TEVA Respiratory

November 15, 2013 5907 13 NOV 15 A11 :28

VIA HAND DELIVERY

Dockets Management Branch, HFA-305
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition Requesting That FDA Establish a Policy Requiring All Rescue Inhalers to Include an Integrated Dose Counter and Refrain From Approving Any New Rescue Inhaler (Brand or Generic) Without an Integrated Dose Counter

Dear Sir or Madam:

On behalf of Teva Pharmaceutical Industries Ltd., Teva Respiratory, LLC ("Teva") hereby submits this Citizen Petition pursuant to 21 C.F.R. § 10.30 and section 505 of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355. Teva manufactures and distributes ProAir® HFA (albuterol sulfate) inhalation aerosol ("ProAir® HFA"), which is indicated for the treatment or prevention of bronchospasm in patients ages 4 and older with reversible obstructive airway disease as well as for the prevention of exercise-induced bronchospasm in patients ages 4 and older.[1]

Asthma is a chronic inflammatory disorder of the large and small airways that causes recurrent episodes of wheezing, breathlessness, tightening of the chest and coughing. While symptoms range from minor to severe and vary from person to person, acute asthma attacks can be life-threatening. When acute asthma attacks occur, patients depend upon medications commonly referred to as "rescue" or quick-relief inhalers to rapidly reverse bronchospasm and restore regular breathing. These metered-dose inhalers ("MDIs") most commonly contain a short-acting beta agonist ("SABA") such as albuterol or levalbuterol.

[1] Teva Pharmaceutical Industries Ltd. is a global pharmaceutical company specializing in the development, production, and marketing of generic, proprietary, and branded pharmaceuticals, and active pharmaceutical ingredients. The company is among the top 20 pharmaceutical companies and is the leading generic pharmaceutical company in the world. Teva Respiratory, LLC, is the branded respiratory products subsidiary of Teva Pharmaceutical Industries Ltd. and is responsible for the clinical development, registration, and marketing of Teva's branded respiratory products in North America, including ProAir® HFA.

FDA-2013-P-1505

2013-9768

CP

Teva Pharmaceuticals
41 Moores Road, P.O. Box 4011 | Frazer, PA 19355 | Tel. 610.344.0200 | Fax 610.344.0065 | www.tevapharm-na.com

Due to the potential life-saving nature of SABAs during an asthma attack, it is important that patients know how much medication remains in their rescue inhalers at any given time. Accurate counting of SABA usage is also crucial for the proper assessment of asthma control by health care practitioners.[2] Underreporting of SABA use could lead to under-prescribing of controller medicines and increase the likelihood of impairment (*e.g.* inability to exercise, missing work or school) and/or risk (*e.g.* exacerbations leading to resource utilization, morbidity and mortality). Indeed, a recent study found that the incidence of respiratory-related emergency room visits was estimated to be significantly lower among patients using MDIs with integrated dose counters compared with patients using MDIs without dose counters.[3]

Because integrated dose counters provide an accurate and practical method of determining the remaining number of effective doses in rescue inhalers, Teva believes they are critical to the safety and effectiveness of such products. Teva thus believes that integrated dose counting mechanisms should be required on all SABA inhalers. The attainment of integrated dose counters on all SABA inhalers, however, will require a clarification of the Food and Drug Administration's ("FDA's") current policies regarding dose counters. Although FDA has encouraged developers of new MDI drug products to include dose counters in their products since 2003 and recently indicated that some generic MDI products would be *required* to include dose counters, the Agency has not, to date, announced a requirement for dose counters for *all* new and currently marketed MDI drug products. Based upon the new data discussed below, Teva believes that the lack of dose counters for all SABA inhalers poses a significant and unnecessary risk to the public health. Accordingly, Teva respectfully requests that FDA strengthen and clarify its existing policies with respect to dose counters.

I. Actions Requested

For the reasons that follow, Teva respectfully requests that the Commissioner:

1. Refrain from approving any new rescue inhalers (brand or generic) unless those inhalers contain a dose counter; and

2. Implement a plan to transition already approved rescue inhalers without a dose counter to versions that incorporate an integrated dose counter.

---

[2] National Heart, Lung, and Blood Institute. Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma. 2007 ("The frequency of SABA use can be clinically useful as a barometer of disease activity, because increasing use of SABA has been associated with increased risk for death or near death in patients who have asthma") (Exhibit 1), *available at*, http://www.nhlbi.nih.gov/guidelines/asthma/07_sec3_comp4.pdf.

[3] Data on File.

II. Statement of Grounds

A. Factual Background

1. The Burden of Asthma

Asthma is a potentially deadly, disruptive and expensive disease affecting one out of every 12 Americans, or approximately 25 million people in the United States. According to the Centers for Disease Control and Prevention ("CDC"), the number of people with asthma increased nearly three percent (2.9%) each year between 2001 and 2010, reaching 25 million in 2010, more than 7 million of whom are children.[4] Nearly half of the 25 million people with asthma experience asthma attacks, and the disease resulted in 3,447 deaths in 2007, or more than 9 deaths per day.[5]

Medical care for asthma is costly for individuals and the overall United States healthcare system. Asthma accounts for more than 15 million physician office and hospital outpatient department visits and nearly 2 million emergency room visits per year.[6] Nearly half of all asthma hospitalizations are for children, making asthma the third-ranking cause of hospitalization in children.[7] Asthma is also linked to lost days of work for adults and lost school days for children. In 2008, more than half (59%) of children and one-third (33%) of adults who had an asthma attack missed school or work because of their condition.[8]

2. The Role of SABAs in Treating Asthma

Despite improvements in asthma diagnosis and the availability of comprehensive clinical practice guidelines for managing the disease, morbidity and mortality rates remain high and continue to rise. Avoiding triggers such as pets, tobacco smoke and environmental allergens is an important first step in asthma management. However, adherence to these lifestyle changes is poor because many patients find them too difficult to initiate or maintain. Instead, most patients rely on therapeutic interventions to control and treat asthma symptoms when they occur.

Expert panel guidelines on the diagnosis and management of asthma recognize the importance of rescue medications in addition to controller medications for all patients with

---

[4] Centers for Disease Control and Prevention. National Surveillance of Asthma: United States, 2001-2010. November 2012, *available at* http://www.cdc.gov/nchs/data/series/sr_03/sr03_035.pdf.

[5] Centers for Disease Control and Prevention, *Vital Signs*, May 2011, *available at* http://www.cdc.gov/vitalsigns/asthma/ .

[6] United States Environmental Protection Agency, *Asthma Facts,* EPA-402-F-04-019, March 2013, *available at* http://www.epa.gov/asthma/pdfs/asthma_fact_sheet_en.pdf .

[7] Asthma and Allergy Foundation of America. Asthma Facts and Figures – Age, *available at* http://www.aafa.org/display.cfm?id=9&sub=42#_ftnref20.

[8] Centers for Disease Control and Prevention, *Vital Signs*, May 2011.

persistent asthma.[9] Therapies for asthma are categorized into two general classes: long-term control medications used to achieve and maintain control of persistent asthma and quick-relief or rescue medications used to treat acute symptoms and exacerbations. Most asthma medications are delivered as orally-inhaled products in order to achieve local effects in the lungs while minimizing systemic adverse effects. Rescue medicines are delivered primarily through MDIs.

As noted previously, rescue medications typically contain SABAs, such as albuterol or levalbuterol. They are often referred to by patients and healthcare providers as "rescue" medications due to their use at the onset of an asthma "attack." These medications act quickly to reverse the airway constriction patients experience during an asthma attack by relaxing airway smooth muscle resulting in reopening of the airways for more normal breathing within five to ten minutes of administration.[10] Thus, the patient may be "rescued" from a potentially life-threatening airway constriction. Given the potential life-saving implications of rescue therapies like albuterol, the value of knowing whether medication is available is immeasurable. Furthermore, in national guidelines SABA use is considered a key determinant of control, and accurate reporting of SABA use to a patient's health care provider thus is important to the management of asthma control.

3. Dose Counters Are Important to Patient Safety Because They Help Ensure Proper Dosing

There are four approved rescue inhaler products currently available in the United States: ProAir® HFA, Ventolin® HFA (albuterol sulfate) inhalation aerosol, Proventil® HFA (albuterol sulfate) inhalation aerosol, and Xopenex® HFA (levalbuterol tartrate) inhalation aerosol. To date, only ProAir® HFA and Ventolin® HFA have transitioned to versions with integrated dose counters. Teva also understands that an NDA for Primatene® HFA has been filed and would consider this product, if approved, to be within the scope of this petition.

MDIs only deliver a limited number of effective medication doses as listed in the prescribing information for each product. For example, the maximum number of effective doses listed in ProAir® HFA's approved labeling is 200. However, even after the labeled number of doses is expelled, the MDI will continue to emit doses. In one study, MDIs with HFA propellant had 52% more actuations than the labeled dose number.[11] ProAir® HFA itself is filled with enough suspension for approximately 270 actuations. However, these additional actuations may

---

[9] National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, National Heart, Lung, and Blood Institute (US), NIH Publication .: 07-4051, 2007, *available at* http://www.ncbi.nlm.nih.gov/books/NBK7232/.

[10] The Mayo Clinic. "Asthma Medications: Know Your Options," *available at* http://www.mayoclinic.com/health/asthma-medications/AP00008.

[11] Rubin BK, Durotoye L. How do patients determine that their metered-dose inhaler is empty? Chest 2004; 126: 1134-1137 (Exhibit 2).

not deliver a reliable dose of medication. Therefore, accurately assessing the number of administered doses in an MDI is critically important, especially for rescue medications like albuterol MDIs. It should be noted that unlike a dose counter, a dose indicator does not provide an exact count of the number of doses possibly leading to a patient overestimating remaining doses. Dose indicators, therefore, may have less value than dose counters.

Failure of efficacy of an asthma treatment can be attributed to a number of factors, including patient non-adherence to therapy. Non-adherence is often volitional, but it also can be inadvertent, such as when prescribed medications are taken improperly. Specifically, patients may assume they are receiving the prescribed dosage of their inhaled asthma medication when instead they are actuating an inhaler that contains little or no medication (because the inhaler was used beyond the labeled number of actuations).

An integrated dose counter is a reliable way to determine how many doses remain in an inhaler, with advantages over, for example, recording every actuation in a diary (which patients are rarely instructed to do,[12] and are almost certainly unable to do for the entire life of an inhaler). Inhalers with integrated dose counters, such as ProAir® HFA and Ventolin® HFA, are designed to help patients, as well as caregivers, easily and accurately keep track of the number of doses remaining in the inhaler. Dose counters thus reduce the risk of utilizing an inhaler that no longer contains an adequate dose of the medication when asthma symptoms occur.[13]

The significant value of an integrated dose counter has been verified in the published literature. Research indicates that asthma patients may overestimate the remaining amount of asthma medication in inhalers without dose counters. Methods patients use to estimate how much medicine remains, such as weight of the canister, force of the spray or taste of the actuation, are ineffective. Many patients do not know how many actuations are recommended for their inhaler[14] and may overestimate the remaining medication by up to 40 doses.[15] In one study, researchers found that up to 40 percent of patients believe they are taking their asthma medication when they are activating an empty or nearly empty inhaler.[16]

---

[12] Sander N. Dose counting and the use of pressurized metered-dose inhalers; running on empty. *Annals of Allergy, Asthma & Immunology*. Volume 97, July 2006;34-38 (Exhibit 3).

[13] National Center for Biotechnology Information. Metered Dose Inhalers: a Need for Dose Counters. 2005, *available at* http://www.ncbi.nlm.nih.gov/pubmed/15691246.

[14] Ogren RA, Baldwin JL, Simon RA. How patients determine when to replace their metered-dose inhalers. Ann Allergy Asthma Immunol 1995; 75:485-489 (Exhibit 4).

[15] Holt S, Holt A, Weatherall M, Masoli M, Beasley R. Metered dose inhalers: a need for dose counters. Respirology 2005; 10: 105-106 (Exhibit 5).

[16] Conner and Buck. Journal of Asthma. Improving Asthma Management; The Case for Mandatory Inclusion of Dose Counters on All Rescue Bronchodiliators. June 2013 (Exhibit 6).

New research confirms the value of integrated dose counters with respect to the safety and effectiveness of MDIs. An analysis of a United Healthcare Retrospective Claims Database found that patients using a rescue inhaler with a dose counter had fewer respiratory-related ER visits compared to patients in the non-dose counter cohort.[17] After adjusting for baseline confounders, the incidence rate of respiratory-related ER visits in the dose-counter cohort was estimated to be 51% lower for asthma patients (rate ratio=0.49; 95% CI=0.41, 0.59, significant with p-value <0.001). This was an intent-to-treat, retrospective cohort study to estimate and compare incidence of respiratory-related emergency room visits, average daily SABA usage, and exacerbation rate between patients prescribed an Albuterol Inhaler with dose-counter (Ventolin®) against patients prescribed an Albuterol inhaler without dose-counter (ProAir® or Proventil®). Data were obtained from the Clinformatics™ Data Mart and included patients aged 4-64 years with a diagnosis of asthma, COPD, or exercise induced bronchospasm (EIB) and a first prescription for Ventolin®, ProAir®, or Proventil® between January 2010 and September 2011 (n=93,980).

The above data indicate the importance of dose counters in reducing the rate of respiratory-related ER visits, perhaps by providing an "early warning" of exacerbation that can lead to earlier treatment with corticosteroids and other therapies. A separate analysis using Truven Health Analytics MarketScan Databases was performed to mitigate against brand differences confounding the interpretation of the above results from Clinformatics™ Data Mart. In this analysis, patients who had received Ventolin® HFA without a dose-counter (pre-2006) were compared to those who then received Ventolin® HFA with a dose-counter (post-2006). The results showed that patients who received the dose-counter were less likely to have an asthma-related ER visit (rate ratio= 0.51). This effect size is similar to that found in the results presented above verifying the lack of brand effect, although the result was not statistically significant (95% CI = 0.24, 1.12; p-value = 0.095) given the small cohort size (dose counter group n=287; control group n=320).[18]

In another study involving 12 academic emergency rooms ("ERs") across seven states, researchers found that among 479 ER patients with acute asthma, 20 percent reported that they ran out of their rescue medication before presenting in the emergency room. Of that 20 percent, 72 percent reported that their inhaler ran out of medication within the previous two days.[19] Furthermore, in a 2013 Asthma and Allergy Foundation of America ("AAFA") Asthma ID Survey (n=590), nearly half of respondents (48.2 percent) have previously found their rescue inhalers to be empty when needed, and of those who ran out, one in 10 (10.4 percent) had to go to the ER and two in 10 (20 percent) had to go without treatment.[20]

---

[17] Data on File.

[18] Data on File.

[19] Brenner BE, Leber M, Kohn S, Camargo CA Jr. ED visits for acute asthma by patients who recently ran out of their β-agonist inhaler [abstract]. *Ann Emerg Med* 1997; 30:427 (Exhibit 7).

[20] Teva and AAFA data on file.

A telephone survey conducted by the Asthma and Allergy Network, Mother of Asthmatics in the pre-dose counter era found that within 342 families with asthma, 87 (25%) reported finding their rescue inhaler empty during an asthma attack and of these 87 patients, seven patients (8%) needed to call 911 due to the lack of medication at the onset of the attack.[21] Had these inhalers had dose counters, patients would have had information available to them to know whether medicine was available to treat their acute symptoms, thereby potentially avoiding the need for emergency services and its associated costs.

In addition to providing information about medication availability, dose counters can provide an important signal to patients and physicians that a patient is using too much of his or her rescue inhaler, which may indicate uncontrolled asthma. This knowledge allows parents, physicians and patients to work together to improve overall management and achieve control of the condition. Dose counters may also instill patient confidence in the inhaler and relieve patient anxiety during asthma attacks.

In a study in which patients received actuations from a rescue inhaler with an integrated dose counter for all 200 actuations of the inhaler, 92 percent agreed that the integration of a dose counter helped prevent them from running out of medication. This is especially significant because in this same study, 62 percent of patients reported feeling anxiety about not knowing the quantity of medication remaining in their inhaler.[22]

4. FDA's Guidance Documents Regarding Dose Counters Recognize Their Critical Role in Promoting the Safe and Effective Use of MDIs

The FDA has recognized the importance of dose counters for the safe and effective use of MDI drug products. In a final guidance document entitled *Integration of Dose-Counting Mechanisms into MDI Drug Products* (hereinafter referred to as the *MDI Dose Counter Guidance*), FDA specifically encouraged pharmaceutical companies to include dose counting mechanisms in all MDI drug products developed after 2003.[23]

According to FDA, a "major disadvantage" of MDIs without integrated dose counters is that they "offer no practical way for patients to track the remaining number of doses or amount of medication."[24] The Agency recognized that this creates a "potentially dangerous" safety risk,

---

[21] Sander N. Dose counting and the use of pressurized metered-dose inhalers; running on empty. *Annals of Allergy, Asthma & Immunology*. Volume 97, July 2006;34-38 (Exhibit 3).

[22] Wasserman, R. Real-world assessment of a metered-dose inhaler with integrated dose counter. Allergy and Asthma Proceedings. Nov-Dec 2006. Vol 26, No.6 p486-492 (Exhibit 8).

[23] *Integration of Dose-Counting Mechanisms into MDI Drug Products* (March 2003), at 2 (hereinafter referred to as the *MDI Dose Counter Guidance*) (Exhibit 9).

[24] *Id.*

particularly for life-saving drug products like albuterol sulfate MDIs that are intended to treat acute airway diseases, because the patient might use the MDI "beyond the recommended number of doses and risk not receiving the correct drug dose."[25] The addition of a dose counter is intended to eliminate this risk by informing patients of the precise number of effective, labeled doses remaining in the canister and thereby preventing patients from "using the product beyond the recommendations provided in the labeling for the product."[26] The *MDI Dose Counter Guidance* thus strongly recommends that "manufacturers with metered-dose inhalers under development for oral inhalation integrate a dose-counting device into the development of their MDI drug product."[27]

Likewise, in April 2013, FDA released a draft bioequivalence guidance on albuterol sulfate MDIs, which was revised in June 2013 (hereinafter referred to as "*Draft Albuterol BE Guidance*"). Among other things, the *Draft Albuterol BE Guidance* explicitly states that a proposed generic albuterol MDI "should have a dose counter if the [RLD] has a dose counter."[28] In addition, the draft guidance provides that "[i]n vitro and in-use studies should be conducted to support the functionality, accuracy and robustness of the proposed dose counter of the [proposed generic] product." Although the *Draft Albuterol BE Guidance* has not yet been finalized, it underscores the importance from both a safety and effectiveness perspective of incorporating integrated dose counters into MDI drug products, particularly rescue inhalers like ProAir® HFA.

B. FDA Should Update and Strengthen Its Policies Regarding Dose Counters in Rescue Inhaler Drug Products

Although FDA deserves praise for recognizing the importance of integrated dose counters to the safety and effectiveness of MDI drug products more than ten years ago, its current policies nevertheless need to be strengthened to better safeguard the public health. The data and information discussed above clearly demonstrates that integrated dose counters promote the safe and effective use of SABA inhalers and reduce the morbidity and costs associated with asthma exacerbations. FDA's current policies, however, are not sufficient to prevent the approval or continued marketing of SABA drug products *without* integrated dose counters.

First, despite the fact that the *MDI Dose Counter Guidance* was finalized more than ten years ago, there are still approved SABA inhalers that do not have integrated dose counters. In fact, of the four SABA inhalers currently available in the United States, only ProAir® HFA and Ventolin® HFA (albuterol sulfate) inhalation aerosol are approved and marketed with integrated dose counters. Given the important public health concerns discussed above, Teva believes FDA

---

[25] *Id.*

[26] *Id.*

[27] *Id.* at 3.

[28] *Draft Guidance on Albuterol Sulfate*, at 7 (June 2013) (hereinafter referred to as the *Draft Albuterol BE Guidance)* (Exhibit 10).

should strengthen its existing policies to require *all* approved SABA inhalers to transition to formulations that incorporate an integrated dose counter.

Second, FDA's existing policies likely do not go far enough because they may permit the approval of generic MDI drug products without dose counters, to the detriment of the public health. Although the *Draft Albuterol BE Guidance* states that a proposed generic albuterol MDI "should have a dose counter if the [RLD] has a dose counter," the draft guidance does not require a dose counter if the RLD does not have one. This is problematic because FDA has identified some albuterol and levalbuterol products as RLDs in the *Orange Book* even though they lack integrated dose counters. This means that generic SABA MDIs without dose counters could be approved by FDA contrary to the policy announced in FDA's *MDI Dose Counter Guidance* by relying upon the RLDs that likewise lack dose counters. As discussed further below, due to important clinical safety and efficacy concerns, Teva believes this is contrary to the public interest and could place patients using any such generic product unnecessarily at risk. Teva thus strongly recommends that FDA amend its current policies to require all proposed generic SABA MDIs to include an integrated dose counter regardless of the proposed RLD and, if necessary, to require proposed generic SABA MDIs to rely only upon RLDs that incorporate an integrated dose counter.

The approval of generic SABA products without dose counters could lead to widespread confusion and negatively impact the public health. In today's market, approximately 85 percent of prescriptions filled for rescue inhalers include a dose counter.[29] Currently, it is common practice for healthcare providers to write "albuterol HFA" or "albuterol MDI" and not use the brand name of the product on their prescriptions. Consequently, if a generic rescue inhaler were approved without a dose counter because it relied upon an RLD that lacked a dose counter, there is real potential for it to be substituted for brands or generics that offer a dose counter. This could interrupt the continuum of care patients and caregivers have come to expect and rely on when it comes to their rescue MDIs and undermine the effective management of patients' asthma symptoms leading to poor outcomes.

The scientific body of research has clearly established that quick relief or "rescue" inhalers with dose counters can improve asthma management and potentially decrease asthma-related morbidity and mortality, and improve patients' quality of life. If a generic rescue inhaler were to come to market without a dose counter, many of the 85 percent of patients currently using a rescue inhaler with a dose counter could experience an interruption in their continuity of care. Instead of receiving the dose counter they have come to trust to measure their medication, these patients could receive a generic option without a dose counter. This could cause significant confusion and unnecessary anxiety for these patients and caregivers about whether or not there is enough medication in the event of an asthma attack. It also could result in adverse health consequences.

[29] IMS NPA Audit, February 2013.

Teva believes that approval of generic SABAs without dose counters could negatively impact patient safety and would reverse the advancements in drug delivery innovation that the FDA has fostered by requesting that manufacturers of these inhalers include dose counters. FDA thus should take all appropriate steps to update and strengthen its policies with respect to dose counters.

C. Conclusion

For the foregoing reasons, FDA should grant the relief requested in this Petition.

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31(a).

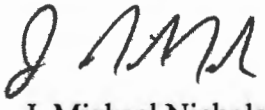
IV. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

V. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: September 30, 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organization: my employer, Teva. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



J. Michael Nicholas, Ph.D.
Vice President, Global Specialty Medicines

cc: Kathleen Uhl, M.D., Acting Director
Office of Generic Drugs

Badrul Chowdhury, M.D., Ph.D., Director
Division of Pulmonary, Allergy and Rheumatology Products