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November 21, 2007

### VIA MESSENGER

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

Re: Pre-Hearing Comments for Docket No. 2007N-0262 (RIN 0910-AF92): "Use of Ozone-Depleting Substances; Removal of Essential-Use Designation (Epinephrine)"

Dear Sir or Madam:

We submit the following pre-hearing comments to the United State Food and Drug Administration's ("FDA's") Proposed Rule on the "Use of Ozone-Depleting Substances; Removal of Essential-Use Designation (Epinephrine)" (Docket No. 2007N-0262, the "Proposed Rule") on behalf of Armstrong Pharmaceuticals, Inc., a wholly-owned subsidiary of Amphastar Pharmaceuticals, Inc. ("Armstrong"). Specifically, we write to request that the FDA revise the Proposed Rule to provide for an effective date of December 31, 2011 instead of the currently proposed December 31, 2010. Armstrong, a manufacturer and distributor of epinephrine metered-dose inhalers ("MDIs") distributed Over-The-Counter ("OTC") which currently use chlorofluorocarbons ("CFCs") as the propellant, believes that it will have a non-Ozone Depleted Substance ("ODS") alternative available and approved for OTC distribution in 2011. With a one year delay in the currently proposed effective date for the Proposed Rule, Armstrong believes that it will be able to meet current market demand for this critical OTC product and transition individuals who use the OTC inhaler to the non-ODS inhaler. Without this one year delay, many asthmatic patients will have no access to emergency relief medication without seeking emergency room care and expensive hospitalizations.

The Proposed Rule would change FDA's regulation, 21 C.F.R. § 2.125(e), on the use of CFCs to remove the "essential-use" designation of epinephrine. Specifically, under FDA's proposed rule, FDA would require that all epinephrine MDIs containing CFCs be removed from the market by the end of 2010. Epinephrine MDIs are the only OTC rescue asthma medication available in the United States. Eliminating the availability of this OTC product without a non-ODS OTC alternative will have significant detrimental public health effects. Armstrong is diligently working to develop a non-ODS propellant formulation. Despite Armstrong's best efforts, a non-ODS epinephrine MDI will not be available by the end of 2010. Based upon its current development efforts and its pre-development discussions with FDA, Armstrong anticipates a non-ODS epinephrine MDI will be commercially available before the end of 2011.

Although Armstrong disagrees with some of FDA's conclusions and interpretations of data within the preamble to the Proposed Rule, Armstrong does not oppose FDA's ultimate conclusion that the "essential use" status for epinephrine MDIs should be eliminated. However, Armstrong requests that FDA revise its Proposed Rule to reflect an effective date of December 31, 2011, in order to provide sufficient time for the development and approval of an OTC non-ODS epinephrine MDI to permit the safe transition of patients from the CFC formulation to the non-ODS formulation, and to eliminate the time period in which an OTC epinephrine formulation will be unavailable which will occur under FDA's Proposed Rule as currently drafted. Armstrong therefore submits these comments to address certain issues raised in FDA's preamble to the Proposed Rule and to request that FDA delay the effective date for the proposed rule to December 31, 2011.

## **I. THE PROPOSED RULE**

On September 20, 2007, FDA announced its proposed change to its regulation on the use of CFCs in MDIs for epinephrine. This proposed change would remove the "essential-use" designation from epinephrine MDIs that allows the use of CFCs in these medical devices. In developing this proposal, FDA consulted with the U.S. Environmental Protection Agency ("EPA") and considered information and comments presented during a January 24, 2006 advisory committee meeting conducted jointly by the Nonprescription Drug Advisory Committee ("NDAC") and the Pulmonary-Allergy Drugs Advisory Committee ("PADAC") on the essential-use status of OTC MDIs containing epinephrine (the "NDAC/PADAC meeting"). Based upon this consultation and consideration, FDA evaluated whether or not epinephrine MDIs continued to meet all three elements of essential use as defined in 21 C.F.R. § 2.125(f), which include:

- (i) Substantial technical barriers exist to formulating the product without ODSs;
- (ii) The product provides an unavailable important public health benefit; and
- (iii) 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.

In its Proposed Rule, FDA tentatively concluded that there are no substantial technical barriers to formulating epinephrine as a product that does not release CFCs. FDA stated that if even one of the three essential use elements was not satisfied, then the use was not essential. As a result, FDA did not reach a conclusion on the other two elements. Nevertheless, FDA provided its analysis of the essential use elements and detailed additional information that would assist in its analysis, including whether epinephrine provides a greater therapeutic benefit than similar adrenergic bronchodilators and whether OTC marketing of epinephrine MDIs provides an important public health benefit. After concluding that the essential use status should be eliminated, FDA considered what the appropriate effective date for removing the essential use designation, including (i) whether adequate time exists to provide patient education for users of OTC epinephrine MDIs, particularly those who do not consult doctors, pharmacists, and other health care professionals, and (ii) whether adequate production capacity and supplies are

available to meet the new, presumably increased, demand for the therapeutic alternatives once OTC epinephrine MDIs are no longer sold.

In the Proposed Rule, FDA suggests that December 31, 2010 is an appropriate effective date for removing the essential use status for epinephrine MDIs and thus requiring their removal from the market by that date. In establishing the Effective Date, FDA articulated numerous concerns and requested comments on whether December 31, 2011 or 2012 might be more appropriate effective dates. FDA's concerns included:

- New avenues of communication would need to be opened to reach all OTC epinephrine MDI users since many purchasers do not interact with a health care provider to purchase this OTC medication.
- Many OTC epinephrine MDI users may need to be provided information to help them select a physician.
- Some OTC epinephrine MDI users who face economic barriers to appropriate health care may need even more time to find and avail themselves of free or low-cost health care and prescription drug programs.

In proposing the Effective Date, FDA said that it was assuming that a non-ODS inhaled epinephrine product will not be on the market. However, Armstrong believes, based upon current development timelines that the availability of an OTC non-ODS epinephrine product is on the horizon. Indeed, Armstrong intends to submit an NDA under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") for such a product to the FDA by October 2009, which the Company believes, depending upon FDA approval, will enable it to have a marketed non-ODS OTC product on the market by the beginning of 2011. Armstrong further believes that it will be able to transition patients from the current CFC-containing OTC epinephrine formulation to the non-ODS OTC product by the end of 2011.

FDA should consider the potential availability of a non-ODS OTC product in its rule making. Specifically, FDA's concerns regarding the impact of removing the only OTC emergency asthma medication from the market on the public health should not be disregarded. The likely health impact of this decision will be significant. Further, the goal of communicating with the OTC patient population, by 2010 is not realistic and creates a serious risk of marketplace disruption and confusion which could be harmful to the large population of asthma sufferers for whom an OTC MDI is an essential rescue drug. Finally, in light of the potential availability of a non-ODS OTC product by 2011, a delay in the effective date would eliminate the expensive and cumbersome task of transitioning patients off of the OTC medication to prescription medications for such a limited time.

## **II. OTC EPINEPHRINE MDI PROVIDES AN IMPORTANT HEALTH BENEFIT TO APPROXIMATELY TWO MILLION ASTHMATICS**

Consumers have relied upon Epinephrine MDI for more than 40 years. FDA approved the first OTC epinephrine MDI in 1956 (NDA 10-374) for the temporary relief of asthma

symptoms. As such, this product has a long history of safe and effective use in the United States. Epinephrine MDI is indicated for the temporary relief of occasional symptoms of mild asthma: wheezing, tightness of chest, and shortness of breath. It is the only asthma inhaler available OTC. As the FDA articulated in the preamble to its proposed rule, Epinephrine MDI is not the drug of choice for physicians treating asthma patients. Nevertheless, this product serves a vital and irreplaceable role in serving this patient population. Indeed, it is a product relied upon by as many as 1.7 to 2.3 million people with asthma. Many of these patients rely on the product as their sole asthma medication or to back up their prescription medications during an acute asthmatic episode. Removing this OTC product from the market, without a comparable OTC alternative may result in many of these asthmatic patients having no access to treatment.<sup>1</sup>

Further, FDA has recently confirmed the need for OTC bronchodilator drug products. Specifically, in July 2005, FDA stated that “FDA continues to believe that people with mild asthma can properly use OTC bronchodilator drug products to self-treat occasional wheezing, shortness of breath, and tightness of chest after their asthma has been diagnosed by a physician.”<sup>2</sup> FDA also estimated that between 9 percent and 14 percent of all people with asthma who use OTC epinephrine MDIs do so because of barriers to health care, including barriers to accessing appropriate medical care to obtain a necessary prescription and barriers to paying for the increased costs associated with the prescription.<sup>3</sup> In other words, between 150,000 and 320,000 people with asthma who use OTC epinephrine MDIs do so because of barriers to health care. In its preamble, FDA acknowledges that at least “a small population of people with asthma who face barriers to health care may derive some benefit from having epinephrine MDIs available OTC.”<sup>4</sup> By removing OTC epinephrine MDIs from the market without an available OTC alternative, FDA would be removing this health benefit from this critical patient population.

### **III. REMOVING OTC EPINEPHRINE FROM THE MARKET WITHOUT AN OTC NON-ODS EPINEPHRINE ALTERNATIVE WILL CREATE UNNECESSARY TRANSITION EXPENSES AND HARM TO PATIENTS.**

In the preamble to the proposed rule, FDA concludes that a transition away from OTC epinephrine MDIs may be more difficult than a transition in which patients are merely switching

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<sup>1</sup> See, e.g., statement of Dr. Mary E. Tinetti, NDAC/PADAC meeting minutes, 183 (“in the ideal world, we are talking about this less effective medication versus clearly more effective care, but it is still not clear to me with all the discussion that we have had today, and I think because we really don’t have the information, is are we in some cases talking about a less than effective medication versus no treatment . . .”).

<sup>2</sup> 70 Fed. Reg. 40237, 40242 (July 13, 2005).

<sup>3</sup> *Id.* at 53722.

<sup>4</sup> 72 Fed. Reg. 53722.

from one prescription to another.<sup>5</sup> The transition will require patients to see a physician and obtain new medications for their asthma. These transition requirements are further complicated because, as FDA acknowledged, for at least some patients who use OTC epinephrine MDIs there are barriers to health care. With a transition from one OTC product to another OTC product, patients will not face the harsh consequences of not having access to the OTC product as an emergency relief measure that they might endure during the transition from an OTC product to a prescription product, with no OTC product available.

Indeed, some members on the NDAC/PADAC panel questioned the idea that removing a product that 1.7 to 2.3 million people used from the market would result in these patients obtaining better healthcare. As one panel member said, “[y]ou are making the assumption that by withdrawing [the OTC medication], people will get optimal health care, and I just haven’t seen evidence.”<sup>6</sup> Similarly, another panel member was concerned that “we may risk taking a step backward in the present level of health care for asthma in this effort to move forward with better control and better management of asthma.”<sup>7</sup> Further, FDA estimates that removing OTC epinephrine MDIs from the market, without an OTC alternative, will result in considerable increases in emergency room visits and hospitalizations to treat asthmatic episodes. Specifically, FDA estimates that removing OTC epinephrine MDIs from the market would result in 40,000 to 120,000 more hospitalizations for asthma annually, and up to 440,000 more asthma-related emergency department visits each year.<sup>8</sup> These estimates do not capture the decreased quality of life of OTC epinephrine MDI users, lost productivity, or the cost of alternative therapies. These costs can be minimized by delaying the effective date of the Proposed Rule for one year which would provide sufficient opportunity to transition patients to a non-ODS OTC epinephrine MDI.

#### **IV. ARMSTRONG IS DEVELOPING A NON-ODS EPINEPHRINE MDI FOR MARKET BY 2011.**

Developing an alternative to a CFC propellant is a challenging endeavor. Initially, a manufacturer must develop a formula that delivers the appropriate amount of medication to the appropriate part of the lung. Once the manufacturer has developed this formulation, then the formulation must undergo clinical testing to demonstrate that the product is equivalent to the existing CFC product. This new formulation must obtain FDA approval prior to marketing.

On March 27, 2007, Armstrong met with FDA for the purpose of discussing Armstrong’s proposed non-ODS epinephrine MDI and the proposed clinical development plan. Based upon feedback from the FDA during this meeting, Armstrong anticipates being able to successfully develop and receive approval for its non-ODS epinephrine MDI by the beginning of 2011. Based on the long marketing history of epinephrine MDI as a CFC propelled product, Armstrong

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<sup>5</sup> *Id.* at 53725.

<sup>6</sup> Dr. David A. Schoenfeld, NDAC/PADAC Meeting Minutes, page 190.

<sup>7</sup> Dr. Erik R. Swenson, NDAC/PADAC Meeting Minutes, page 194.

<sup>8</sup> 72 Fed. Reg. 53728.

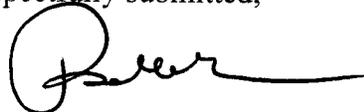
intends to seek approval for its non-ODS formulation through FDA's abbreviated approval pathway under Section 505(b)(2) of the FDCA. FDA has agreed that this is an acceptable approach to seeking approval of non-ODS epinephrine MDI. By the end of 2008, Armstrong anticipates that it will have successfully completed necessary work to establish an optimal formulation for its non-ODS epinephrine MDI. From November 2008 through March 2009, Armstrong intends to complete pilot stability tests, validate analytical methods, and establish all relevant SOPs. Armstrong anticipates filing an investigational new drug application ("IND") no later than the end of March 2009. Armstrong will then spend the duration of 2009 manufacturing and testing stability batches, validating its manufacturing process, characterizing the product, and initiating and completing clinical trials. Armstrong anticipates that this clinical development program will provide sufficient data to support the submission of an approvable 505(b)(2) application for non-ODS epinephrine MDI by October 2009. If the FDA is able to review and act upon our NDA within FDA's performance review goals for 2009, Armstrong anticipates receiving FDA approval to market its OTC non-ODS epinephrine MDI by August 2010. Therefore, by the beginning of 2011, Armstrong anticipates being able to manufacture and distribute a non-ODS OTC epinephrine MDI.

**V. THE PROPOSED RULE EFFECTIVE DATE SHOULD BE DECEMBER 31, 2011.**

OTC epinephrine MDI provides an important public health benefit and prematurely removing an OTC product from the market and attempting to switch patients to prescription medications will have significant costs and health consequences for asthmatics. FDA has acknowledged that as many as 1.7 to 2.3 million people with asthma rely upon OTC epinephrine MDI. Having an alternative, non-ODS epinephrine MDI available before December 31, 2010 is not realistic and creates a serious risk of marketplace disruption and confusion which could be harmful to the large population of asthma sufferers for whom an OTC MDI is an essential rescue drug. Based upon past experience in transferring patients from CFC inhalers and HFA inhalers, FDA and patient advocates have consistently stressed the importance of a measured and orderly market transition which shifts patients to HFA inhalers. This orderly transition will only be possible if FDA revises its proposed rule to provide for an effective date of October 31, 2011.

In order to minimize negative and costly public health effects from removing OTC epinephrine MDIs from the market, any final rule FDA issues removing the "essential use" status should have a December 31, 2011 effective date.

Respectfully submitted,



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of LATHAM & WATKINS LLP