DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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APR 10 2014

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41 Moores Road
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Re: Docket No. FDA-2013-P-1505

Dear Dr. Nicholas:

This letter responds to your citizen petition received on November 15, 2013 (Petition), requesting that the Food and Drug Administration (FDA or the Agency) (1) refrain from approving any new rescue inhaler (generally a metered-dose inhaler (MDI) containing a short-acting beta agonist (SABA), such as albuterol or levalbuterol), brand or generic,[1] unless the inhaler contains 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.

On December 9, 2013, we responded to a dose counter-related petition (ProAir Petition) submitted by Teva Respiratory, LLC (Teva), requesting that FDA refrain from approving any ANDA or 505(b)(2) NDA that relies on ProAir HFA as the reference listed drug (RLD) unless the actuator for the proposed generic or 505(b)(2) product incorporates a dose counter and meets certain other conditions set forth in that petition.[2] We responded to the ProAir Petition by stating that generally we would expect a proposed generic albuterol sulfate MDI to have a dose counter if the RLD has a dose counter.[3]

We have carefully considered the issues raised in your Petition and comments submitted to the docket.[4] For the reasons stated below, your Petition is granted in part and denied in part.

[1] For purposes of this response, the term *brand* refers to a new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)). The terms *generic* and *generic product* refer to a new drug product for which approval is sought in an abbreviated new drug application (ANDA) submitted under section 505(j) of the FD&C Act.
[2] Docket No. FDA-2013-P-0850.
[3] Response to ProAir Petition at 7.
[4] We have also received another citizen petition submitted by Teva raising issues related to dose counters and rescue inhalers (FDA-2014-P-0404), and we intend to respond separately.

I. BACKGROUND

A. Rescue Inhalers

A rescue inhaler commonly contains a SABA, such as albuterol or levalbuterol, and is used to treat or prevent bronchospasm in patients with reversible obstructive airway disease. Rescue inhalers provide quick relief in treating acute asthma symptoms and exacerbations. Currently, there are four FDA approved rescue inhaler products -- ProAir HFA (albuterol sulfate) Inhalation Aerosol, Ventolin HFA (albuterol sulfate) Inhalation Aerosol, Proventil HFA (albuterol sulfate) Inhalation Aerosol, and Xopenex HFA (levalbuterol sulfate) Inhalation Aerosol. Both ProAir HFA and Ventolin HFA have integrated dose counters.

Ventolin HFA (albuterol sulfate HFA inhalation aerosol) is a microcrystalline suspension of albuterol sulfate in propellant HFA-134a in a pressurized metered-dose aerosol unit for oral inhalation. It contains no other excipients. GlaxoSmithKline submitted NDA 20-983 in 1998 and FDA approved NDA 20-983 on April 19, 2001. FDA approved the product with a dose-counter on April 19, 2005.

ProAir HFA is a suspension of racemic albuterol sulfate in hydrofluoroalkane (HFA-134a) and ethanol in a pressurized canister, coupled with a standard press-and-breathe actuator, providing 90 micrograms of albuterol sulfate per actuation. Teva submitted NDA 21-457 for ProAir HFA as a 505(b)(2) application referencing Proventil HFA Inhalation Aerosol. FDA approved NDA 21-457 on October 29, 2004. At the time of initial approval, ProAir HFA was indicated for treating or preventing bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older. ProAir HFA was subsequently approved for preventing exercise-induced bronchospasm,[5] and the patient population for both indications was later expanded to include patients 4 to 11 years of age.[6] The version of ProAir HFA approved in the original NDA and each of these supplements did not include an integrated dose counter.

Teva's supplement to add a dose-counting mechanism to the approved ProAir HFA product was submitted as a prior approval manufacturing supplement on November 8, 2011, and approved on March 7, 2012.[7] To support the addition of the dose counting mechanism to the plastic actuator, the supplement included in vitro data and the results of an in-use study.[8]

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[5] Supplement S-003, approved on February 3, 2006.
[6] Supplement S-013, approved on September 16, 2008.
[7] Supplement S-026.
[8] Study ABM-AS-307.

B. Statutory and Regulatory Standards

1. 505(b)(1) NDAs

Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(b)(1)) sets forth the requirements for submitting an NDA. The application must contain the following information:

- full reports of investigations to show that the drug is safe and effective
- a list of articles used as components of the drug
- a statement of the drug's composition
- a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug
- samples of the drug as necessary
- proposed labeling for the drug
- pediatric assessments[9]

FDA approves an NDA if we find that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling.

2. Abbreviated Pathways - 505(b)(2) NDAs and ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created the statutory provisions governing 505(b)(2) NDAs and ANDAs. Section 505(b)(2) of the FD&C Act provides that an application may be submitted under section 505(b)(1) for a drug for which the safety and effectiveness investigations relied upon by the applicant to support approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.[10] In contrast to an ANDA (other than a petitioned ANDA), a 505(b)(2) application is not required to be therapeutically equivalent to or have the *same* labeling as the listed drug it references.

To obtain ANDA approval, an ANDA applicant is not required to submit clinical studies to establish the safety and effectiveness of the proposed generic drug product. Instead, an ANDA applicant relies on the Agency's previous finding that the RLD is safe and

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[9] See also 21 CFR 314.50 for a description of the NDA approval requirements.
[10] See 21 CFR 314.54(a); see also the draft guidance for industry *Applications Covered by Section 505(b)(2)*) (October 1999), available at http://www.fda.gov/downloads/drugs/guidances/ucm079345.pdf.

effective.[11] To rely on FDA's previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that the proposed generic drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act).[12] In addition, other than a petitioned ANDA, an ANDA must contain sufficient information to show that the proposed generic drug product has the same active ingredient(s), previously approved conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD (section 505(j)(2)(A) and (j)(4) of the FD&C Act). The Agency must approve the ANDA unless, among other things, the ANDA applicant has provided insufficient evidence of the foregoing, or if "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity" (section 505(j)(4) of the FD&C Act). An ANDA is generally not required to be the same as the listed drug it references in certain respects (e.g., it can differ in inactive ingredients or container closure system). However, if differences in these aspects of the products are significant enough that they require clinical studies to demonstrate the safety or effectiveness of the product or necessitate such significant labeling differences that the labeling no longer satisfies *the same* labeling requirement within the meaning of the FD&C Act and implementing regulations, FDA will deny an ANDA approval.

Drug products that meet the approval requirements under section 505(j) of the FD&C Act generally will be considered by FDA to be *therapeutically equivalent* to the RLD.[13] FDA classifies as therapeutically equivalent the following: the products (1) are approved as safe and effective; (2) are pharmaceutical equivalents in that they (a) contain identical amounts of the same active ingredient(s) in the same route of administration and dosage form; and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) are bioequivalent; (4) are manufactured in compliance with current good

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[11] A *reference listed drug* (or RLD) is defined in 21 CFR 314.3 as "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." Section 314.3 further defines a *listed drug* as "a new drug product that has an effective approval under section 505(c) of the [FD&C Act] for safety and effectiveness or under section 505(j) of the [FD&C Act], which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the [FD&C Act], and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as "the Orange Book."

[12] Under the FD&C Act, "[a] drug shall be considered to be bioequivalent to a listed drug if . . . the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses" (see section 505(j)(8)(B)(i)). The FD&C Act also provides that "[f]or a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect" (see section (j)(8)(C); see also implementing regulations at 21 CFR part 320).

[13] Drug products approved in ANDAs submitted under the suitability petition provisions of section 505(j)(2)(C) of the FD&C Act (petitioned ANDAs) will not be therapeutically equivalent to the RLD that serves as the basis for the petition.

manufacturing practices regulations; and (4) are adequately labeled.[14] Products classified as therapeutically equivalent can be substituted with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.[15]

C. Summary of Statutory and Regulatory Provisions Related to Combination Products

Section 503(g)(1) of the FD&C Act (21 U.S.C. 353(g)(1)) vests authority in the Secretary of the Department of Health and Human Services[16] to assign an Agency center to regulate products that constitute a combination of a drug, device, or biological product. Section 503(g)(1) further specifies that if the primary mode of action of the combination product is that of a drug, the Agency center charged with premarket review of drugs (i.e., the Center for Drug Evaluation and Research (CDER)) will have primary jurisdiction. Section 503(g)(4)(H) further specifies that "nothing in this paragraph shall be construed to limit the regulatory authority of any [A]gency center." Section 563 of the FD&C Act (21 U.S.C. 360bbb-2) establishes a procedure whereby applicants may request a determination respecting the classification of a product as a drug, biological product, device, or a combination product. The Agency has adopted regulations implementing sections 503(g) and 563 of the FD&C Act, codified at 21 CFR part 3. Under the operation of these provisions, a product consisting of a drug suspension in a pressurized metered-dose canister with a standard press-and-breathe actuator generally will be assigned to CDER as the lead center for premarket review in accordance with the drug as the primary mode of action. CDER may consult with the Center for Devices and Radiological Health (CDRH) to ensure acceptability of provided information. We note that the subject of your Petition meets the definition of a combination product (see 21 CFR 3.2(e)).[17]

D. FDA Guidance for Industry

In 2003, FDA issued a guidance for industry on *Integration of Dose-Counting Mechanisms into MDI Drug Products* (Dose Counter Guidance) that reflects the Agency's recommendations regarding the integration of dose-counting mechanisms into MDI drug products for oral inhalation.[18] The Dose Counter Guidance recommends that

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[14] See the Orange Book, 34rd ed., at vii.
[15] Orange Book, 34rd ed., at vii.
[16] The Secretary has delegated this authority to the Commissioner of Food and Drugs.
[17] In addition, codified at 21 CFR part 4 are the Current Good Manufacturing Practice Requirements for Combination Products (available at http://www.Federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products).
[18] This guidance published on FDA's Web site in March 2003 and is available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm under Clinical/Medical.

MDIs under development for oral inhalation include an integrated dose-counting device.[19] As explained in the Dose Counter Guidance, the purpose of a dose counter is to allow the patient to reliably track the number of actuations used from an individual MDI, which helps prevent the patient from discarding an MDI unnecessarily or using it beyond the labeled number of actuations.[20] The Dose Counter Guidance recommends that dose counters should be engineered to reliably track actuations and should be designed to be as close to 100 percent reliable as possible; however, if some low frequency of error is unavoidable, the device should be designed to specifically avoid undercounting (i.e., the metered-dose inhaler sprays, but the counter does not advance).[21]

FDA's 2013 draft guidance on *Albuterol Sulfate* (Albuterol Draft Guidance) provides recommendations on studies to establish bioequivalence in support of ANDAs for albuterol sulfate MDIs.[22] In addition, the Albuterol Draft Guidance includes a section on "Formulation and Device" which states that the test product (generic albuterol sulfate MDI) should have a dose counter if the reference product has a dose counter.[23]

II. DISCUSSION

You request that FDA refrain from approving any new rescue inhaler containing a SABA, brand or generic, unless the inhaler contains a dose counter. You also request that FDA implement a plan to transition already-approved rescue inhalers without a dose counter to versions that incorporate a dose counter. Below we address the issues raised in your Petition.

A. Integrated Dose Counters

You state that FDA should update and strengthen its policies regarding integrated dose counters in rescue inhaler drug products and require that all such products, NDAs and ANDAs, contain a dose counter (Petition at 8-9). You assert that an integrated dose counter provides a reliable way to determine how many doses remain in an inhaler, thereby reducing the risk of using an inhaler that no longer contains an adequate dose of the medication when asthma symptoms occur (Petition at 5). You state that new research and data confirm the value of integrated dose counters with respect to safety and efficacy and in reducing the rate of respiratory-related emergency room visits (Petition at 6).

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[19] Dose Counter Guidance at 3.
[20] Id.
[21] Id.
[22] This draft guidance published on FDA's Web site in June 2013. When finalized, it will represent FDA's current thinking on this topic (available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm).
[23] Albuterol Draft Guidance at 7.

As noted above, there are four FDA-approved rescue inhaler products -- ProAir HFA (albuterol sulfate) Inhalation Aerosol, Ventolin HFA (albuterol sulfate) Inhalation Aerosol, Proventil HFA (albuterol sulfate) Inhalation Aerosol, and Xopenex HFA (levalbuterol sulfate) Inhalation Aerosol. FDA approved all four MDIs as safe and effective. Although we encourage NDA sponsors of MDIs to include an integrated dose counter, we do not intend at this time to impose a universal requirement that all NDAs for MDI products include an integrated dose counter. We intend to consider the inclusion of an integrated dose counter on a case-by-case basis and in the context of a specific NDA.[24]

With respect to ANDAs, our position remains the same as that set forth in our response to the ProAir Petition on December 9, 2013. As stated in the response to the ProAir Petition, generally we would expect a proposed generic albuterol sulfate MDI to have a dose counter if the RLD has a dose counter, consistent with the recommendations of relevant FDA guidances for industry.[25]

B. FDA Guidance and Policies on Integrated Dose Counters

In your Petition, you cite the FDA guidance documents, the Dose Counter Guidance and the Albuterol Draft Guidance, in support of your statement that FDA should require dose counters in all rescue inhalers and implement a plan to transition already-approved rescue inhalers to include an integrated dose counter (Petition at 7-8). You contend that the data and research provided in the petition clearly demonstrate that dose counters promote the safe and effective use of rescue inhalers (Petition at 8). You state that the Dose Counter Guidance strongly recommends that manufacturers with metered-dose inhalers under development integrate a dose counter, but more than 10 years have passed since finalizing the guidance and there are still rescue inhalers on the market that do not have an integrated dose counter (Petition at 8). As such, you suggest that FDA strengthen its policies regarding dose counters in rescue inhalers and, among other things, recommend that FDA require all proposed generic rescue inhalers to include an integrated dose counter regardless of whether the RLD includes an integrated dose counter and, if necessary, require proposed generic rescue inhalers to rely only upon RLDs that incorporate an integrated dose counter (Petition at 9). You believe that the approval of generic rescue inhalers without dose counters could lead to widespread confusion and have a negative impact on the public health (Petition at 9).

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[24] This response does not reach the issue of whether any particular product without a dose counter would be unsafe. FDA intends to consider the safety issues for individual products in the context of individual applications.

[25] See, for example, the Albuterol Draft Guidance that recommends that a test product (generic albuterol sulfate metered-dose inhaler) should have a dose counter if the RLD has a dose counter (Albuterol Draft Guidance at 7).

As stated above, the Agency recommends the inclusion of an integrated dose counter for MDIs as set forth in the Dose Counter Guidance and the Albuterol Draft Guidance. With respect to NDAs for rescue inhalers, the Agency believes it is important for patients to have therapeutic options in treating respiratory diseases, such as asthma. Thus, although we encourage sponsors to develop MDIs that contain an integrated dose counter, we do not at this time consider it necessary or prudent to transition all FDA-approved rescue inhalers to those that contain an integrated dose counter if it means limiting the therapeutic options for patients.

We believe that our current policy of evaluating a product in the context of a particular application and encouraging sponsors to include an integrated dose counter for metered-dose rescue inhalers is the best approach to foster a variety of safe and effective therapeutic options for treating asthma. Moreover, in accordance with both policy and practice, the Agency intends to continue to monitor the adverse events reported for products, including rescue inhalers.

III. CONCLUSION

For the reasons explained above, your Petition is granted in part and denied in part.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research