both the Clean Air Act and the Montreal Protocol recognize that essential-uses may be exempted from the general ban on CFCs. The ODS framework incorporates the idea that a product may continue to be essential if it does not place a significant incremental burden on the environment. Whether the Parties to the Montreal Protocol are at the later stages of the process does not change the words, or the meaning of the words, in the regulation. If the product does not have a significant impact on the environment, then there is no compelling reason to remove it from the market at this time.[10]

Comment No. 16

When compared with other MDI products, Maxair Autohaler releases a relatively small amount of CFCs. On a per puff basis, Maxair Autohaler releases fewer CFCs than any other essential-use product. If the agency factors in market size, the release is even smaller on a comparative basis. For example, when compared to a large market product, Maxair Autohaler releases less than one-tenth the amount of CFCs on an annual basis. Considering the unique benefits of the product, Maxair Autohaler represents an efficient and prudent use of the limited supply of pharmaceutical grade CFCs.

The incremental release of CFCs from Maxair Autohaler is decidedly less than that of other products on the essential-use list. As shown below, on a per puff basis Maxair Autohaler releases one-half to less than one-fourth the amount of CFCs.

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[10] *See* Tab 54, J. Pyle, *Report on chlorine loading calculations – CFCs in metered-dose inhalers* (1993) (finding that the difference between no CFC emissions and 15000 metric tons of emissions resulted in only a very small difference in the chlorine loading, active chlorine levels, and recovery of the ozone).

Products	Unit Size	Inhalations per unit	CFC per inhalation[11]
Aerobid & AerobidM (flunisolide)	7.0g	100	0.070g
Alupent (metaproterenol sulfate)	7.0g 14.0g	100 200	0.070g
Azmacort (triamcinolone acetonide)	20.0g	240	0.083g
Combivent (ipratropium bromide and albuterol sulfate)	14.7g	200	0.074g
Intal (cromolyn sodium)	14.2g 8.1g	200 112	0.071g 0.072g
[redacted]			
Tilade (nedocromil sodium)	16.2g	104	0.156g

Maxair Autohaler also has a relatively small share of the asthma and COPD markets. When market size and product efficiency (*see* table above) are considered together, Maxair Autohaler requires for production, and would release, far less CFCs than other comparable products. For example, in 2005, 778,792 units of Maxair Autohaler were sold. At this market volume, only 12 tonnes of CFCs are required to supply patients with Maxair Autohaler for an entire year.[12] In comparison, in 2005, more than 12.2 million units of Combivent® were sold. At this market volume, Combivent requires more than 198 tonnes of CFCs to supply the market. Put another way, Maxair Autohaler represents a highly efficient and effective use of the limited supply of CFCs.

Comment No. 17

The amount of CFCs released by the use of Maxair Autohaler is warranted in light of the otherwise unavailable public health benefits of the product.

FDA's regulatory scheme is designed to promote reduction in overall CFC emissions while ensuring that important patient needs are met. Accordingly, the applicable regulation requires the agency to balance the otherwise unavailable important health benefits of a product

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[11] MDI canisters generally consist of between 95 and 99 percent propellant. These calculations assume that the weight of the canister is 100 percent propellant and that all propellant is released from the product.

[12] Sales and CFC calculations are based on 2005 unit data and gram totals extracted from Wolters Kluwer PHAST National Trends Prescription and Institutional Monthly Audits. Tab 55. Calculations of total CFCs released are based on gram totals and add 10% for production losses in accord with the Proposed Rule. 72 FR at 32043.

against that product's CFC emissions, to determine whether a product should retain its essential-use designation. This balancing favors preserving the health benefit or, as FDA has stated, "[i]f there is a portion of the population that cannot medically be served by the available alternatives, then such CFC use would remain essential." 64 FR at 47727.

As discussed in Comments 1 through 14 above, Maxair Autohaler provides an otherwise unavailable important health benefit to an array of patients, including patients who have previously failed on albuterol therapy, patients who may not be able to tolerate certain side effects associated with albuterol and levalbuterol, and patients who require an alternative to a press-and-breathe delivery system. These health benefits more than offset the negligible release of CFCs that result from the use of the Maxair Autohaler.

C. Substantial Technical Barriers Exist to Formulating Maxair Autohaler Without ODSs

Comment No. 18

Reformulating Maxair Autohaler presents substantial chemistry and manufacturing challenges. Graceway's predecessor, 3M, has unmatched expertise in developing bronchodilator products, including the first successful HFA reformulation of an albuterol product. Nevertheless, 3M encountered substantial barriers to the reformulation of Maxair Autohaler. 3M experimented with several forms of the molecule and alternative types of surfactants and co-solvents. All posed substantial technical challenges. 3M also recognized that novel components may need to be developed for an HFA-based Autohaler device and that alternative technologies, such as the components used with HFA-based press-and-breathe systems, may not be suitable for use with a re-designed Autohaler device. Finally, reformulation of the product may require a fundamental and costly change in the manufacturing process for the product, including a change in the fill process.[13]

In general, HFA propellants have different physical and chemical properties than CFCs. When applied to a specific moiety, in a specific delivery system, the differences can present a range of substantial technical challenges. HFA suspension formulations tend to aggregate and adhere to surfaces. HFAs also have a higher affinity for moisture, which can exacerbate issues involving aggregation and adhesion. As Graceway's predecessor, 3M, recognized in its initial

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[13] Many of the technical issues associated with the reformulation program implicate information that is confidential and which cannot be disclosed in a public rulemaking proceeding. In addition, Graceway itself may not have unilateral discretion to reveal confidential commercial and trade secret information that is held by third party contractors or which may be under development jointly with third party formulation experts. The discussion provided in this section represents Graceway's best effort to address the relevant criteria for rulemaking purposes while also preserving relevant proprietary and confidential information.

efforts to reformulate Maxair Autohaler, these properties may require a novel set of components, co-solvents, and suspension agents when applied to pirbuterol.[14]

Each moiety also has its own physical and chemical properties and presents unique chemistry and manufacturing challenges. 3M evaluated several potential pirbuterol HFA formulations, including several ethanol-based formulations and two different salts of pirbuterol. Some formulations were found to be too corrosive to be viable; some showed evidence of "stickiness" in the presence of HFA, requiring unique technical solutions to minimize issues of aggregation and adhesion. 3M also investigated an oligogalactic acid platform as a strategy to minimize the need for co-solvents and increase the functionality of the eventual product, and completed the preclinical and early clinical safety studies needed to move forward. [15]

The technical challenges to reformulating are further complicated by Maxair Autohaler's novel breath-actuated system. A breath-actuated system is more sensitive than a press-and-breathe system, both with respect to particle size and the energy or force that drives the formulation through the actuator. For example, Maxair Autohaler operates with an already small 25 micro-liter valve. Decreasing the size to address the higher vapor pressure of HFA may increase the potential for clogging of the delivery device.[16]

The challenges involved in formulating breath-actuated HFA products are illustrated by other publicly-reported efforts to develop breath-actuated HFA systems. Teva/Ivax's breath-actuated non-ODS inhaler has taken more than five years to develop and, were it to receive FDA approval this year, will have required at least four years of review time. 70 FR 17168, 17173 (Apr. 4, 2005) (noting statement by Ivax to FDA PADAC that the company had submitted an application for a breath-actuated inhaler in August 2003).

A final technical barrier is the manufacturing process. Maxair Autohaler was developed in the 1980s and approved by FDA in 1992. Graceway anticipates that the reformulation of the product to a non-ODS format may also require, for practical and economic purposes, a fundamental change to the manufacturing process currently used for the product. This change introduces an additional set of substantial technical barriers that are specific to the product.

In the Proposed Rule, FDA tentatively concluded that it has no evidence to suggest that ODS-containing pirbuterol products "pose unique technical challenges to formulation without

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[14] Co-solvents are often used to increase the solvent capabilities of a propellant to allow medications to adequately dissolve into the propellant. Surfactants perform a key role in MDIs by creating a stable suspension of drug particles, controlling the size of the droplets and preventing aggregation of the particles, as well as lubricating the metering valve to prevent sticking.

[15] Some of these efforts are noted in a published article. *See* Tab 56 , J. Stefley, *Novel Excipients for Inhalation Drug Delivery: Expanding the Capability of the MDI*, DRUG DELIVERY TECHNOLOGY at 4. The balance of the information is confidential and proprietary.

[16] In addition, HFA propellants present a significantly different release profile than CFC propellants. To maintain approximately similar drug size distribution in HFA products, the diameter of actuator nozzles must be reduced. In one reported instance, involving the change in valve size for Proventil HFA, the change resulted in a softer mist but also caused clogging and stiction of the delivery device. *See* Tab 57, J. Sciarra, *The Next Generation of Metered Dose Inhalers*, 22 U.S. PHARMACIST (1997).

ODSs." 72 FR at 32037. The agency also noted that others in the industry have had success formulating short-acting bronchodilators without ODSs. Maxair Autohaler, however, contains a unique moiety and a unique delivery system. The point that others in the industry have reformulated products with other moieties, in other delivery systems, does not make the challenges associated with Maxair Autohaler any less "substantial."

Comment No. 19

The cost of reformulating Maxair Autohaler, relative to the market size of the product, raises a substantial barrier and magnifies the technical barriers described in the preceding Comments. It has been recognized by FDA that cost itself may be considered a technical barrier, particularly where the cost of moving to a non-ODS is prohibitively high compared to the cost of continuing to use an ODS. *See* 67 FR at 48373; 64 FR at 47721-22. While manufacturers of large market products have invested significantly in overcoming the technical barriers associated with reformulation, the economic case for making a similar investment in Maxair Autohaler is itself a barrier. Graceway, however, recognizes the important public health benefits provided by the product, and is prepared to invest fully in a reformulation program that is designed to address all technical barriers associated with moving to a non-ODS format.

Maxair Autohaler consists of the active ingredient, pirbuterol acetate, in a formulation of CFC-based propellants and the inactive ingredient, sorbitan triolate, contained in a breath-actuated inhalation system.[17] The product was developed by 3M, a company with unmatched expertise in the development of MDIs.[18] In 1996, 3M led the field by completing the first successful reformulation of a CFC-containing albuterol product, Proventil, to a non-ODS formulation known as Proventil HFA. Not including prior industry-wide research to identify suitable alternative propellants, this effort involved the investment of 500 person-years over the course of approximately eight calendar years, and required research and development expenditures totaling approximately $125 million. *See* Tab 58, Transcript of April 11, 1997, PADAC Meeting at 165 (M. DuVal, 3M Division Counsel).

With the data and know-how developed in reformulating albuterol products, the capital expenditures needed to reformulate Maxair Autohaler are lower. Nevertheless, the estimated investment for a non-ODS reformulation of breath-actuated pirbuterol may exceed $50 million – approximately equal to annual revenues from the sale of the product.

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[17] The active moiety, pirbuterol, has been approved in both a press-and-breathe and a breath-actuated format. *See* NDA 19-009 (discontinued) and NDA 20-014. However, marketing of the press-and-breathe product was discontinued in 2003 following performance issues with the delivery system and strong patient preference for the Autohaler system.

[18] 3M and its predecessor, Riker Labs, developed the first MDI products, the Medihaler-Epi and the Medihaler-ISP, which were approved by FDA in 1957.

Thus, a substantial barrier to reformulating the Maxair Autohaler is the cost of the project relative to market size. *See* 64 FR at 47724 ("some companies are unlikely to reformulate their CFC products into non-ODS products because of economic considerations"); *see also id.* at 47721-22 (indicating that cost may be considered a technical barrier, particularly where the cost of reformulation is prohibitively high). While the large market for albuterol products could support substantial investments in reformulation, the smaller market for pirbuterol has been a significant constraint to date. That said, Graceway has concluded that investment in reformulating the product is warranted.[19] Graceway is also committed to ensuring that patients who depend on Maxair Autohaler are not unfairly penalized, simply because they rely on a second-line therapy. Thus, Graceway has already undertaken to build on 3M's efforts, and will fully support the program to develop a non-ODS Maxair Autohaler.

II. CFC Allocation Comments

Comment No. 20

At the Public Meeting, the FDA panel requested information on Graceway's process for obtaining CFCs. Graceway works closely with its contract manufacturer, 3M, to manage the CFC nomination and allowance process and maintain adequate CFC supplies to meet the manufacturing needs for Maxair Autohaler.

On December 29, 2006, Graceway Pharmaceuticals, LLC completed the acquisition of 3M's branded pharmaceutical business in the United States. The acquisition included the new drug application (NDA 20-014) in support of Maxair Autohaler.[20]

As part of the transaction with 3M, Graceway contracted with 3M's Drug Delivery Systems subsidiary for the continued production of Maxair Autohaler. Under the terms of this agreement, 3M is required to obtain all components and ingredients, including CFC propellant, necessary for the manufacturer of Maxair Autohaler. Accordingly, CFC allocations provided to 3M can and will be applied to the manufacture of Maxair Autohaler.

For example, on June 12, 2007, EPA granted an allowance to 3M Pharmaceuticals of 65 Metric Tons of CFCs for calendar year 2007. 72 FR 32212, 32220 (Jun. 12, 2007). This allowance will be applied to the manufacture of Maxair Autohaler, among others, by 3M for Graceway. Similarly, on or about January 3, 2007, 3M submitted to EPA an application for the nomination of Maxair Autohaler as an essential-use product, and requested allocation of CFCs

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[19] There is no economic rationale, however, for reformulating the Maxair Autohaler to a press-and-breathe system. Graceway believes that the market for each component in isolation is too speculative to support a large capital investment.

[20] Concurrent with the acquisition, Graceway and 3M notified the agency that all rights and responsibilities under the NDA had been transferred to Graceway. Tab 77, Letter from J. Gregory to B. A. Chowdhury, M.D. (Dec. 29, 2006); Tab 78, Letter from M. Kuker to B. A. Chowdhury, M.D. (Dec. 29, 2006). The Agency acknowledged the transfer in a subsequent letter. Tab 79, Letter from M. Raggio to J. Gregory (Jan. 18, 2007).

for calendar years 2008 and 2009. The submission notes that Graceway Pharmaceuticals is the owner of Maxair Autohaler and was consulted on the requested allocations. Graceway will continue to work closely with 3M on obtaining allowances for pharmaceutical grade CFCs under the EPA process for the continued production of Maxair Autohaler.

With regard to the amount of CFC's Graceway may need during its transition to an ODS-free Maxair Autohaler, Graceway notes that the Maxair Autohaler is an efficient device and serves a relatively small market. It requires a small amount of CFCs relative to other products, and represents a prudent use – from a public health perspective – of the limited amount of CFCs that will be available after 2009. For example, the amount of CFCs needed to extend the effective date of a large-market product for less than one year be support a multi-year reformulation program for Maxair Autohaler.

Graceway is working closely with 3M to assess the adequacy of available CFC supplies to continue to manufacture Maxair Autohaler throughout the planned reformulation of the product. Graceway also notes that Honeywell, the leading domestic manufacturer of CFCs, has stated its intent and ability to continue to manufacture pharmaceutical grade CFCs for as long as needed. Tab 86, Honeywell Comment (July 25, 2007).

Comment No. 21

At the Public Meeting, the FDA panel expressed concern about the continued availability of CFCs and the potential for a precipitous interruption in supply. The panel suggested that such an event might not leave time for a well planned transition to other products, and asked whether this issue should be a consideration. As the agency itself suggested during the Public Meeting, the future availability of CFCs is a separate issue from the analysis of whether a product meets the essential-use criteria. The Agency's concerns over the availability of CFCs beyond 2009 are properly addressed at the level of the Montreal Protocol through negotiation for continued availability of CFCs for essential-use MDIs, not through the removal of essential-use designations.

Graceway appreciates the agency's efforts to manage the transition to ODS-free MDIs and is aware that this rulemaking has implications for future meetings of the Montreal Protocol (particularly with respect to future CFC production). *See* 72 FR at 32044; *see also* Tab 8, Aug. 2, 2007, Transcript at 174-177. However, the future availability of CFCs is not one of the criteria for determining whether a product should remain on the essential-use list. As the agency explained in the preamble to the regulations, "[t]he use of CFC's in a product is either nonessential or essential." 64 FR at 47727. This is true regardless of the availability of CFCs.

The issue in this rulemaking is whether Maxair Autohaler remains essential under FDA's criteria as set out in 21 CFR 2.125 which, consistent with the goals of the Clean Air Act and Montreal Protocol, focuses on reducing overall CFC emissions while ensuring important patient needs are met. To this end, and as set forth in FDA's own regulation, a careful product-by-product balancing of health benefits versus environmental costs is required. Once a product has

been designated essential, the issues related to obtaining necessary CFCs are resolved using the mechanisms provided by the Clean Air Act and Montreal Protocol.

With respect to the availability of CFCs beyond 2009, it is important to clarify that the Montreal Protocol does not establish a terminal date for the use of CFCs in essential-use products. Rather, the Parties to the Protocol have agreed to "permit the level of [CFC] production or consumption that is necessary to satisfy uses agreed by [the Parties] to be essential." *See* Montreal Protocol 2A(4). To this end, the plan for transitioning from ODS to non-ODS MDIs is expressly conditioned on both the availability of "technically and economically feasible alternatives or substitutes," and the necessity of a given MDI in light of the health, safety, or critical functioning of society. *See, e.g.*, Decision IV/25, 1(a).

Currently, there is continued production of CFCs to meet the domestic needs of developing or "Article 5" countries, and for essential-uses in non-Article 5 developed countries. The Protocol contemplates that this production may cease at the end of 2009. Montreal Protocol 2A(8). However, the Parties have already recognized the need to plan for CFCs use beyond 2010. One approach under consideration is to reach agreement on a final "campaign production" to meet the Parties' going-forward needs. *See* Decision XVIII/16, 12; Issues for discussion by and information for the attention of the Nineteenth Meeting of the Parties at ¶¶ 29-31 (Jun. 10, 2007); Annotated Provisional Agenda for the Nineteenth Meeting of the Parties at ¶ 32 (Jun. 26, 2007).

As a Party to the Montreal Protocol, the United States can address FDA's concerns regarding the availability of CFCs beyond 2009 by advocating for the continued production, or a final campaign production, in an amount sufficient to satisfy the requirements of any MDI designated essential by FDA. The first step in that process, however, is for FDA to apply the three-part standard set forth in the ODS regulations at 21 CFR 2.125.

III. The Essential-Use Rulemaking Process

The issue of whether to remove a safe and effective moiety from the essential-use list, when there is no non-ODS product that offers the same moiety, is extraordinarily sensitive and rife with uncertainty. As a result, the agency included two exceptional information gathering steps to the process, in addition to the usual process for seeking input through notice-and-comment rulemaking.

First, FDA committed to consult with an advisory committee on whether a given moiety and product remain essential for patients. Second, the agency committed to obtain first-hand, in-person comments from patients and clinicians on whether a given product provides an essential health benefit. The agency incorporated both of these steps into the rules that govern essential-use determinations. *See* 21 CFR 2.125(g)(2). Thus far, FDA has fallen short of fulfilling either the letter or the spirit of the regulation with respect to these two additional steps. As a result, FDA has deprived itself of relevant facts and analysis that the agency committed, by law, to consider as part of this rulemaking process.

A. Consultation with a Relevant Advisory Committee

Comment No. 22

The July 14, 2005, Meeting of the Pulmonary and Allergy Drugs Advisory Committee (PADAC) did not fulfill the requirement that FDA consult an advisory committee under 21 CFR 2.125(g)(2). The notice of the meeting failed to identify the products and moieties at issue and failed to state that the meeting was intended to fulfill the requirements of 2.125(g)(2). The agency briefing document was wholly inadequate for purposes of obtaining informed views from committee members.

FDA contends that the July 14, 2005, PADAC meeting satisfied the requirement for a pre-rulemaking advisory committee consultation. *See* 72 FR at 32035. From its conception, however, the PADAC meeting was so flawed that it failed to meet either the letter or spirit of 21 CFR 2.125(g)(2).

In the notice of the meeting, FDA generically stated that the PADAC was being convened to "discuss the continued need for the essential-use designations of prescription drugs for the treatment of asthma and chronic obstructive pulmonary disease." 70 FR 24605, 24606 (May 10, 2005). The notice did not mention pirbuterol, much less alert anyone that this would be "the" advisory committee before the initiation of rulemaking to remove pirbuterol's essential-use designation.[21] In contrast, the notices announcing advisory committee meetings for albuterol and epinephrine specifically identified the drugs to be considered by the committee. 69 FR 26169, 26169-70 (May 11, 2004) ("The committee will discuss the possible removal of the essential-use designation of albuterol"); 70 FR 71538 (Nov. 29, 2005) ("The committee will discuss the continued need for the designation of OTC epinephrine-metered dose inhalers for the treatment of asthma as an essential-use of ozone depleting substances . . . ."). In the case of epinephrine, FDA also specifically solicited "comments and data to support or refute" the continued essential-use designation, and notified the sponsors of epinephrine MDIs of the meeting. 70 FR at 71538; Tab 59, Transcript of January 24, 2006, PADAC Meeting at 12 ("Wyeth and Armstrong . . . are going to present today. We contacted them in early October and told them about the meeting . . . .").

The notice of the 2005 PADAC meeting, in contrast, was so superficial as to be inadequate. For example, based on a search of the trade press, it appears that the substance of the meeting did not become evident to observers until FDA released an "Office Director's Background Memorandum" dated July 5, 2005. Tab 60, Office Director's Background Memorandum (July 5, 2005); *see* Tab 61, *Advisory Committee to Decide if Azmacort, Alupent, Intal Remain 'Essential' Drugs*, THE PINK SHEET (July 13, 2005). We were unable to locate any trade press coverage of the meeting before FDA released the memorandum.

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[21] A notice of an FDA advisory committee meeting must include "[a] list of all agenda items, showing whether each will be discussed in an open or closed portion of the meeting." 21 CFR 14.20(b)(4).

As a result of the lack of notice, there was scant opportunity for interested persons to present data and analysis for the benefit of the advisory committee members. Though FDA invited such participation in the notice (70 FR at 24606), it hid from view the purpose and scope of the meeting. It must have appeared to the committee members, for example, that there was little interest in retaining the moieties and products discussed at the meeting, when few outside individuals and sponsors came prepared to participate.

As for the Background Memorandum provided to committee members, it was uncharacteristically brief (only four pages) and woefully short on substance. Tab 60, Background Memorandum. The document discusses historical background on the process for removing products from the essential-use list, but omits many of the factors that bear on whether a product is considered essential (*e.g.,* cost, convenience, portability, ease of use, improved quality of life, and potential utility in subpopulations that may not respond to or tolerate alternative therapies). Second, the Background Memorandum contains no substantive information on the moieties or products under consideration. *Id.* There is no summary of the clinical data in support of each product, and no attempt to compare the safety and efficacy of each product with its proposed therapeutic alternatives. For example, as discussed in Comment 2 above, the FDA-approved labeling and approval records contain significant amounts of information on intolerance and non-response to albuterol, but the agency provided no information on these issues in the briefing materials. *See, e.g.,* Tab 62, Transcript of July 14, 2005, PADAC Meeting at 80-81 (noting the lack of scientific evidence provided to the committee for purposes of advising the agency on whether each proposed moiety and product remains essential).

FDA also failed to give PADAC members sufficient time to meaningfully prepare for the meeting. Even assuming that members received the memorandum the same day it was dated (July 5), which is unlikely, there would have been only nine calendar days remaining before the meeting. That exceedingly brief preparation time is a departure from FDA's standard practice, which is to make background materials available to advisory committee members "at least 3 weeks in advance." Tab 63, L. Sherman (former Director of FDA's Advisory Committee Oversight & Management Staff), *FDA 101: Advisory Committees* at 43 (Apr. 20, 2005).

In comparison to a typical advisory committee briefing document, which may run into the hundreds of pages, the document the agency prepared was wholly uninformative. Neither the document nor the amount of time provided for its review fostered an informed and probing "consultation." Indeed, the FDA's inadequate pre-meeting preparations and materials undermined the agency's ability to obtain well-informed and carefully considered advice from independent experts in the field, a bedrock principle of the advisory committee process.

Comment No. 23

At the PADAC meeting, agency representatives failed to substantively consult with committee members on the seven products at issue in the Proposed Rule. Rather, the agency took several straw polls at the meeting, and walked the members through basic historical background on the phase out of CFCs. Committee members expressed confusion over the issues and

concern about the lack of data being provided by the agency. They answered general and leading questions, but were never asked to give a meaningful analysis of the potential health benefits of the products and moieties at issue. By failing to provide adequate background, and failing to engage committee members in a discussion of the role of each product, the agency did not meet its commitment under the rule to consult with an advisory committee. Before finalizing the Proposed Rule, FDA must properly reconvene the PADAC.

Like the notice document, the PADAC meeting itself was less than a model of clarity. From the outset, the committee expressed confusion about its charge and the criteria for determining whether a moiety was essential. *See, e.g.,* Tab 62, July 14, 2005, PADAC Transcript at 55 (Dr. Newman) ("I want to make sure I understand exactly what you are asking of us today, because I think that if you are asking us whether the essential question is to provide a substantial health benefit, that is a little different than asking us whether it provides substantial public benefit.").

PADAC members were also concerned about the paucity of data on which to rely in making their determinations.[22] Their repeated inquiries, however, went largely unanswered, leading one PADAC member to openly challenge the methodology being used at the meeting:

> Maybe this would occur at the public hearing, at the subsequent public hearing, but I am a little concerned about the process here in that it seems that a regulatory decision is made without really relying on evidence-based medicine in the same way that, for instance, regulatory decisions were made yesterday.
>
> That is, it would seem a better process would be to ask each of these companies that make these products to marshal scientific evidence in the form of maybe what they initially submitted to gain approval for these products plus subsequent papers in the medical literature, and then have these documents just as they are in new drug applications reviewed by your staff and a report written, and in that case, we would be making these decisions based on the usual level of evidence that we are used to seeing in making important decisions like this.

Id. at 80-81 (Dr. Schoenfeld).

Several minutes later, another committee member (Dr. Moss) repeatedly asked an FDA representative whether the companies that make the products at issue were given an opportunity to participate in the meeting. *Id.* at 84-85. In response, an agency representative told the committee that the meeting was announced "per usual" and that manufacturers of the products at issue were provided notice of the meeting in the Federal Register. *Id.* at 85.

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22 *See, e.g., id.* at 48 (Dr. Schatz) ("I am wondering whether there is any information available as to how many patients are using these drugs current[ly], that would I think help us get some sense as to at least how many patients think they are useful or essential."); *id.* at 52 (Dr. Martinez) ("Are costs available as information for us at this meeting?").

In fact, as discussed in Comment 20, above, the notice of the PADAC meeting failed to identify any of the drugs or products to be discussed at the meeting. The brevity of the notice and the background materials were not consistent with "usual" agency practice, particularly where specific products are being considered by an advisory committee. The impression left at the meeting was that companies whose products were impacted had chosen not to participate and thus were not committed to the continued marketing of the products. *See, e.g., id.* at 84-85, 101-102. In fact, the notice provided by the agency made it very unlikely that the companies would or could meaningfully participate.[23]

At one point, an agency lawyer added to the confusion by suggesting that FDA would likely move ahead with proposing to remove each of the products, irrespective of what the committee advised, unless members determined that a specific product is "absolutely an essential use . . . ." *Id.* at 106. This comment not only articulated an inaccurate standard, but also suggests that FDA's consultation with the committee was not meaningful.

Overall, the meeting was marked by questions, confusion, and uncertainty as to the purpose of the meeting, the factors to be considered, and the role of the meeting in the overall rulemaking process. The agency therefore did not meet its obligation under the rule to consult with an advisory committee, and must reconvene the PADAC in order to do so.[24]

Comment No. 24

To the extent FDA received advice from the PADAC, the agency failed to consider it in the Proposed Rule. With respect to Maxair Autohaler, the only point noted in the Proposed Rule is that PADAC members "gave their opinion, without dissent, that . . . pirbuterol [is] no longer essential." 72 FR at 32037. In fact, there were several important statements made during the meeting about the essential role of pirbuterol and Maxair Autohaler, as well as two abstentions in the straw poll regarding its essentiality. Also, the agency led the committee to believe that if pirbuterol were included in a proposed rule, it would be based on "very tentative" findings accompanied by specific questions about niche uses of the product and advantages provided by the Autohaler, particularly for pediatric patients. Tab 62, July 14, 2005, PADAC Transcript at 106. The agency carried none of these points over to the Proposed Rule.

With respect to pirbuterol, some PADAC members discussed the benefits of Maxair Autohaler's breath-actuated MDI for asthma sufferers who have difficulty using a press-and-breathe MDI, and requested information regarding Maxair Autohaler's patient population and

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23 A representative of 3M addressed PADAC very briefly during the "open forum" portion of the meeting. He stated that "the only comment I would like to make is that . . . the committee should not assume that activities are not going on with these molecules simply because presentations weren't here." *Id.* at 104.

24 When FDA reconvenes the PADAC, the agency should take care to exclude committee members with disqualifying financial interests in the sponsors of products that are proposed as alternatives to CFC-containing MDIs. *See* 21 USC 355(n); 18 USC 208(b).

reformulation. Tab 62, July 14, 2005, PADAC Transcript at 87-89. At one point, a committee member (Dr. Newman) suggested that there was consensus on seeking additional information about the product. *Id.* at 89. The agency, however, then "changed [its] request to the panel" and asked for an informal poll rather than further discussion. *Id.* at 89-90.[25]

Later in the meeting, an agency lawyer addressed the committee and assured the members that the issues that had been raised about pirbuterol and Maxair Autohaler would be highlighted by the agency in future proceedings:

> The first thing is the next step is a Notice of Proposed Rulemaking, and in that, our conclusions are very tentative or can be very tentative.
>
> The other thing we can do . . . and I am certainly listening to the discussions on pirbuterol and the cromones, is we can ask specific questions, ask for specific comments on what sort of niche market a particular drug has, whether the Maxair mechanism presents special advantages for pediatric patients. We can ask for specific comments on those sorts of things.
>
> That is one of the things I am trying to derive from not so much the polling, but from the discussion that precedes the polling, or what sort of comments we should be looking for, which we would be asking for.

Id. at 105-06. Instead, in the Proposed Rule, FDA cited *only* the straw poll vote, and made it appear as if the PADAC decisively determined that pirbuterol should no longer be available. The agency made no effort to highlight or continue the discussion of the issues raised by the committee. Similarly, the "Summary Minutes" of the meeting prepared by the agency listed only the results of the poll, as if it had been a formal vote. Tab 64, FDA "Quick Minutes" of July 14, 2005, PADAC Meeting. None of the discussion points raised by committee members with respect to pirbuterol was included in the minutes.

In sum, the agency fell well short of "consulting" with the PADAC on pirbuterol. The agency truncated the committee's discussion by abruptly asking for a straw poll and then assured the committee that the concerns they had begun to raise regarding Maxair Autohaler would be highlighted in a proposed rule. The agency even assured the committee that any proposal as to pirbuterol would be "very tentative," as another way to abbreviate the discussion. Finally, in the Proposed Rule itself, the agency failed to recognize any issues raised by the committee. Instead, FDA focused solely on the straw poll vote which, the agency had assured the committee, would not be given "the formality of a vote." Tab 62, July 14, 2005, PADAC Transcript at 90. For all of these reasons, the July 2005 meeting was inadequate for purposes of 21 CFR 2.125(g)(2).

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[25] None of the votes taken at the meeting was considered by members to have the weight of a "formal vote" or to represent the opinion of the PADAC. *See, e.g.*, Tab 62, July 14, 2005, PADAC Transcript at 85.

B. The Open Public Meeting

Comment No. 25

The Public Meeting represented a first step toward fulfilling the agency's commitment to enrich the notice-and-comment rulemaking process with input through a public meeting. However, the scheduling of the meeting in early August, with less than three weeks' notice, presented a barrier to participation by patients, clinicians, and outside experts. The lack of publicity by the agency about the meeting, or about the Proposed Rule, also made widespread participation by patients and clinicians highly unlikely. These barriers, and the decision to hold a single meeting in Rockville, Maryland, frustrated participation by patients and clinicians in other parts of the country. In all, the agency failed to meet the spirit of the public meeting requirement under 21 CFR 2.125(g)(2).

On July 9, 2007, FDA announced that it would hold a single open public meeting to solicit comments on its proposal to remove the essential-use designations for specified ODS-containing MDIs. 72 FR at 37137; *see* 72 FR at 32030. The meeting was scheduled in Rockville, Maryland on August 2, 2007 – less than 30 days after the announcement – and anyone wishing to attend or speak at the meeting was required to register no later than July 25, 2007 – only 16 days after the announcement.[26] By providing such short notice, the agency effectively minimized the opportunity for the public to participate in the meeting and, as a result, undermined the quality and quantity of the evidence to be considered.

Many clinicians who would have liked to participate in the public meeting were unable to do so because the short notice made it impossible for them to clear their schedules or obtain coverage for patients in order to attend in person. Tab 66 (Dr. R. Panettieri) ("I wanted to attend the August 2, 2007, public meeting, but given the short notice, I was unable to reschedule my appointments and thus cannot attend."). In addition, the agency resisted efforts to broaden the opportunity to participate by denying a request for clinicians to participate by telephone even though FDA regulations provide that advisory committee meetings can be held "by conference telephone call," suggesting that telephone participation is or should be within the agency's technical capabilities. 21 CFR 14.22(g).

FDA made no apparent effort to publicize the meeting and or use its own website to communicate information about the meeting. It did not issue a press release, for example, even though as of July 30, the agency had issued more than 130 other releases in 2007 including, ironically, a release touting FDA's new initiatives to enhance the communication of health information to consumers. Tab 68, "FDA Launches New Web Page, E-Newsletter to Enhance Online Consumer Health Information" (May 3, 2007). There were no postings regarding the

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[26] On July 17, 2007, out of concern that FDA had allotted only 16 days between the notice and registration deadline for the meeting and had failed to publicize the meeting, Graceway submitted a comment requesting deferral of the meeting until the Fall of 2007. Tab 65, Graceway, "Request to Reschedule Public Meeting," (July 17, 2007).

meeting on the main FDA homepage, the Center for Drug Evaluation and Research homepage, or the Consumer Health Information page.

Comment No. 26

One purpose of the public meeting was to collect first-hand feedback from patients on their experience with alternative products that might replace ODS-containing products proposed for removal. The agency failed to solicit such feedback and, as noted above, failed to provide adequate notice and an opportunity for patients to present their experience with, for example, HFA-containing alternative products. FDA must schedule at least one additional public meeting, in a geographically distinct location, to fulfill the public meeting requirement under 21 CFR 2.125(g)(2).

The public meeting requirement in 21 CFR 2.125(g)(2) is designed to secure "first-hand feedback" from patients and clinicians regarding changes in their asthma management program and their experience with newly available therapies. 67 FR at 48378 ("FDA ... will ask patients to provide first-hand feedback [and] will carefully consider all such comments in determining whether a use remains essential"). Asthma management programs are patient-specific and changes in these programs raise significant health care issues for patients.

By limiting the public meeting to a single, poorly publicized meeting, held on short notice, the agency frustrated its own effort to solicit and consider first-hand patient experiences. The agency also made no apparent effort to hear from patients in other regions of the country or in known "asthma hot spots," such as urban centers in the Western United States. *See, e.g.,* Tab 71, *Seeking Relief Where the Air Is Deemed The Dirtiest*, N.Y. TIMES (Aug. 12, 2007) (reporting that in Kern County, California 17.5 percent of children under 18 suffer from asthma, compared to the state average of 14.8 percent and the national average of 12.2 percent).

By failing to effectively solicit first-hand patient feedback, FDA limited the scope of the administrative record on a category of evidence the agency itself identified as important and relevant.[27] To fulfill the intent behind the public meeting requirement, FDA should schedule at least one additional public meeting in a distinct geographic region of the country.

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[27] Interested persons in the asthma community are still just learning of the Proposed Rule. *See, e.g.,* Tab 72 (T. Ballweg, RRT), received Aug. 31, 2007 (stating "I only found out about this web site today so am asking you to re-consider your plans to remove Maxair from the market. I teach and instruct asthma patients daily and can order this medication under authority of co-signature from a Physician. My patients need an alternative to albuterol for a wide variety of reasons. The most important is the appar[]ent lessoning of side effects from Beta 1 activity. Other reasons to keep it is for patients who cannot work an inhaler that requires timing their breath etc.").

C. The Comment Process

Comment No. 27

The public response to the Proposed Rule likely understates the views of patients who depend upon the seven products at issue in the rule, including Maxair Autohaler. FDA failed to accompany the publication of the Proposed Rule with a press release or other public announcement and the agency's patient, consumer, and clinician directed web pages made no mention of the Proposed Rule. FDA's actions were inconsistent with numerous other FDA proceedings and matters, in which FDA made a concerted effort to inform patients and consumers of important developments, including other rulemakings related to essential-use designations.

FDA routinely publicizes important agency developments and decisions. For example, when the agency recently issued a new proposed rule on testing and labeling of sunscreen products, it posted an announcement prominently on the FDA home page. *See* Tab 73, "FDA Proposes New Rule for Sunscreen Products" (Aug. 23, 2007). Accordingly, the sunscreen proposal has received widespread media coverage. FDA has also actively publicized other rulemakings related to essential-use designations. *See* Tab 58, Transcript of April 11, 1997, PADAC Meeting at 29 (describing FDA's efforts to communicate to the public proposal on CFC phase-out).

In this instance, and despite the important and immediate impact the Proposed Rule will have on patients, the agency issued no press release announcing the Proposed Rule or the Public Meeting. It also failed to post any information on the Proposed Rule on FDA's patient and consumer directed web pages. As a result, there has been no visible media coverage of the Proposed Rule, to ensure that patients and clinician who do not routinely follow the arcane process of federal rulemaking would be made aware of the process,.

In the course of developing the essential-use regulatory framework, FDA specifically assured commenters that the agency would "publicize [proposals to remove moieties from the essential-use list] in its educational programs, through its Internet site, and through press releases." 64 FR at 47731. The agency made clear that it would be important in such a proceeding to publicize the proposal, to encourage maximum public participation. *Id.*; *see also id.* at 47735 (noting that the agency chose notice and comment rulemaking to make essential use determinations "[t]o maximize public input").

The agency, however, clearly failed to follow-through on this commitment. For asthma and COPD patients who depend on drugs other than, or in addition to, albuterol, the Proposed Rule represents a critical development in the management of their disease. The rule should not be finalized until they have been given a reasonable opportunity to participate in the process.

Comment No. 28

FDA must give weight to the quality and the quantity of comments submitted in response to the Proposed Rule. Individual reports from patients, and the clinical experience of the physicians who have commented on the Proposed Rule, must also be given substantial weight in this proceeding.

Following publication of the Proposed Rule, and in light of FDA's anemic public education efforts, Graceway sought to inform potential interested persons about the proposal and the right to comment. In particular, Graceway sent letters with business reply cards (BRCs) that allowed for direct comment to the agency, and also created a website to assist clinicians, patients, and caregivers in commenting with more detailed letters. Patients demonstrated their concern over the proposal to remove Maxair Autohaler as an essential-use by submitting more than 7,000 cards, and more than 200 letters describing first-hand experiences with the product and, in some instances, the proposed alternatives. Both the quantity and quality of these submissions add considerable weight to the determination that Maxair Autohaler is an essential medical product.[28]

The agency has specifically recognized the importance of patient-specific experiences in making essential-use determinations:

> FDA recognizes that each patient is important. FDA also recognizes that patients' asthma management programs are individualized, and changes to these programs require patience, education, and consultation with health care providers. FDA . . . will ask patients to provide first-hand feedback to FDA as part of notice-and-comment rulemaking to remove an essential use. *FDA will carefully consider all such comments in determining whether a use remains essential.*

67 FR at 48378 (emphasis added). Here, the quality of the comments is notable, with patients and care givers providing specific reports of experiences with albuterol or the need for breath-actuated delivery, and with physicians and pharmacists offering their substantial clinical experience to the record.

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[28] At the Public Meeting, one FDA official dismissed the importance of these comments, stating that "these types of pre-printed reply cards do not, as a rule, do a good job on informing our decisions . . . . [they] do not really help us very much." Tab 8, Aug. 2, 2007, Transcript at 180 (W. Mitchell). To the contrary, FDA regulations explicitly provide that, in addition to the "quality and persuasiveness" of comments, "the *number* of comments is material where the degree of public interest is a legitimate factor for consideration." 21 CFR 10.40(c)(1) (emphasis added). Here, FDA specifically chose to use notice and comment rulemaking to make essential use determinations, "[t]o maximize public input." 64 FR at 47735; *see also id.* at 47731; 67 FR at 48378. Also during the meeting, one speaker questioned the value of certain patient comments and specifically identified comments from Maxair Autohaler patients. Tab 8, Aug. 2, 2007, Transcript at 23, 26. Although not disclosed at the Public Meeting, the organization the speaker represented at the meeting receives significant financial support from Sepracor, Inc., the sponsor of Xopenex HFA. Xopenex is one of the proposed alternatives to Maxair Autohaler and Sepracor would certainly stand to gain from the removal of Maxair Autohaler.

In terms of the quantity of patient comments that may bear on the final determination, the agency stated that:

> [J]ust as all patients are not adequately served by one CFC-MDI, all patients will not be served by an alternative product. Therefore, FDA does not believe it appropriate to make essential-use determinations on a patient-by-patient basis, just as the agency would not make determinations about whether a drug should remain on the market based on the experience of one patient or a small handful of patients.

Id. Here, the quantity of evidence goes well beyond the experience of a single patient or a "small handful" of patients.

Reliance on patient and clinician experiences is a key element of this particular regulatory framework. As noted above, the agency's process requires not only notice-and-comment rulemaking, but also consultation with an appropriate advisory committee and the presentation of public views and experiences in an "open public meeting." *See* 21 CFR 2.125(g)(2). Through these choices, FDA has made clear that essential-use determinations must incorporate patient, care giver, physician, and pharmacists reports, as well as any available data, literature, and analysis. In this regard, essential-use determinations, made through notice-and-comment rulemaking, are different than application-specific findings, such as new drug approval decisions under section 505 of the Food, Drug, and Cosmetic Act, which must be based on "adequate and well-controlled" clinical trials. 21 USC 355(d); *see* 21 CFR 314.126.[29] For essential-use determinations, public input and experiences are central, because the decision-making involves the weighing of important and competing public policy considerations.

Comment No. 29

FDA's failure to create a confidential docket prevented companies from commenting more meaningfully on certain aspects of the proposed rule, especially on issues related to the development of non-ODS formulations of Maxair Autohaler.

Despite requests from industry that FDA create a mechanism by which sponsors may submit confidential commercial and trade secret information for consideration as part of the rulemaking proceeding, FDA has failed to create such a mechanism. Tab 75, Graceway, "Request for Extension of Comment Period," (Jun. 26, 2007); Tab 76, Statement of Dr. R. Jain, Abbott Laboratories (Aug. 2, 2007). In fact, at the August 2, 2007, public meeting, an agency official commented that the agency has "never established a mechanism" and doing so "would require us to amend some of our regulations in Part 10." *See* Tab 8, Aug. 2, 2007, Transcript at 184.

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[29] The agency routinely relies on individual patient and clinician reports when making regulatory decisions. For example, FDA may rely on adverse drug experience (ADE) reports received through the MedWatch system as the basis for safety-related changes to prescribing information. Even a single ADE report may be sufficient to support the need for heightened warnings, or even a boxed warning, in the labeling of a drug product.

FDA has, however, created a mechanism to allow the submission and consideration of confidential information and trade secrets. For instance, in the context of the tobacco proposed rulemaking and jurisdictional analysis, FDA created a confidential docket for the submission of industry confidential and proprietary information and trade secrets, such as documents supporting pending drug applications. *See* 61 FR 44619, 45279-80 (Aug. 28, 1996). The agency noted that its use of the confidential docket was "a carefully developed . . . . mechanism to accommodate the industry's need to protect its confidential commercial information and its trade secrets . . . ." *Id.* at 45285. FDA also noted that "reliance on protected documents" in the context of a rulemaking has been supported by the courts. *Id.* at 45283 (citing *United States v. Nova Scotia Food Products Corp.*, 568 F.2d 240, 251 (2d Cir. 1977); *Home Box Office, Inc. v. Federal Communications Commission*, 567 F.2d 9, 58 (D.C. Cir. 1977)).

IV. Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) requires an agency to analyze and describe the impact of a proposed rule on "small entities." 5 USC 603(a). Specifically, the agency must: (1) certify that a proposal does not have a "significant economic impact on a substantial number of small entities"; or (2) prepare an initial regulatory flexibility analysis on the proposal. *Id.* at 603 and 605(b). As part of the analysis, the agency must discuss alternatives that would "minimize any significant economic impact . . . on small entities." *Id.* at 603(c).

The agency failed to conduct the required analysis in the Proposed Rule, despite the fact that the rule will have a significant impact on a substantial number of small businesses. The failure to do so in this instance requires that FDA re-propose the rule with an initial regulatory flexibility analysis and allow a meaningful opportunity for comment on alternatives to the rule that could help minimize the impact on small businesses.

Comment No. 30

FDA's statement in the Proposed Rule that none of the firms impacted by the rule is a small entity for purposes of the RFA is incorrect. Graceway is a small entity within the meaning of the RFA and is a small entity based on the standard established by the agency in the Proposed Rule.

In the Proposed Rule, FDA dismisses its obligations under the RFA on the grounds that "[n]one of the firms that manufacture the seven CFC MDIs, including the firms that distribute CFC MDIs that are manufactured under contract for them, employ fewer than 750 people and therefore none are small entities." 72 FR at 32048. This finding is simply inaccurate. As noted by the agency in the Proposed Rule, pharmaceutical manufacturers are considered to be small businesses if they employ fewer than 750 people. *Id.* With fewer than 300 full-time employees in the United States (and fewer than 100 outside of the United States), Graceway is a small entity within the meaning of the RFA and for purposes of this rule.

Graceway is the holder of the approved NDA for Maxair Autohaler (NDA 20-014). As the NDA holder, Graceway is ultimately accountable to patients and to FDA for all aspects of the

manufacturing and marketing of Maxair Autohaler. *See* Tab 77, Letter from J. Gregory to B. Chowdhury, M.D. (Dec. 29, 2006).

In accordance with FDA regulations, Graceway and 3M notified the agency that Graceway had assumed responsibility for the NDA in December 2006. *Id.*; Tab 78, Letter from M. Kuker to B. Chowdhury, M.D. (Dec. 29, 2006). FDA was therefore on notice approximately six months before the agency issued the Proposed Rule that Graceway was the NDA holder. FDA even acknowledged the transfer in writing. Tab 79, Letter from M. Raggio to J. Gregory (Jan. 18, 2007).

Comment No. 31

The Proposed Rule would have a significant economic impact on Graceway and, in the context of this rulemaking, an impact on only one sponsor represents an impact on a substantial number of small entities.

Maxair Autohaler sales account for approximately 15% of Graceway's United States revenues, roughly three times the threshold for significance set by HHS. *See* Tab 81, *Guidance on Proper Consideration of Small Entities in Rulemakings of the U.S. Department of Health and Human Services* at 7 (May 2003) (establishing a 3 – 5% average annual impact as significant). Moreover, Maxair Autohaler is Graceway's only respiratory product. Without Maxair Autohaler, the company would be almost entirely dependent on its dermatologic product line. That dependence would impair Graceway's ability to diversify into other product lines. *See generally* Tab 80, Small Business Administration Office of Advocacy, *A Guide for Government Agencies: How to Comply with the Regulatory Flexibility Act* at 1 (May 2003) (discussing how rules may have a disproportionate impact on small businesses because they have "fewer options for recovering them").

In the Proposed Rule, FDA identifies the set of entities impacted as "firms that manufacture the seven CFC MDIs, including firms that distribute CFC MDIs that are manufactured under contract for them." 72 FR at 32048; *cf.* 70 FR 55038, 55051-52 (Sept. 1, 2005) (analyzing the number of "producers of PET drug products" affected by the proposed rule). According to the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also known as the "Orange Book," there are five sponsors of prescription CFC MDI products.[30] According to HHS, in the interest of "ensuring that a broad range of impacts are fully considered in the [Regulatory Flexibility] analysis," a "substantial" number means "5 percent or more of the affected small entities within an identified industry." Tab 81, HHS Guidance at 7. As one of the five NDA holders, Graceway constitutes 20% of the impacted entities and 100% of the impacted small businesses. Thus, for purposes of the RFA, the Proposed Rule has a significant impact on a substantial number of small entities. *See* Tab 80, SBA Guidance at 19.

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30 In addition to Graceway's NDA for Maxair Autohaler, Roche holds the NDA for Aerobid (flunisolide); Abbott holds the NDA for Azmacort (triamcinolone); Boehringer Ingelheim holds the NDAs for Alupent (metaproterenol) and Combivent (albuterol sulfate and ipratropium bromide); and King Pharmaceuticals holds the NDAs for Intal (cromolyn) and Tilade (nedocromil).

Comment No. 32

FDA failed to describe the impact of the Proposed Rule on small businesses such as Graceway, and failed to consider alternatives that would minimize the impact of the rule on small businesses. The agency failed to comply with its obligations under the RFA, and must issue an Initial Regulatory Flexibility Analysis (IRFA) for comment prior to finalizing the rule.

As shown above, FDA was on notice – more than six months before the Proposed Rule issued – that Graceway had acquired Maxair Autohaler and had accepted transfer of ownership of the applicable NDA from 3M. With minimal investigation, the agency could have determined that Graceway is a small business or, in the alternative, the agency could have asked Graceway in advance of issuing the proposal whether the company might meet relevant small business measures. Instead, FDA stated that it "does not believe that this proposed rule would have a significant economic impact on a substantial number of small entities" and "request[ed] comment on the issue." 72 FR at 32039, 32048. By failing to consider or propose any alternatives to meaningfully lessen the impact on small businesses, FDA effectively transferred its statutory RFA mandate "to those entities that can least afford or have the least expertise in rulemaking processes," the small entities themselves. Tab 80, SBA Guidance at 51.

Because the Proposed Rule would have a significant effect on a substantial number of small entities, FDA must prepare and disseminate an initial regulatory flexibility analysis. 5 USC 603(a). The IRFA must identify alternatives to the Proposed Rule, including "the establishment of differing compliance or reporting requirements *or timetables* that take into account the resources available to small entities." *Id.* at (c) (emphasis added).

FDA also must "assure that small entities have been given an opportunity to participate in the rulemaking," by making reasonable use of techniques such as:

(1) the inclusion in an advanced notice of proposed rulemaking (ANPR), if issued, of a statement that the proposed rule may have a significant economic effect on a substantial number of small entities;

(2) the publication of a general notice of proposed rulemaking in publications likely to be obtained by small entities;

(3) the direct notification of interested small entities;

(4) the conduct of open conferences or public hearings concerning the rule for small entities including soliciting and receiving comments over computer networks; and

(5) the adoption or modification of agency procedural rules to reduce the cost or complexity of participation in the rulemaking by small entities.

5 USC 609(a). The agency, has, as yet, taken none of these steps. FDA must at least consider doing so before it re-proposes the rule with an IRFA.

If FDA seeks to cure these defects simply by publishing a new economic analysis, the agency would deprive Graceway a meaningful opportunity to comment, particularly on

alternatives directed to small businesses, thus "making the notice and comment process irrelevant." Tab 80, SBA Guidance at 37. The agency's failure to identify and consider alternatives until after a proposed rule is finished also would "violate the basic tenet of rational rulemaking under the APA." *Id.* Graceway is an entrepreneurial company that is seeking to grow as an entity and as an employer in Tennessee, Pennsylvania, and elsewhere. It is committed to working with the agency on moving away from an ODS formulation of Maxair Autohaler, but it requires an approach that may be different than what is suitable for a large, highly diversified pharmaceutical company.

In sum, as part of this rulemaking, FDA must reach out to and consult with small businesses such as Graceway, and must actively and thoughtfully consider alternatives to the Proposed Rule that would minimize the impact of the rule on Graceway. Unfortunately, the agency fell well short of meeting these obligations, and must correct this error by issuing an IRFA and otherwise meeting all requirements of the RFA.

V. The National Environmental Policy Act

The National Environmental Policy Act (NEPA) requires federal agencies to consider the environmental impacts of "actions significantly affecting the quality of the human environment," and reasonable alternatives to those actions. 42 USC 4332(c); *see* 40 CFR Parts 1500-1508; *see also* 21 CFR Part 25. Implementing regulations require federal agencies such as FDA to consider impacts that "can result from individually minor but collectively significant actions taking place over a period of time." 40 CFR 1508.7; *see id.* at 1508.27(b)(7). Thus, in this rulemaking, FDA must consider both direct and indirect effects that may be "later in time or farther removed in distance, but are still reasonably foreseeable." *See id.* at 1508.8. The agency's own environmental impact regulations require FDA also to consider environmental effects abroad, including potential environmental effects on the global commons. 21 CFR 25.60(a)(1).

Comment No. 33

FDA's tentative conclusion that the Proposed Rule will not have a significant adverse impact on the human environment lacks both factual and analytical support. FDA failed to consider the potentially significant global warming impact of the alternatives to Maxair Autohaler, and the overall impact of shifting the entire market to HFA-based formulations which, according to the agency, would increase the volume of HFA products by 33 percent or more. FDA therefore failed to meet its obligations under NEPA.

The agency tentatively concluded in the Proposed Rule that its actions "will not have a significant adverse impact on the human environment, and that an environmental impact statement is not required." 72 FR at 32039. This conclusion is clearly in error. The agency failed to identify – let alone discuss – the significant global warming impact of the proposed alternatives to Maxair Autohaler: Proair HFA, Proventil HFA, Ventolin HFA, and Xopenex

HFA, as well as the overall impact of continuing to remove CFC-containing products from the market in favor of HFA-containing products.

For example, all four alternatives to Maxair Autohaler use HFA-134a as a propellant instead of CFCs.[31] HFA-134a is known "greenhouse gas;" it traps heat in the atmosphere and is known to contribute to climate change. *See* Tab 83, EPA, *Inventory of U.S. Greenhouse Gas Emissions and Sinks: 1990-2005* (Apr. 15, 2007) at 2-3; Tab 82, IPCC Special Report at 135, 160. Emissions of HFC-134a in all applications—including MDIs—have increased from less than 0.05 Tg in 1990 to 74.0 Tg in 2005.[32] Tab 83, EPA Inventory at 4-47. With respect to MDIs, these emissions are expected to rise further. *See* 72 FR at 32034-35.

In the Proposed Rule, FDA concluded that releases of relatively small quantities of ODSs from MDIs, while individually minor, would over time have cumulatively significant impacts. *Id.* This same logic applies to the global warming potential of HFA-134a, as additional CFC essential uses are removed and HFA use increases, the potential for cumulative impact increases. Indeed, FDA previously recognized that increased use of HFA-134a for MDIs could have significant environmental impacts with respect to global warming when it proposed to remove the essential-use designation for albuterol in 2003. *See* Tab 84, Environmental Assessment: Removal of Essential-Use Designation: Albuterol Used in Oral Pressurized Metered Dose Inhalers (MDIs) (Dec. 15, 2003).

Furthermore, the market for MDIs worldwide is expected to increase rapidly in the future, which will also lead to increased emissions of HFA-134a. The IPCC estimates that MDI market growth will be about 1.5 to 3% per year; the total number of MDI units will be 680 million in 2015. Tab 82, IPCC Special Report at 357. The IPCC also expects additional use of HFA-134a MDIs as developing nations gain access to medication and as cases of asthma and COPD rise. *See id.* at 352, 357. All these factors clearly indicate the potential for HFA-134a emissions to have a significant cumulative impact on global warming. The agency – without any basis in law or fact – concluded that the rule will have no significant impact on the environment. This conclusion is plainly wrong.

Comment No. 34

FDA's Environmental Assessment failed to provide sufficient evidence and analysis to support the conclusion that the rule will have "no significant adverse environmental impact." The Environmental Assessment is based on out-of-date information and on a complete failure to consider the

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31 Significant investments of time and money by the international pharmaceutical industry went into research, development, testing and formulation of alternatives to CFCs as propellants in MDIs. These efforts led to the emergence of HFA-134a and HFA-227ea (1,1,1,2,3,3,3,-Heptafluoropropane) as the only two viable alternatives to CFCs. IPCC Special Report at 355. Like HFA-134a, HFA-227ea is a known greenhouse gas. HFA-227ea has a higher GWP than HFA-134a: (100-year) of 3140; its atmospheric lifetime is 34.2 years. Tab 82, Intergovernmental Panel on Climate Change (IPCC), *Special Report on Safeguarding the Ozone Layer and the Global Climate System: Issues Related to Hydrofluorocarbons and Perfluorocarbons* (Sept. 2005) at 160, Table 2.6.

32 EPA measures GWP-weighted emissions in teragrams (Tg) of CO_2 equivalent.

environmental impact of alternative products that use HFA propellants in place of CFCs. FDA also neglected to consider alternatives that could help mitigate the impact that HFA propellants may have on the environment. For example, the agency did not consider the option of continuing the essential-use designation of certain products to allow sufficient time to investigate non-HFA formulations and delivery systems. As such, the agency failed to meet its legal obligations under NEPA and applicable regulations.

The environmental assessment that accompanies the Proposed Rule relies solely on an outdated 1978 assessment. *See* Tab 85, Environmental Assessment (May 31, 2007). Ironically, even in 1978, FDA noted that the greenhouse effect is an environmental impact and assessed both the greenhouse gas and the ozone depletion impacts of CFCs. Final Environmental Impact Statement, Fluorocarbons: Environmental and Health Implications (Feb. 1978). Almost 30 years later, with much more scientific evidence regarding the causes and effects of global warming, FDA has even more reason to evaluate this impact, but failed to do so in the Proposed Rule.

FDA must provide "evidence and analysis" in support of a determination on whether the agency must prepare an environmental impact statement (EIS) or a finding of no significant impact (FONSI). 21 CFR 25.40(a). The agency is also required to discuss in its environmental assessment the impact of the proposed action, as well as alternative approaches. *Id.* Here, the agency failed to provide any analysis, let alone a well-supported and well-reasoned explanation, of the impact of directing more patients to HFA-based formulations. FDA is required by regulation to consider the impact of the use of FDA-regulated products, including the increased use of HFA-based products, that would be the direct result of the Proposed Rule. *Id.*

FDA's environmental assessment also neglects to discuss alternatives to the Proposed Rule, as required by NEPA. The agency simply stated that "limits in available data prevent us from quantifying the costs and benefits of the proposed rule and weighing them in comparable terms." 72 FR at 32048. However, as noted above, there is clear evidence of potential adverse impacts. FDA itself acknowledged these impacts in an earlier rulemaking on albuterol. Moreover, there is a specific IPCC report devoted solely to the potential global warming impacts of ODS substitutes. FDA should have considered these impacts and reasonable alternatives, such as continuation of the *status quo* (*i.e.*, continuing the current essential-use designations) or allowing additional time for the pharmaceutical industry to develop new environmentally benign technology, such as dry powder inhalers (DPIs).

In sum, it may be the case that the rule is a "wash" or, even worse, a net loss for the public. The rule may achieve no net material environmental benefit, while also imposing substantial costs on individual patients and the healthcare system.

VI. Effective Date

Under the Proposed Rule, the removal of a moiety from the essential-use list would not become effective until December 31, 2009. The agency, however, stated that different essential-uses may require different effective dates and requested comment on the issue. 72 FR at 32034; *see also* 72 FR at 37138. Please note that the support for each of the following comments can be found in the prior Comments and supporting statements, as indicated by the cross-references provided below.

Comment No. 35

Because Maxair Autohaler continues to meet the criteria for essential-use designation, the Proposed Rule should be finalized with no change in the current listing of pirbuterol. The essential-use listing may be revisited in a subsequent proceeding but, at the present time, neither the final rule nor the effective date of the rule should apply to Maxair Autohaler. *See* Comments 1-19.

Comment No. 36

Graceway agrees with the important goal of full and final elimination of ODS-containing inhalation products. Graceway is committed financially to developing a non-ODS formulation of Maxair Autohaler, and looks forward to working with the agency to move this project forward expeditiously. *See* Comment 19. Graceway is confident in its ability to obtain sufficient CFCs to continue to supply the market with Maxair Autohaler throughout the transition to a non-ODS product. Consistent with the goal of managing down the use of CFCs while ensuring that essential products remain available to patients, Graceway recommends that the agency revisit the essential-use status of pirbuterol in or after December 2012. The time for revisiting the status of the product should be memorialized in the preamble to the final rule, to provide a level of certainty to Graceway, patients, and participants in the Montreal Protocol proceedings. *See* Comments 20-21.

Comment No. 37

At the open public meeting, several sponsors asked for extensions of the proposed effective date as to their products. As the agency manages down the use of CFCs, it faces decisions that become increasingly difficult and require greater prudence. In making these decisions, it is important to consider how best to allocate the remaining use of CFCs. Because of its efficiency, small market, and unique active moiety and delivery system, Maxair Autohaler represents a prudent use of CFCs. For example, a six-month extension of the effective date as applied to other products may require a quantity of CFCs in excess of what would be needed to support the

continued availability of Maxair Autohaler throughout its redevelopment program. *See* Comment 16.

Comment No. 38

Even if the agency were to determine that pirbuterol should be removed from the list of essential uses in 21 CFR 2.125(e), the effective date for the removal of pirbuterol should be deferred to December 31, 2015.[33] This effective date will ensure that pirbuterol patients will continue to have access to the drug during the reformulation and regulatory review phases of the development of a non-ODS pirbuterol product. This period of time is consistent with typical time periods for reformulating and gaining regulatory approval of other non-ODS MDI products. *See* Comments 18-19. It represents Graceway's best estimate at this time for completion of the non-ODS development program for Maxair Autohaler, including regulatory review. This deferral will require minimal use of CFCs, particularly compared with the amounts required to support even brief deferral periods for other products at issue in this proceeding. *See* Comment 16. It is consistent with the need to protect the interests of a relatively small but important patient population. *See* Comments 1-14. Finally, it is consistent with principles of federal rulemaking, in which measures should be taken to minimize the impact of a rule on small businesses, such as Graceway. *See* Comments 30-32.

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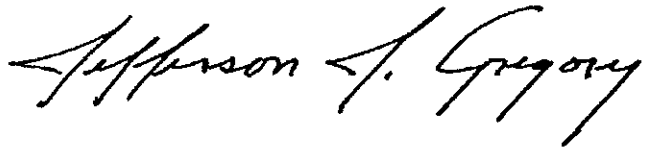
33 The amount of time described here is in line with deferrals provided in other rulemaking proceedings. For example, FDA issued a final rule setting standards for sunscreen products in 1999, but then deferred implementation of certain provisions in the rule for more than eight years. 64 FR 27666 (May 21, 1999) (final rule); *see generally* 72 FR 49070, 49071 (Aug. 27, 2007) (discussing history of deferrals of the final rule to the present). The sunscreen rule, like the ODS rule, involves the same general public health issues (minimizing fatal and nonfatal skin cancers). And, like the ODS rule, the sunscreen rule was issued under a direct statutory mandate. *See* Food and Drug Administration Modernization Act, Section 129 (requiring issuance of a sunscreen rule within 18 months of enactment). Similarly, FDA delayed by six years the effective date of the rules implementing pedigree requirements of the Prescription Drug Marketing Act (from Dec. 2000 to Dec. 2006). *See* 65 FR 25969, 25641 (May 3, 2000); 66 FR 12850, 12853 (Mar. 1, 2001); 67 FR 6645, 6647 (Feb. 13, 2002); 68 FR. 4912, 4913 (Jan. 31, 2003); 69 FR 8105, 8107 (Feb. 23, 2004); 69 FR 12792, 12794 (Mar. 18, 2004) (correction); 71 FR 34249 (June 14, 2006).

CONCLUSION

We thank the agency in advance for its careful consideration of these Comments, and the administrative record as a whole, and urge the agency to contact us if we can provide clarification or additional information on any issues of concern.

Respectfully Submitted,



Jefferson J. Gregory
Chief Executive Officer

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7	D. Taylor, *et al.*, *Bronchodilator Response in Relation to β2-Adrenoreceptor Haplotype in Patients with Asthma*, 172 AM. J. RESPIR. CRIT. CARE MED. at 700-03 (2005)
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9	C. Rodrigo & G. Rodrigo, *Therapeutic Response Patterns to High and Cumulative Doses of Salbutamol in Acute Severe Asthma*, 113 CHEST at 593-98 (1998)
10	L. Strauss, *et al.*, *Observations on the Effects of Aerosolized Albuterol in Acute Asthma*, 155 AM. J. RESPIR. CRIT. CARE MED.at 454-58 (1997)
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