UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DEC 20 2011

ASSISTANT ADMINISTRATOR
FOR ENFORCEMENT AND
COMPLIANCE ASSURANCE

Kevin N. Nicholson, R. Ph., Esq.
Vice President
Government Affairs and Public Policy
National Association of Chain Drug Stores
413 North Lee Street
P.O. Box 1417-D49
Alexandria, Virginia 22313-1480

Dear Mr. Nicholson:

Thank you for your letter of November 22, 2011, expressing your concern over asthmatics' access to Primatene Mist, an over-the-counter (OTC) inhaler, and requesting that your member pharmacies of the National Association of Chain Drug Stores (NACDS) be allowed to sell current stocks of Primatene Mist after December 31, 2011. I wanted to update you on the status of your request, which we have discussed with our colleagues at the Food and Drug Administration (FDA).

Before addressing the public health concerns you raise, I wanted to provide some context regarding when the Environmental Protection Agency (EPA) grants this type of relief. In general, the EPA has a policy that disfavors "No Action Assurances" except: (1) "where expressly provided by applicable statute or regulation," or (2) "in extremely unusual cases in which a no action assurance is clearly necessary to serve the public interest." Policy Against "No Action" Assurances, Courtney M. Price, Assistant Administrator for Enforcement and Compliance Monitoring (Nov. 16, 1984). "Public interest" encompasses well-documented public health concerns.

We share your concern for Americans who struggle with asthma, and we recognize that after December 31, 2011, Primatene Mist will be prohibited from being sold or distributed. We have discussed and will continue to discuss this matter with our colleagues at the FDA. Before making a decision in this matter, we wanted to provide you a summary of what we have heard throughout FDA's process that led to their final rule in November 2008, as well as since, to provide you an opportunity to respond to or supplement the record.

The FDA's rulemaking in this case was completed in 2008, was not challenged, and was responsive to requests made by stakeholders in the process of its development. FDA has shared its view that this rulemaking proceeded in an orderly, transparent and open fashion that included relevant medical and public health authorities, as well as stakeholders such as Armstrong and other manufacturers of inhalers containing chlorofluorocarbons (CFCs).

As stated in its final rule, the FDA does not believe that continued use of OTC epinephrine metered dose inhalers (MDIs) is necessary to save lives, to reduce or prevent asthma morbidity or to significantly increase patient quality of life. This is particularly the case in light of the availability of albuterol MDIs as therapeutic alternatives, and the possibility that, in the absence of the OTC drug product, additional patients may seek assessment and treatment for their asthma conditions from health care professionals and reduce their asthma morbidity as a result.

In September 2011, EPA held a meeting including other government agencies such as the Department of State and the FDA. The meeting was widely attended by key stakeholders such as patient organizations, medical specialty associations and retailers and retail representatives including your own organization, the NACDS. While this was an important opportunity to hear various perspectives, we did not hear concerns in this meeting or after that would indicate an expected significant disruption of public health. To the contrary, in an October 28, 2011, letter to Senators Pat Roberts and Jim DeMint, a broad-based coalition of patient advocacy groups including the Allergy & Asthma Network, Mothers of Asthmatics, COPD Foundation/Alpha-1 Foundation, American Association for Respiratory Care, Asthma Allies and the American Latex Allergy Association expressed concern instead that efforts to delay the phase-out of epinephrine CFC MDIs do "nothing to address and solve the problem of patients' access to NIH guideline-level care" and called epinephrine CFC MDIs an "outdated, inferior CFC-propelled drug no longer recommended for the treatment of asthma."

We are aware that the national asthma guidelines published by the National Institutes of Health's (NIH) National Heart, Lung, and Blood Institute have consistently recommended against use of epinephrine MDIs. Accordingly, a November 22, 2011, letter to Senators Roberts, DeMint and to both the EPA and the FDA from the American College of Allergy, Asthma and Immunology notes that given the availability of albuterol MDIs as therapeutic alternatives, the absence of OTC epinephrine may spur additional patients to seek assessment and treatment for their asthma conditions from health care professionals, and reduce their asthma morbidity as a result. They state: "We would like to see that inhaled epinephrine is banned since it is not in patients' best interest to use this product to manage their asthma symptoms."

We recognize the concern you raise with respect to cost and access. However, in the October 28 letter, leading patient advocacy groups note that the average dose of epinephrine will provide relief for 15 to 30 minutes while the average dose of a prescription bronchodilator alternative will provide relief for 3 to 6 hours. They conclude that: "Primatene Mist is not a cheaper alternative." Further, in a November 4, 2011, letter to the FDA, the International Pharmaceutical Aerosol Consortium (IPAC), an international association of companies that manufacture medicines for treatment of respiratory illnesses including asthma, noted the availability of patient assistance programs and product samples that will help users of epinephrine CFC MDIs successfully transition to CFC-free alternatives. An IPAC member company, Teva Pharmaceuticals, shared in a November 28, 2011, letter to EPA Administrator Lisa P. Jackson that although Primatene Mist buyers are sometimes characterized as uninsured, low-income patients, a recent survey conducted by Teva found that 84% of Primatene Mist users were insured, 83% had a personal physician, and 80% had prescription drug coverage. We also note that since mid-2010, Primatene Mist packaging has contained the following message: "Primatene Mist (CFC) will not be available after December 31, 2011. Talk to your doctor or pharmacist about other asthma medications." In light of this, some stakeholders have even raised concerns that extending the deadline beyond December 31, 2011, will confuse patients.

This information, shared by many leading medical authorities, major pharmaceutical manufacturers, as well as by leading regulatory and scientific organizations – the FDA and the NIH – responsible for the safety of medications and for establishing standard of care guidelines for treatment of disease, seems to us substantial. We intend to continue to consult with our colleagues at FDA on the health concerns raised in your letter. If you have additional relevant information on this topic, we invite you to share it with us. We look forward to continuing to work with you and NACDS, medical and patient health organizations, manufacturers of asthma treatments, the FDA and medical professionals to monitor the situation and to review any new relevant information as we approach the December 31, 2011, date set by the FDA's 2008 rule.

Thank you for your letter,

Sincerely,

Cynthia Giles
Assistant Administrator,
Office of Enforcement
and Compliance Assurance

Enclosures

cc: The Honorable Bart Stupak, Attorney for Amphastar and Armstrong Pharmaceuticals, Venable LLP
Commissioner Margaret A. Hamburg, U.S. Food and Drug Administration

October 28, 2011

Honorable Pat Roberts
109 Hart Senate Office Building
Washington, DC 20510-1605
RE: S. 1752 Freedom to Breathe Act of 2011

Honorable Jim DeMint
167 Russell Senate Office Building
Washington, DC 20510
RE: Amendment OTC Epinephrine inhalers

Dear Senator Roberts and Senator DeMint:

Thank you for your interest and concern for patients living with asthma.

Allergy & Asthma Network Mothers of Asthmatics, Alpha-1 Foundation/COPD Foundation, American Association of Respiratory Care, American Latex Allergy Association and Asthma Allies do not support the Freedom to Breathe Act of 2011 or the amendment as both would continue access to an Over The Counter (OTC) bronchodilator, Primatene Mist, developed over 50 years ago that is no longer recommended for use by patients with asthma. Twenty years ago, National Guidelines for the Diagnosis and Management of Asthma were developed by the National Institutes of Health and since then have been updated three times as a result of new evidence-based science about the disease of asthma. Neither NIH guidelines nor the Global Initiative for Asthma (GINA) recommend epinephrine inhalers for the treatment of asthma.

On December 31, 2011, after nearly 20 years' warning, epinephrine inhalers (Primatene Mist and its generic copies made by Armstrong Pharmaceuticals) will no longer be sold in the United States because they contain CFCs and do not meet the criteria for an essential use exemption from US and international treaties signed by Congress to eliminate ozone-depleting CFC propellants.

Of the 20 different brands and types of prescription-only inhalers currently sold in the US, 19 are now CFC-free. Pharmaceutical manufacturers were required to comply with laws and change their products or have them removed them from the market. More than

24 million asthma and COPD patients and their medical care providers were required by law to change treatment plans, pay for additional office visits, and pay higher co-pays and out of pocket costs for newly approved medications.

Badrul Chowdhury MD, director of FDA's Division of Pulmonary, Allergy and Rheumatology Products stated, "There is no technical barrier preventing a non-CFC version of inhaled epinephrine." The manufacturer failed to develop a non-CFC alternative even though they were granted a three-year extension beyond the 2008 deadline other manufacturers met for their bronchodilators, albuterol and levalbuterol.

Inhaled epinephrine, the only nonprescription drug inhaler available, is **not** recommended for the treatment of asthma. It is one of the grandfathered vestiges predating FDA, but it is still subject to the same laws, regulations and treaty that banned every available prescription CFC-containing inhaler for asthma and COPD.

It is stated in your press release that millions of patients will be affected if OTC epinephrine goes away; however, no one really knows if that is true. Armstrong, at several FDA meetings, reported they didn't know how many actual patients use their canisters or how many canisters each patient buys, much less the age, income, or regional locations of epinephrine inhaler users.

Armstrong's customers, as they refer to them, are the wholesalers and retailers — not patients. The numbers of 1.7 to 2.3 million stated in the press release are numbers the manufacturer provided FDA at a meeting. Nobody really knows how many people use this product and the company can only make a guess based on numbers of canisters sold divided by how many canisters they "think" each patient buys.

Two inhalations of epinephrine provide breathing relief and serious side effects for approximately 15-30 minutes, whereas two inhalations of prescription bronchodilators, which is the recommended medication by NIH, last 3-6 hours with less unwanted cardiac stimulation. Primatene Mist is not a cheaper alternative.

Assertions that Medicaid families and thus states will be hard hit should OTC epinephrine evaporate are highly suspect. Inhaled epinephrine is not the drug of choice or last resort for Medicaid patients. Medicaid patients have prescription coverage and access to medical care. Prescription bronchodilators and inhaled corticosteroids recommended by NIH for asthma are covered under Medicaid.

The real problem Medicaid families face is that pharmacies do not always dispense the medication or inhalation devices their doctors prescribe. Patients also tell us that they don't always receive referrals to allergists and pulmonologists, as recommended in NIH guidelines. We would love your help to ensure that NIH Asthma Guidelines-based, cost-effective and patient-centered care is available to every patient — while saving state and federal government funds currently wasted on chronically urgent care, as shown at AANMA's congressional briefing (http://www.aanma.org/advocacy/congressional-asthma-and-allergy-caucus/) earlier this month.

Fifty years ago, epinephrine inhalers were all we had to treat asthma. But like most older medications, it has been replaced with far safer and more effective medications

that treat both the noisy obvious symptom of asthma, bronchospasm, as well as the underlying, smoldering silent cause of symptoms, airway inflammation. Knowledge of the disease of asthma has drastically changed the way it is treated, and 1950s treatments are no longer considered safe.

Today's treatment plans also are not based solely on one or more inhaled or oral medications. They require identifying the cause(s) of symptoms, removing environmental or occupational exposures, repairing airway inflammation using anti-inflammatories and restoring the patient to full and healthy function.

Asthma is not a disease for do-it-yourselfers. Asthma is a serious, potentially life-threatening disease that kills 11 people every day and it deserves serious attention.

Rather than defend a manufacturer's right to continue making an outdated, inferior CFC-propelled drug no longer recommended for the treatment of asthma, AANMA urges Congress to issue vouchers through physicians, clinics and hospitals to offset patient expenses associated with purchasing NIH guideline-recommended medications for asthma.

The Freedom to Breathe Act of 2011 does nothing to address and solve the problem of patients' access to NIH guideline-level care, but rather grants special favors to a manufacturer — the only one who will benefit from the Freedom to Breathe Act of 2011.

AANMA is prepared to help in any way to ensure patients with asthma receive NIH guideline-level care and appropriate medical treatment.

Thank you for your time and attention to our concerns. We look forward to discussing this most important issue with you. Please feel free to contact AANMA at 703-641-9595 or Sandra Fusco-Walker, AANMA's Director of Patient Advocacy, at 703-641-9595 x1524.

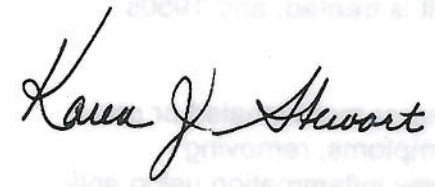
Sincerely,

Nancy Sander

Nancy Sander, President and Founder
Allergy & Asthma Network Mothers of Asthmatics

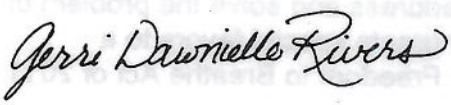
John W. Walsh

John W. Walsh, President and CEO
Alpha-1 Foundation
COPD Foundation



Karen J. Stewart, President
American Association of Respiratory Care

Sue Lockwood, Executive Director and Co-Founder
American Latex Allergy Association



Gerri Dawnielle Rivers, Co-Founder
Asthma Allies

ACAAI American College of Allergy, Asthma & Immunology

Follow the Leader Into the Future

AMERICAN ACADEMY OF ALLERGY ASTHMA & IMMUNOLOGY

November 22, 2011

Honorable Pat Roberts
109 Hart Senate Office Building
Washington, DC 20510-1605
RE: S. 1752 Freedom to Breathe Act of 2011

Honorable Lisa Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Honorable Jim DeMint
167 Russell Senate Office Building
Washington, DC 20510
RE: Amendment OTC Epinephrine Inhalers

The Honorable Margaret H. Hamburg, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Senator Roberts, Senator DeMint, Administrator Jackson and Commissioner Dr. Hamburg:

The United States Food and Drug Administration's decision to remove over the counter epinephrine asthma inhalers will take effect on January 1, 2012. This action has been proposed to eliminate the CFC propellants in inhalers that could affect the ozone layer. Over the counter epinephrine is the only asthma inhaler remaining on the market with a CFC propellant. All other manufacturers of asthma medications have switched to different delivery systems and have eliminated CFC propellants from their metered doses inhalers in favor of HFA which likely does not effect the environment. We would like to see that inhaled epinephrine is banned since it is not in patients' best interest to use this product to manage their asthma symptoms.

Optimal asthma care requires consultation with health care professionals including asthma specialists and the use of appropriate medications. Evidenced based guidelines do not recommend the use of inhaled epinephrine for treatment or control of either acute or chronic asthma symptoms.

It is important to recognize that appropriate care of asthma with more effective rescue medications and chronic controller medications will ultimately decrease morbidity and mortality due to this common disease. Not only will this benefit patients, but this will provide considerable cost savings to the health care system and the economy as a whole due to decreases in lost productivity at work and school, urgent care visits and hospitalizations, all of which result from inadequate asthma control.

In summary, although the cost of epinephrine inhalers are approximately 50 -70% less than prescription albuterol, the use of these inhalers for the management of asthma will ultimately cost the health care system considerably more and imperil the lives of those patients with asthma who rely on this treatment and do not seek the most appropriate care. As representatives of asthma specialists, we support the removal of over the counter epinephrine inhalers from the market and urge optimal care for patients with asthma.

Sincerely,

Stanley M. Fineman, MD, MBA
President, ACAAI

Dennis K. Ledford, MD
President, AAAAI

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November 4, 2011

Via Email

Commissioner Margaret A. Hamburg
U.S. Food and Drug Administration
Office of the Commissioner
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Commissioner Hamburg,

This letter is submitted on behalf of the International Pharmaceutical Aerosol Consortium (IPAC) to express strong support for FDA's Final Rule establishing 31 December 2011 as the deadline for the transition of CFC-based epinephrine metered-dose inhalers (MDIs) (*brand name: Primatene Mist*). IPAC is an association of companies that manufacture medicines for the treatment of respiratory illnesses, such as asthma and chronic obstructive pulmonary disease (COPD). IPAC was formed more than two decades ago in response to the mandates of the *Montreal Protocol on Substances that Deplete the Ozone Layer*. IPAC is firmly committed to the transition from CFC MDIs to CFC-free alternatives, pursuant to the Montreal Protocol, and has actively engaged in the transition process in the United States. IPAC's member companies have invested substantial resources to develop CFC-free alternatives in order to accomplish the phase-out of CFC-based MDIs in furtherance of the United States' international commitments under the Protocol.

IPAC is extremely concerned about recent efforts within the US Congress to delay or suspend the phase out of epinephrine CFC MDIs and believes that such proposals would have negative implications for patient health. IPAC is encouraged that the amendment proposed by Senator DeMint and considered last week by the Senate was defeated, but wishes to share some perspectives on this issue in case similar delays are introduced.

IPAC notes that FDA undertook a careful, deliberative, and thoughtful open public rulemaking process that included input from patient and physician stakeholders and other key experts to establish the transition deadline for Primatene Mist. This deadline has provided three full years to transition patients to one of the several CFC-free alternatives available. Since the Final Rule was issued in 2008, FDA has worked hard – in collaboration with patients, physicians, and other interested stakeholders – to prepare for a smooth transition for Primatene Mist users. In

addition, available patient assistance programs (and product samples) will help many users of Primatene Mist successfully transition to safe and effective CFC-free alternatives.

Even if Congress were to override FDA's well-considered deadline on Primatene Mist, it would only briefly forestall the inevitable. Due to a global ban on CFC production, safe and adequate supplies of pharmaceutical-grade CFCs do not exist for the continued manufacture of Primatene Mist. It is therefore important for users to transition now pursuant to the deadline established by FDA. Even a small shift of the end 2011 deadline (e.g. 3 to 6 months) could be quite counterproductive for the following reasons: (i) it would introduce confusion and uncertainty for, most importantly, patients, and also for the supply chain; and (ii) it could hamper EPA efforts to enforce the transition when it actually occurs.

In the past, EPA and FDA have firmly denied MDI companies' requests for any extension to transition deadlines (e.g., to use up existing already-produced stockpiles of CRC MDIs), and there is no reason that there should be a different result in the case of Primatene Mist. FDA has made a significant effort to raise awareness of the 31 December 2011 deadline and changing that now would send very mixed signals to patients, consumers, health care providers and other stakeholders.

The phase-out of Primatene Mist and other ozone-depleting MDIs was initiated more than two decades ago. The "essential use" process established under the Montreal Protocol has provided the MDI industry ample time to reformulate and seek approvals of CFC-free alternatives. After long ago "seeing the writing on the wall", MDI manufacturers worked diligently to research and develop CFC-free products. Most companies (including all IPAC members) have invested hundreds of millions of dollars to accomplish this important objective. Introducing even a brief delay at this late stage would send a very negative signal to the manufacturers that responded to the US Government's call to be a partner in meeting the Montreal Protocol commitments.

For the sake of the environment, compliant manufacturers and, most importantly for the patients, FDA must not waiver in their commitment on this matter merely for the economic interests of a few.

Sincerely,

Maureen Donahue Hardwick
IPAC Secretariat and Legal Counsel

cc: Badrul Chowdhury, *Office of New Drugs, CDER*
Lisa P. Jackson, *EPA Administrator*
Gina A. McCarthy, *Assistant Administrator for Office of Air and Radiation, US EPA*
Sarah Dunham, *Director of the Office of Atmospheric Programs*
Drusilla Hufford, *Director, Stratospheric Protection Division, US EPA*
Dan Reifsnyder, *Deputy Assistant Secretary for Environment and Sustainable Development, US Department of State*
John Thompson, *Foreign Affairs Officer, Office of Environmental Policy, US Department of State*

November 28, 2011

The Honorable Lisa Jackson
Administrator
Environmental Protection Agency
Ariel Rios Federal Building
1200 Pennsylvania Avenue, NW
Room 3000
Washington, DC 20460

Dear Administrator Jackson:

I am writing on behalf of Teva Respiratory, a brand division of Teva Pharmaceuticals, to provide a profile of Primatene Mist CFC users. As you know, concerns have been raised about the impact on patients of the regulation that would prohibit the selling of over-the-counter epinephrine inhalers, primarily Primatene Mist, after December 31, 2011. Regretfully, there seems to be a lot of misperceptions and faulty assumptions about who the Primatene Mist CFC customer is and his/her access to appropriate medication alternatives.

In order to prepare for the transition, Teva Respiratory conducted a market research survey to better understand how to best educate patients and health care providers of the transition from Primatene Mist CFC to albuterol HFA. While this information is proprietary, I did want to share some of the top line findings in order to provide a better understanding of the current Primatene Mist user.

We surveyed consumers between the ages of 20 and 75 who have purchased and used Primatene Mist CFC within the past two years. The findings included:

- Primatene Mist CFC users are well educated, well above the general population
  - 28% had graduated college compared to 19% of the U.S. population
  - 21% had done post graduate work compared to 10% of the U.S. population;
- The median number of Primatene Mist CFC inhalers used in the past 18 months is 2;
- 84% of Primatene Mist CFC users are insured;
- 80% of Primatene Mist CFC users have prescription drug coverage;
- 83% of Primatene Mist CFC users have a personal physician and 72% have seen their physician in the past year;

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- Tier 2 copays for insured patients average $20-$25 (similar to retail costs of Primatene Mist CFC inhalers)
  - For the 16% of those not insured, low income patients (200% or less of the Federal Poverty Level) would qualify for The Teva Assistance Program for free albuterol HFA inhalers;

- 88% of Primatene Mist CFC users have a respiratory diagnosis and nearly 40% are already taking a prescription inhaler;

- Only 11% of Primatene Mist CFC users cited cost as a factor when citing reasons for using the product over a prescription inhaler.

The data clearly suggests that the majority of Primatene Mist CFC users are already in the health care system have access to a physician and visit their physician on a regular basis.

Many of the concerns raised about this transition are similar to those raised during the 2008 "CFC to HFA" albuterol switch. Due to the hard work and efforts of all the stakeholders – the federal government, patient groups, medical societies, pharmacies and drug manufacturers – it was extremely successful with virtually no disruption in access or harm to patients. Teva Respiratory, and indeed all of our competitors, initiated numerous programs to educate patients and health care providers. Although the scale was much greater for the 2008 transition – 50 million albuterol units compared to 2-3 million Primatene Mist CFC units – the effort has been similar. Significant resources were invested to drive awareness of the albuterol CFC-HFA transition, just as they have been in this switch, with the goal of ensuring that all were prepared. Patients and health care providers were ready for the transition in 2008 and they are ready for the switch this year.

I hope you find this information helpful. Please do not hesitate to contact me should you have additional questions.

Sincerely,

Mark Salyer

Mark Salyer
Executive Vice President and General Manager

cc: Margaret Hamburg, MD
Commissioner
Food and Drug Administration

Cynthia Giles
Assistant Administrator, Office of Enforcement and Compliance Assurance
Environmental Protection Agency

Regina McCarthy
Assistant Administrator, Office of Air and Radiation
Environmental Protection Agency

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