July 12, 2013

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 Refrain From Approving Any Abbreviated New Drug Application or 505(b)(2) Application Referencing ProAir® HFA (albuterol sulfate) Inhalation Aerosol Until Certain Conditions Are Met

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 sections 505(b)(2), 505(j) and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. §§ 355(b)(2), 355(j), and 355(q). 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]

I. Actions Requested

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

1. Refrain from approving any abbreviated new drug application ("ANDA") or 505(b)(2) application that relies upon ProAir® HFA as the listed drug unless:

[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.

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

- the actuator for the proposed generic or 505(b)(2) product incorporates a dose counter;

- the dose counter in the proposed generic product functions in the same manner and has the same labeled instructions for use as ProAir® HFA's dose counter; and

- the ANDA or 505(b)(2) application contains *in vitro* and clinical data establishing the functionality, accuracy and robustness of the proposed dose counter; and

2. Refrain from approving any ANDA or 505(b)(2) application that relies upon ProAir® HFA as the listed drug unless the applicant successfully mitigates the risk of a canister/actuator mismatch.[2]

II. Statement of Grounds

A. Factual Background

1. The Risks 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 25.7 million in 2010, more than 7 million of whom are children.[3] 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.[4]

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.[5] Nearly half of all asthma hospitalizations are for children, making asthma the third-ranking cause of

[2] For the purposes of this citizen petition, the term "generic" product refers to a product that is submitted and/or approved under section 505(j) of the FFDCA, 21 U.S.C. § 355(j), and the terms "505(b)(2) product" or "505(b)(2) version" refer to a product that is submitted and/or approved under section 505(b)(2) of the FFDCA, *id.* § 355(b)(2).

[3] 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.

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

[5] 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 .

hospitalization in children.[6] 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.[7]

Expert panel guidelines on the diagnosis and management of asthma recognize the importance of rescue and maintenance medications for all patients.[8] 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 lung. Rescue medicines are delivered primarily through a metered-dose inhaler ("MDI").

Rescue medications are typically short-acting beta agonists 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 the smooth bronchial muscles and reopening the airways for more normal breathing within five to 10 minutes of administration. Thus, the patient is literally "rescued" from a potentially life-threatening airway constriction.

2. The Value of Dose Counters and FDA's MDI Dose Counter Guidances

Poor asthma control can be attributed to a number of factors, including patient non-adherence to therapy. Non-adherence is often volitional, such as when patients do not follow prescribed dosing regimens, 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 is clogged (because not properly cleaned) or that contains little or no medication (because used beyond the labeled number of actuations). 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 actuate propellant that contains little or no medication. Therefore, accurately assessing the number of administered doses in an MDI is critically important, especially for rescue medications like albuterol MDIs.

---

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

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

[8] 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/.

The reason that all MDI's will continue to deliver propellant even after the drug has been depleted is due to the design of the metered-dose valve. With current valve designs, it is not possible for an MDI to cease delivering doses even when those doses contain little or no drug due to depletion of the drug in the canister. In fact, MDIs may continue to deliver a spray for up to twice the nominal number of recommended doses. In one study, MDIs with HFA propellant had 52% more actuations than the labeled dose number.[9] Drug delivery per actuation becomes increasingly inconsistent and unpredictable after the recommended number of actuations has been exceeded, with the amount of active drug eventually becoming negligible, a phenomenon known as "tail-off."[10] Tail-off is particularly problematic when the medication delivered by the MDI is formulated as a suspension rather than a solution. All albuterol sulfate MDIs currently available, including ProAir® HFA, are formulated as suspensions.

Given the above characteristics of MDIs, the value of an integrated dose counter is significant. Research indicates that many asthma patients do not know how many actuations are recommended for their inhaler[11] and overestimate the remaining medication in inhalers without dose counters *by up to 40 doses.*[12] 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. 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 MDI."[13] In another study involving 12 academic emergency rooms ("ERs") across seven states, researchers found that among 479 ER patients with acute asthma, 20 percent ran out of their rescue inhaler before presenting in the emergency room. Of that 20 percent, 72 percent ran out of their inhaler within the previous two days.[14] 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, a compelling one in 10 (10.4 percent) had to go to the ER and two in 10 (20 percent) had to go without treatment.[15]

---

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

[10] Schultz RK. *Drug* delivery characteristics of metered-dose inhalers. J Allergy Clin Immunol 1995; 96:284-287; Hess DR. Aerosol delivery devices in the treatment of asthma. Respir Care 2008; 53:699-723.

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

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

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

[14] 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.

[15] Teva and AAFA data on file.

The FDA sought to address this problem by releasing a final guidance document in March 2003 entitled *Integration of Dose-Counting Mechanisms into MDI Drug Products* (hereinafter referred to as the *MDI Dose Counter Guidance*). The *MDI Dose Counter Guidance* encourages pharmaceutical companies to include dose counting mechanisms in subsequently developed MDI drug products.[16] 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."[17] The Agency recognized that this creates a "potentially dangerous" safety risk, 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."[18] 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."[19] 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."[20]

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."[21] 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.

3. ProAir® HFA with an Integrated Dose Counter

ProAir® HFA is an inhaled drug product 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 brochospasm in patients ages 4 and older. It consists of a

---

[16] *Integration of Dose-Counting Mechanisms into MDI Drug Products* (March 2003), at 2 (hereinafter referred to as the *MDI Dose Counter Guidance*) (Exhibit 1).

[17] *Id.*

[18] *Id.*

[19] *Id.*

[20] *Id.* at 3.

[21] *Draft Guidance on Albuterol Sulfate*, at 7 (June 2013) (hereinafter referred to as the *Draft Albuterol BE Guidance)* (Exhibit 2).

pressurized aluminum canister containing 8.5 grams of an albuterol sulfate formulation packaged together with a red plastic actuator with an integrated dose counter and white dust cap. Each canister provides 200 actuations, and each actuation delivers 120 mcg of albuterol sulfate from the canister valve and 108 mcg of albuterol sulfate from the actuator mouthpiece.

ProAir® HFA initially was approved on October 29, 2004 via New Drug Application ("NDA") No. 21-457. The original version, like most other MDIs available at the time, did not include an integrated dose counter. A supplemental new drug application ("sNDA") was approved by the FDA on March 7, 2012, whereby the FDA approved a new version of ProAir® HFA that incorporates a dose counter, consistent with the requirements delineated in FDA's *MDI Dose Counter Guidance.*

Teva's sNDA seeking approval of the integrated dose counter contained the results of a prospective, open-label, multi-center study assessing the performance, handling characteristics and safety of the ProAir® HFA inhaler with integrated dose counter (hereinafter referred to as the "patient handling study"). The patient handling study, which enrolled 306 male and female subjects aged 4 years and older with a diagnosis of asthma or chronic obstructive pulmonary disease ("COPD"), demonstrated that the new version of ProAir® HFA is robust and functions reliably and accurately in the clinical setting. The study also showed that ProAir® HFA with an integrated dose counter was well tolerated and that the inclusion of the integrated dose counter did not alter the safety profile known to be associated with the prior version without a dose counter.

The integrated dose counter in the new product is visible through a window on the back of the actuator and includes a numerical display of the doses remaining in the canister. When the patient receives the inhaler, a black dot is displayed in the viewing window until the product has been primed three times, at which point the number 200 is displayed. Each time a spray is released, the dose counter counts down. When the dose counter reaches 20, the color of the numbers changes from black to red to indicate that the patient should seek a refill from his or her pharmacist or physician. When the dose counter reaches 0, the background changes to solid red, indicating that the maximum number of actuations has been reached and that the ProAir® HFA inhaler should be discarded.

Consistent with FDA's *MDI Dose Counter Guidance,* the redesigned actuator with an integrated dose counter is intended to allow patients to "reliably track the numbers of actuations used from [an] individual inhaler."[22] This, in turn, should provide convenience and safety benefits by preventing patients from discarding the inhaler prematurely or, more importantly, from using the inhaler beyond the maximum number of actuations recommended in the labeling (i.e., 200). Indeed, the ProAir ®HFA labeling specifically cautions patients that they should "not keep using the inhaler after 200 sprays even though the canister may not be completely empty."[23]

---

[22] *MDI Dose Counter Guidance,* at 2.

[23] ProAir HFA Package Insert, §17.9 (Rev. 3/12) (Exhibit 3).

This is a particularly important safety issue for a rescue inhaler such as ProAir ®HFA because, as noted above, the proper, labeled dose of albuterol sulfate cannot be assured beyond 200 actuations.

Although the new version of ProAir® HFA was approved on March 7, 2012, Teva did not begin commercially distributing it until December 2012 because of manufacturing limitations. Trade notifications and physician promotional materials were distributed in December 2012 and January 2013, respectively. Accordingly, as of December 2012, the prior version of ProAir® HFA without an integrated dose counter has been voluntarily withdrawn from sale by Teva. *See* 21 C.F.R. § 314.161(a).

4. Perrigo's Pending ANDA Referencing ProAir® HFA

On May 18, 2012, Perrigo Company ("Perrigo") submitted an ANDA to FDA seeking approval of a generic albuterol sulfate HFA inhalation aerosol that identifies ProAir® HFA as the reference listed drug ("RLD"). The ANDA contains certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV certifications") to several of the patents listed in the *Orange Book* for ProAir® HFA. On information and belief, Perrigo's ANDA was accepted for filing by FDA on or about July 18, 2012, and Perrigo thereafter provided a Paragraph IV notice to Teva and others pursuant to 21 U.S.C. § 355(j)(2)(B).

After receiving the Paragraph IV notice, Teva filed a patent infringement suit against Perrigo on September 5, 2012 in the United States District Court for the District of Delaware. Because the lawsuit was filed within forty-five (45) days of Teva's receipt of the Paragraph IV notice, Perrigo's ANDA is subject to the FFDCA's 30-month stay provision and, in the absence of a prior settlement or favorable court decision, will not be eligible for approval before January 2015, at the earliest. *See* 21 U.S.C. § 355(j)(5)(B)(iii). Teva recently received a new Paragraph IV notice letter from Perrigo, which it currently is assessing. If Teva brings a patent infringement suit within 45 days of receiving the new Paragraph IV notice letter, Perrigo's ANDA will be subject to an additional 30-month stay. Teva is not aware of any other pending ANDAs or 505(b)(2) applications that rely upon ProAir® HFA as the listed drug.

B. FDA Should Refrain from Approving Any ANDA or 505(b)(2) Application That References ProAir® HFA Unless the Proposed Product Incorporates an Integrated Dose Counter Whose Functionality, Reliability and Accuracy Have Been Established in Appropriate *In Vitro* and Clinical Investigations

Because ProAir® HFA incorporates an integrated dose counter to assist patients in tracking the remaining number of effective doses in each individual inhaler, FDA should require proposed generic or 505(b)(2) versions of ProAir® HFA likewise to include an integrated dose counter. Otherwise, the proposed product would have differences in design, operating principles and labeling that introduce new or heightened risks compared to ProAir® HFA. In particular, such a product would entail a higher risk that patients would use it beyond the maximum number of actuations recommended in the labeling and thereby receive an ineffective dose of albuterol

sulfate or no dose at all. If this occurred during an episode of acute bronchospasm, the consequences could be life-threatening.

Moreover, the functionality, reliability and accuracy of any dose counter in a proposed generic or 505(b)(2) albuterol MDI product must be established prior to approval in real world settings. In particular, FDA should require ANDA and 505(b)(2) applicants to submit data from both *in vitro* studies and clinical investigations in accordance with the recommendations in the *MDI Dose Counter Guidance* and/or the *Draft Albuterol BE Guidance,* as applicable, to support approval of the dose counters in their proposed generic or 505(b)(2) products. The bases for these requests are set forth in detail below.

1. Proposed Generic Versions of ProAir® HFA Submitted Via ANDAs Must Include an Integrated Dose Counter That Functions in the Same Manner and Has the Same Labeled Instructions for Use as ProAir® HFA's Dose Counter

For the reasons described below, FDA should refuse to approve any ANDA for a generic version of ProAir® HFA that fails to include a dose counter that functions in the same manner as ProAir® HFA's dose counter and has the same labeled instructions for use. Deviations and differences that might be acceptable in a 505(b)(2) application (discussed in section II.B.2 below) are not acceptable in, and should preclude the approval of, an ANDA. This requirement is consistent with FDA's recently issued *Draft Albuterol BE Guidance,* which provides that a proposed generic product "should have a dose counter if the [RLD] has a dose counter."[24]

a. Failure to Include A Dose Counter Would Result In Impermissible Design Differences

In order to obtain approval of an ANDA, an applicant must demonstrate, *inter alia*, that its proposed generic product is the "same" as a RLD in terms of active ingredient, strength, dosage form, route of administration, labeling, conditions of use, and bioequivalence. 21 U.S.C. § 355(j)(2). For combination products such as the MDI drug products at issue here, FDA's policy is to evaluate both the drug *and* device components to ensure that the proposed generic product is the "same" as the RLD.

For example, in the context of drugs that incorporate an autoinjector, FDA has explained that the Agency "must evaluate the auto-injector constituent part of the combination product for which ANDA approval is sought to ensure that its performance characteristics and critical design attributes will result in a product that will perform *the same as* the RLD."[25] Although FDA does not require all design features of the device constituent to be exactly the same as the RLD, design differences will be permitted only if "they do not significantly alter product performance or

---

[24] *Draft Albuterol BE Guidance*, at 7.

[25] FDA Response to King Petition, Docket Nos. FDA-2009-P-0040 and FDA-2007-P-0128, at 6 (July 29, 2009) (emphasis added) (hereinafter referred to as "King Petition Response").

operating principles and do not result in impermissible differences in labeling."[26] In sum, FDA's review process for ANDAs for combination products "considers whether any difference in materials, design, or operating principles introduces a new risk. . . . This review considers the RLD as a whole and its individual constituent parts."[27]

In this case, the failure to include an integrated dose counter in a proposed generic product would involve significant differences in design, operating principles and labeling that introduce new or heightened risks compared to ProAir® HFA. Indeed, FDA has recognized that, for MDIs without an integrated dose counter, there is "no practical way for patients to track the remaining numbers of doses or amount of medication."[28] Accordingly, patients using such MDIs "must guess how many doses are left in the MDIs and have two practical options: (1) throw away an MDI that may still contain acceptable metered-doses or (2) *use a product when it may be beyond the recommended number of doses and risk not receiving the correct drug dose*."[29] Although the former option is merely wasteful, the latter option is, according to FDA, "potentially dangerous."[30]

Indeed, FDA has long recognized that using an albuterol inhaler past the labeled number of actuations is a significant "safety issue."[31] For this reason, the approved labeling for ProAir® HFA warns that "[t]he labeled amount of medication in each actuation cannot be assured after the counter displays 0, even though the canister is not completely empty and will continue to operate."[32] Moreover, FDA has acknowledged that "the consequences of not receiving an acceptable metered dose are *more clinically important*" for albuterol sulfate MDIs than for other types of drug products because albuterol sulfate MDIs are delivered directly to the lungs and, in some circumstances, are life-saving.[33] The addition of an accurate dose counter to an individual MDI unit helps to minimize this significant safety risk by "allow[ing] the patient to reliably track the numbers of actuations used from that individual inhaler (*i.e.*, to identify when the label claim

---

[26] *Id.*

[27] *Id.*

[28] *MDI Dose Counter Guidance,* at 2.

[29] *Id.* (emphasis added).

[30] *Id.*

[31] *See* Medical Review for Ventolin HFA with Dose Counter (NDA 20-983/S009), at 3 (Apr. 4, 2005) ("Undercounting by the dose counter could lead to a patient using the inhaler past the labeled number of actuations, which is a safety issue.") (Exhibit 4) *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/020983Orig1s009Approv.pdf.

[32] Pro Air HFA Package Insert, §16 (Exhibit 3).

[33] *MDI Dose Counter Guidance,* at 2 (emphasis added); *see also* 70 Fed. Reg. 17168, 17169 (Apr. 4, 2005) ("Albuterol MDIs can be considered lifesaving for some patients at certain times.").

number of actuations has been reached)."[34] This, in turn, "would prevent the patient from . . . using the product beyond the recommendations provided in the labeling for that product."[35]

Consequently, the failure to incorporate a dose counter into a proposed generic version of ProAir® HFA could raise a significant safety risk that is not associated with the newly-approved version of ProAir® HFA, i.e., the heightened risk of using the product beyond the maximum number of actuations recommended in the labeling, which could result in suboptimal therapy during life-threatening attacks of bronchospasm. In light of this heightened risk, a generic product without an integrated dose counter would not be expected to have the same clinical effect and safety profile as ProAir® HFA when administered to patients under the conditions specified in the labeling. As such, it cannot be approved via an ANDA.

FDA's recently issued *Draft Albuterol BE Guidance* appears to recognize these risks and thus explicitly instructs that a proposed generic product "should have a dose counter if the [RLD] has a dose counter."[36] Since ProAir® HFA now includes an integrated dose counter, FDA should confirm that it will follow this recently announced policy in this case and refuse to approve any ANDA for a generic version of ProAir® HFA that does not incorporate a dose counter.

b. Failure to Include A Dose Counter Would Result In Impermissible Labeling Differences

A proposed generic product that fails to incorporate a dose counter could not be approved via the ANDA route for the additional reason that it would require "impermissible differences in labeling" between ProAir® HFA and the proposed generic. Under the FFDCA, FDA generally cannot approve an ANDA for a generic drug unless it has the same labeling as the RLD.[37] This requirement helps to ensure that an approved generic drug product is as safe and effective as the RLD. Although there are some exceptions to this general rule, they are narrow. In particular, a generic drug can have different labeling from the RLD if: (a) the ANDA is submitted pursuant to a suitability petition; (b) labeling is omitted because it is protected by exclusivity or a listed patent; or (c) minor labeling changes reflect permissible differences between the ANDA and its RLD (*e.g.*, different inactive ingredients, container-closure systems, shape or color).[38] Labeling changes that introduce new or increased risks or that otherwise render the proposed generic less

---

[34] *MDI Dose Counter Guidance,* at 2.

[35] *Id.*

[36] *Draft Albuterol BE Guidance*, at 7.

[37] 21 U.S.C. § 355(j)(4)(G); 21 C.F.R. §314.127(a)(7)

[38] 21 U.S.C. §§ 355(j)(2)(A)(v), (j)(2)(A)(viii), (j)(4)(G); 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7); *see also* FDA Response to Xyzal Petition, Docket No. FDA-2010-P-0545, pp. 7-8 (Feb. 24, 2011).

safe or effective than the RLD, however, are not permitted and will result in refusal to approve the ANDA.[39]

In this case, the approved labeling for ProAir® HFA provides detailed instructions to patients on how to monitor usage with the dose counter, when to contact a physician or pharmacist to seek a refill (*i.e.*, when the dose counter reaches 20), and when to discard the inhaler (*i.e.*, when the dose counter reaches 0).[40] The ProAir ®HFA labeling also cautions patients that they should "not keep using the inhaler after 200 sprays even though the canister may not be completely empty" because "[y]ou cannot be sure you will receive any medicine after using 200 sprays."[41]

If a proposed generic product does not incorporate a dose counter, this would necessitate different labeling instructions regarding how patients should monitor usage and discard the inhaler upon reaching the maximum number of actuations. Rather than simply referring to the number of actuations left as indicated by the dose counter, the labeling for a proposed generic would need to either remain silent as to how patients should monitor usage or recommend that patients "carefully and consistently track[] each actuation in writing and subtract[] this total from the labeled number of actuations."[42] As FDA recognizes, however, these options "offer no *practical* way for patients to track the remaining numbers of doses or amount of medication" in an albuterol MDI.[43] In other words, they leave patients with little recourse but to "guess how many doses are left in their MDIs."[44] Because this, in turn, creates a significant danger that patients will use the generic product beyond the recommended number of doses and thereby receive a sub-therapeutic dose or no dose at all, the different labeling instructions necessitated by the absence of a dose counter would render the proposed generic product less safe than ProAir® HFA. Consequently, such labeling differences are "impermissible" and preclude use of the ANDA approval pathway for an albuterol MDI without a dose counter.

c. Any Proposed Generic Dose Counter Must Function In the Same Manner and Have the Same Instructions for Use As the ProAir® HFA Dose Counter

Because the failure to incorporate a dose counter into a proposed generic product would result in impermissible labeling and design differences that would render the proposed generic product less safe or effective than ProAir® HFA, FDA cannot approve an ANDA for a generic

---

[39] 21 C.F.R. §314.127(a)(7); *see also* King Petition Response, at 7.

[40] Pro Air HFA Package Insert, §§ 17.3, 17.9 (Exhibit 3).

[41] Pro Air HFA Package Insert, §17.9 (Exhibit 3).

[42] *MDI Dose Counter Guidance,* at 2.

[43] *Id.* (emphasis added).

[44] *Id.*

albuterol sulfate MDI that fails to incorporate a dose counter. FDA thus should confirm that it will follow the recommendations in its *Draft Albuterol BE Guidance* instructing that if a RLD has an integrated dose counter, the proposed generic albuterol sulfate MDI also must incorporate a dose counter.

Although the *Draft Albuterol BE Guidance* proposes that a generic product must have a dose counter if the RLD does, it does not discuss dose counter comparability from a functional and labeling perspective. In this case, to avoid confusion upon generic substitution, FDA should require the dose counter used in a proposed generic product to function in the same manner and have the same labeled instructions for use as the dose counter in ProAir® HFA. In particular, the proposed generic dose counter should (1) display the remaining number of doses numerically, (2) count backwards from 200 to zero, and (3) be designed so that the numbers cannot be reset.

If the proposed generic dose counter operates in a different manner than the ProAir® HFA dose counter (*e.g.*, non-numerical color coding), it will require corresponding changes to the labeling that, as discussed above, would be impermissible in the context of an ANDA. Indeed, patients who are switched between ProAir® HFA and a generic with a materially different dose counter may become confused and either discard an inhaler that is still functional or use an inhaler past its recommended number of doses. As discussed above, this could raise serious safety issues. Accordingly, FDA should not approve a generic version of ProAir® HFA unless the proposed dose counters functions in the same manner and has the same labeled instructions for use as ProAir® HFA's dose counter.

2. All 505(b)(2) Applications For Proposed 505(b)(2) Versions of ProAir® HFA Likewise Must Include an Integrated Dose Counter

FDA also should require any 505(b)(2) application that relies upon ProAir® HFA as the listed drug to include an integrated dose counter. First, if the proposed product is a duplicate of ProAir® HFA, it should be submitted as an ANDA rather than a 505(b)(2) application and, for the reasons discussed above, have the same design and labeling as ProAir® HFA, including a dose counter and associated labeling. *See* 21 C.F.R. § 314.101(d)(9).

Second, for the reasons discussed above, a 505(b)(2) product without a dose counter would entail a heightened possibility of using the product beyond the maximum number of actuations recommended in the labeling. It is well-established, however, that FDA should not use section 505(b)(2) to approve a drug product that is less safe or effective than the listed drug. For example, in its draft guidance on 505(b)(2) applications, FDA noted that "a 505(b)(2) application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards of bioequivalence."[45] The same rule should be applied here to prevent the use of the 505(b)(2) process to approve 505(b)(2) versions of ProAir® HFA that fail to include an integrated dose counter.

---

[45] *Draft Guidance on Applications Covered by Section 505(b)(2)*, at 6 (Oct. 1999).

Third, requiring a new albuterol inhaler to incorporate a dose counter is consistent with FDA's *MDI Dose Counter Guidance*, which specifically 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."[46] Although the guidance is not binding on either FDA or industry, it is based upon significant safety concerns, as discussed above. FDA thus should follow the policy announced in its *MDI Dose Counter Guidance* and determine that, because ProAir® HFA now incorporates a dose counter, any 505(b)(2) product that fails to incorporate a dose counter will be considered to have an unacceptable benefit/risk profile and, on that basis, will not be approved.[47]

Finally, although a product approved via section 505(b)(2) would not necessarily need to have the *same* dose counter or identical labeling as ProAir® HFA, if it incorporates a dose counter that is materially different than ProAir® HFA's dose counter, FDA should decline to code the new product as therapeutically equivalent to ProAir® HFA. FDA considers two drug products to be "therapeutically equivalent" only if they are pharmaceutically equivalent, bioequivalent, and "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."[48] Where product differences, such as packaging configurations or labeling differences, have therapeutic implications, FDA will not consider two products to be therapeutically equivalent *even if they are pharmaceutically equivalent and bioequivalent.*[49] In this case, the failure of a 505(b)(2) product to incorporate a dose counter that functions in the same manner and has the same labeled instructions for use as ProAir® HFA's dose counter could have a meaningful impact on the safety and/or effectiveness of a proposed 505(b)(2) product. In light of these risks, a 505(b)(2) product would not be expected to have the same clinical effect and safety profile as ProAir® HFA when administered to patients under the conditions specified in the labeling, and FDA thus should decline to code it as "therapeutically equivalent" in the *Orange Book.*

3. *In Vitro* and Clinical Testing Requirements for Integrated Dose Counters

In addition, to support approval of a proposed generic or 505(b)(2) version of ProAir® HFA that incorporates a dose counter, FDA should require the ANDA or 505(b)(2) applicant to submit data establishing the dose counter's functionality, reliability and accuracy in real world settings. A proposed dose counter "should be engineered to reliably track actuations and should be designed to be as close to 100 percent reliable as possible."[50] To the extent some low

---

[46] *MDI Dose Counter Guidance,* at 3.

[47] The Agency has recognized that "a drug's benefit/risk profile can change due to the availability of alternative products." FDA Response to Endo Petition, Docket No. FDA-2012-P-0895, p. 4 (May 10, 2013).

[48] *Approved Drug Products with Therapeutic Equivalence Evaluations*, Preface at vii (33rd ed. 2013) (hereinafter referred to as the "Orange Book").

[49] Orange Book Preface at xv; *see also* King Petition Response, at 4, 7.

[50] *MDI Dose Counter Guidance,* at 3.

frequency of error is unavoidable, "the device should be designed specifically to avoid undercounting," since this could result in the potentially dangerous situation in which a patient believes she has medication remaining in her MDI when she does not.[51]

Consistent with FDA's *MDI Dose Counter Guidance* and *Draft Albuterol BE Guidance,* FDA should require both ANDA and 505(b)(2) applicants to establish the reliability of their dose counters though both *in vitro* testing and clinical studies. Permitting such applicants to rely upon the data submitted to support approval of the ProAir® HFA dose counter would be inappropriate because each dose counter will have different design features that could affect reliability. ANDA and 505(b)(2) applicants thus should be required to address reliability issues specific to their particular dose counters, including ergonomics, ruggedness, and accuracy in clinical settings, through appropriate *in vitro* and clinical testing. Indeed, the *Draft Albuterol BE Guidance* recognizes 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."[52]

Such testing should include "a reasonable representation of special populations likely to use the drug," such as patients with asthma, as well as pediatric and geriatric patients.[53] Moreover, the clinical testing should include a sufficient number of subjects to reach statistically significant conclusions regarding dose counter performance, including the potential for the dose counter to undercount the number of actuations, which could raise safety concerns. For example, to support approval of the dose counter for Ventolin® HFA, FDA required the sponsor to conduct two clinical trials involving 268 patients and 237 patients, respectively.[54] Patients were eligible only if they had been diagnosed with asthma or COPD, and FDA required the studies to include both pediatric and geriatric patients, since both subpopulations use Ventolin® HFA. FDA required similar, robust clinical testing to support approval of the dose counter for ProAir® HFA and should apply the same *in vitro* and clinical testing requirements to proposed generic and 505(b)(2) products that incorporate a dose counter.

C. FDA Should Refrain from Approving Any ANDA or 505(b)(2) Application That References ProAir® HFA Unless the Applicant Successfully Mitigates the Risk of a Canister/Actuator Mismatch

An important feature of ProAir® HFA is that the canister and actuator work like a lock and key; that is, they are designed and approved for use only with each other. Because the design and performance characteristics of these components differ among MDI products, using the ProAir® HFA canister with a different actuator, or *vice versa*, could impact drug

---

[51] *Id.*

[52] *Draft Albuterol BE Guidance,* at 7.

[53] *MDI Dose Counter Guidance,* at 4.

[54] *See* Medical Review for Ventolin HFA with Dose Counter (NDA 20-983/S009), at 8 (Exhibit 4).

administration and thus the safety and effectiveness of the product. For this reason, the FDA-approved labeling for ProAir® HFA cautions:

> Never attach a canister of medication from any other inhaler to the PROAIR HFA actuator and never attach the PROAIR HFA canister to an actuator from any other inhaler. [55]

This language recognizes that the safety and clinical efficacy of an MDI such as ProAir® HFA is directly related to the design and performance characteristics of, *inter alia*, the actuator and canister valve.[56] Possible risks of mismatch include incomplete drug delivery, administration errors and failures, overdosages, and damage to the canister or actuator mouthpiece that could adversely impact future use of the component even when subsequently paired with the correct canister or actuator mouthpiece.

The new version of ProAir® HFA entails an additional mismatch risk related to the integrated dose counter. Because the dose counter is permanently housed in the actuator itself, if a patient pairs the wrong canister with the wrong actuator, the patient will, of necessity, rely upon the wrong dose counter, which may not accurately reflect the number of doses remaining in the canister. This may cause the patient to discard the inhaler prematurely or use the inhaler beyond the maximum number of actuations recommended in the labeling (i.e., 200). As discussed above, this raises a safety issue, since the proper, labeled dose of albuterol sulfate cannot be assured beyond 200 actuations. The FDA-approved labeling for the new version of ProAir® HFA seeks to minimize this risk with the following recommendation:

> If the patient has more than one PROAIR HFA inhaler, the patient should wash each one separately to prevent attaching the wrong canister to the wrong plastic actuator. In this way, the patient can be sure to always know the correct number of remaining doses.[57]

This labeling language was approved by FDA on March 7, 2012 as part of the supplemental NDA for the integrated dose counter.

---

[55] ProAir® HFA Package Insert, §2 (Exhibit 3). The approved labeling also contains a similar warning in section 16:

> The red actuator supplied with PROAIR HFA Inhalation Aerosol should not be used with the canister from any other inhalation aerosol products. The PROAIR HFA Inhalation Aerosol canister should not be used with the actuator from any other inhalation aerosol products.

The patient labeling repeats this warning in bold lettering. *Id.* at §17.8.

[56] *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing and Controls Documentation* [Draft Guidance], at 25 (Oct. 1998) ("*MDI/DPI CMC Draft Guidance*").

[57] Pro Air HFA Package Insert, §2.3 (Exhibit 3).

Although the above-described mismatch risks have been successfully mitigated for ProAir® HFA through labeling alone, this strategy is not likely to be sufficient for subsequently approved generic or 505(b)(2) products. Indeed, these mismatch risks likely will be significantly exacerbated by the approval of generic or 505(b)(2) versions of ProAir® HFA. First, the generic drug substitution laws in many states will require patients using ProAir® HFA to switch automatically to a generic albuterol sulfate inhaler, often without any input or training. Likewise, patients who receive prescriptions for a nonspecific "albuterol" inhaler could receive a 505(b)(2) product even if they historically have used ProAir® HFA. If such patients subsequently attempt to use the generic or 505(b)(2) product's canister with their existing ProAir® HFA actuator mouthpiece, or *vice versa*, the mismatch could lead to adverse consequences, such as incomplete delivery of the drug, component damage or inaccurate dose counts.

While this risk already exists for the subset of patients prescribed more than one MDI drug product, it will become much more widespread and potentially dangerous with the introduction of generic and 505(b)(2) albuterol sulfate MDIs. This is because health care providers recommend that patients keep more than one so-called rescue inhaler to safeguard against product failure or to ensure convenient access to at least one such inhaler at all times.[58] For example, a patient might keep one inhaler in her purse, a second in her gym bag, a third at her home, and a fourth at her place of work. A pharmacy could therefore automatically dispense a generic version of ProAir® HFA to a patient who will continue to possess and use one or more branded versions. Moreover, if several generic or 505(b)(2) versions are approved, bronchospasm patients may receive several different albuterol MDI products over the course of their treatment and thus may be required to correctly match multiple different canisters and actuator mouthpieces at the same time. There is no guarantee that, without training, patients will be able to accomplish this on a consistent basis.

FDA has recognized this confusion risk in a related context. Specifically, in a 2010 letter responding to a supplemental new drug application for ProAir® HFA, FDA reported its awareness of "cases of medication error where ProAir was confused with another drug due to similar colors of the actuator."[59] If patients have difficulty distinguishing between ProAir® HFA and other inhalers, they likely would experience similar or greater difficulty distinguishing between ProAir® HFA's components and those of generic or 505(b)(2) versions.

Second, ProAir® HFA's FDA-approved labeling directs patients to wash the actuator mouthpiece at least weekly and, after washing, allow the actuator mouthpiece "to air-dry

---

[58] *E.g.*, Mayo Clinic Staff, *Asthma in Adults: Creating an Asthma Action Plan* (Jan. 12, 2011), http://www.mayoclinic.com/health/asthma/AS00002/method=print ("Always carry a rescue inhaler with you as well. Keep a second one at home as backup."); Alice! Health Promotion at Columbia University, *Asthma Attack Without an Inhaler – What to Do?* (May 9, 2008), http://goaskalice.columbia.edu/asthma-attack-without-inhaler-mdash-what-do ("One thing to consider is carrying an additional reliever inhaler so that . . . you will have a backup. Many people with asthma have extra inhalers that they keep in different places . . . .").

[59] Letter from Angela H. Robinson, CDER, to Axel Perlwitz, Teva, at 2 (Nov. 19, 2010) (Exhibit 5).

completely, such as overnight."[60] Patients also must separate the canister from the actuator during the recommended washing and drying process.[61] Thus, using ProAir® HFA consistent with the FDA-approved labeling results in frequent and extended periods of time during which the canister must be separated from the actuator mouthpiece. Although the ProAir® HFA labeling also instructs patients with more than one inhaler to wash each inhaler separately, not all patients can be expected to routinely follow these instructions. Patients who wash multiple inhalers at the same time may inadvertently pair the wrong canister with the wrong actuator at the end of the cleaning process. Moreover, this risk of mismatching could arise on a weekly basis (*i.e.*, each time the patient reassembles her albuterol sulfate inhalers after allowing the actuator mouthpieces to dry). The risk is greater still in patients who use other inhaled medications as well as albuterol sulfate.[62]

In order to mitigate the risk of mismatched components and ensure that a proposed generic or 505(b)(2) product is safe and effective, FDA should require ANDA and 505(b)(2) applicants to incorporate one or more design features into the components of their proposed products that dissuade or prevent their actual or attempted use with either the ProAir® HFA canister or its actuator mouthpiece. The Agency recognizes that "[a]ddressing use-related hazards by modifying the device design is generally more effective than revising the labeling or training. Labeling might not be accessible when needed, and training depends on memory, which might not be complete or accurate."[63] For this reason, FDA recommends that applicants pursue a combination of strategies (i.e., design, labeling and training)[64] and that the first priority should be modifying the device design to remove a hazard or reduce its burden.[65]

At a minimum, FDA should require that a competitor's actuator mouthpiece have an appearance that clearly distinguishes it from ProAir® HFA's. As FDA has received reports of "cases of medication error where ProAir was confused with another drug due to similar colors of the actuator,"[66] FDA should require that a generic or 505(b)(2) product's actuator mouthpiece

---

[60] ProAir® HFA Package Insert, §17.8 (Exhibit 3).

[61] ProAir® HFA Package Insert, §17.8 (Exhibit 3)

[62] *See* Letter from Angela H. Robinson, CDER, to Axel Perlwitz, Teva, at 2 ("We have received cases of medication error where ProAir was confused with another drug due to similar colors of the actuator.").

[63] *FDA Draft Guidance on Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, at 14 (June 22, 2011) ("Draft Human Factors Guidance"); *see also FDA Guidance on Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, at 28 (July 18, 2000) ("Final Human Factors Guidance") ("because [instructions, labeling, and training] rely on the user to consistently use the device as directed, these approaches are less effective than modifications to the design of the user interface.").

[64] Final Human Factors Guidance, at 28 ("Use-related hazards often require a combination of mitigation and control strategies.").

[65] Draft Human Factors Guidance, at 22.

[66] *See* Letter from Angela H. Robinson, CDER, to Axel Perlwitz, Teva, at 2 ("Similar actuator colors represent a potential risk for confusion between various medications.").

have a color scheme that is clearly distinguishable from any previously approved inhaler's color scheme, including ProAir® HFA's. To help further distinguish between different albuterol MDI products, FDA should also require that the actuator bear a contrasting label or embossed element that enables patients to easily match the generic or 505(b)(2) actuator with the correct canister formulation.

For example, requiring a proprietary branded name for all proposed generic and 505(b)(2) products would provide additional protection against mismatches by making it easier for users to distinguish between different products and product components.[67] In 2009, the Agency issued a Complete Response letter to King Pharmaceuticals refusing to approve its 505(b)(2) application for a 6 mg sumatriptan succinate autoinjector without a proprietary name.[68] The Agency noted that, for a variety of reasons, "inadvertent substitution may lead to failed use of the product during a migraine attack, or to a safety risk to the patient."[69] Based upon these concerns, FDA concluded that "a proprietary name is necessary to assure safe and effective use of your product, and prevent medication errors . . .."[70]

In this case, inadvertent mismatches between the components of different albuterol MDIs also could lead to a variety treatment failures and safety risks due to, *inter alia*, incomplete drug delivery, administration errors and failures, overdosages, and damage to the canister or actuator mouthpiece. Accordingly, just as it did with King's sumatriptan product, FDA should determine that a proprietary name is necessary to assure safe and effective use of any generic or 505(b)(2) albuterol MDI and prevent medication errors.

D. Conclusion

For the foregoing reasons, no ANDA or 505(b)(2) application that references ProAir® HFA as the listed drug should be approved unless and until the conditions set forth above have been satisfied.

---

[67] Letter from Angela H. Robinson, CDER, to Axel Perlwitz, Teva, at 2 ("We recommend increasing the visibility of the embossed proprietary name . . . on the ProAir actuator by changing its color for increased contrast. If this is not feasible, we recommend adding a sufficiently contrasted label to the actuator that clearly identifies it as the "ProAir HFA Actuator.").

[68] *See* Complete Response Letter from Eric Bastings (May 15, 2009), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022377Orig1s000OtherActionLtrs.pdf.

[69] *Id.*

[70] *Id.*

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 dates: July 18, 2012. 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,

/SML

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

KKB | KLEINFELD KAPLAN & BECKER, LLP

1140 NINETEENTH STREET, N.W.
WASHINGTON, D.C. 20036-6601

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

301-827-6860