DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DEC 0 9 2013

J. Michael Nicholas, Ph.D.
Vice President, Global Specialty Medicines
Teva Respiratory, LLC
41 Moores Road
P.O. Box 4011
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Re: Docket No. FDA-2013-P-0850

Dear Mr. Nicholas:

This letter responds to your citizen petition dated July 12, 2013 (Petition), requesting that the Food and Drug Administration (FDA or the Agency) refrain from approving any abbreviated new drug application (ANDA) or 505(b)(2) application that relies on ProAir HFA as the listed drug unless the following conditions are met:

1. 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; 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. The applicant successfully mitigates the risk of a canister and actuator mismatch.[1]

We have carefully considered the issues raised in your Petition. For the reasons stated below, your Petition is granted in part and denied in part.

I. BACKGROUND

A. ProAir HFA (albuterol sulfate) Inhalation Aerosol

ProAir HFA (albuterol sulfate) Inhalation Aerosol is a suspension of racemic albuterol sulfate in hydrofluoroalkane (HFA-134a) and ethanol in a pressurized metered-dose canister, coupled with a standard press-and-breathe actuator, providing 90 micrograms of albuterol sulfate per actuation. Teva Respiratory, LLC (Teva) submitted new drug

[1] For purposes of this response, the terms "generic" or "generic product" refer to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The term "505(b)(2) product" refers to a product for which approval is sought in an NDA under section 505(b)(2) of the FD&C Act.

application (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 the treatment or prevention of bronchospasm with reversible obstructive airway disease in adults and children 12 years of age and older. ProAir HFA was subsequently approved for the prevention of exercise-induced bronchospasm in the same patient populations.[2] The patient population for both indications was later expanded to include patients 4 to 11 years.[3] 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.[4] 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.[5] Approval of the supplement resulted in certain changes to the Full Prescribing Information, specifically, the addition of information regarding the dose counting mechanism to subsection *2.3 Administration Information* in section 2 DOSAGE AND ADMINISTRATION, section 16 HOW SUPPLIED/STORAGE AND HANDLING, and subsection *17.3 Dose Counter* in section 17 PATIENT COUNSELING INFORMATION.

B. Statutory and Regulatory Standards

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)), which established the ANDA approval process. To obtain 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 reference listed drug (RLD) is safe and effective.[6] 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).[7] In addition, other than a petitioned ANDA, an ANDA must contain

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[2] Supplement S-003, approved on February 3, 2006.
[3] Supplement S-013, approved on September 16, 2008.
[4] Supplement S-026.
[5] Study ABM-AS-307.
[6] An RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as "the Orange Book."
[7] 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

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, where 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 "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.[8] FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.[9] 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.[10]

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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 also implementing regulations at 21 CFR part 320.

[8] 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.

[9] See the Orange Book, 33rd ed., at vii.

[10] Orange Book, 33rd ed., at vii.

Section 505(b)(2) of the 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.[11] 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.

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

Section 503(g)(1) of the FD&C Act vests authority in the Secretary of the Department of Health and Human Services[12] 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) shall 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 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 (21 CFR 3.2(e)).[13]

D. FDA Guidance for Industry

In 2003, FDA issued a guidance for industry on *Integration of Dose-Counting Mechanisms into MDI Drug Products* that reflects the Agency's recommendations regarding the integration of dose-counting mechanisms into metered-dose inhaler (MDI)

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[11] 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.
[12] The Secretary has delegated this authority to the Commissioner of Food and Drugs.
[13] In addition, codified at 21 CFR Part 4 are the Current Good Manufacturing Practice Requirements for Combination Products. See Federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products.

drug products for oral inhalation (Dose Counter Guidance).[14] The Dose Counter Guidance recommends that MDIs under development for oral inhalation include an integrated dose-counting device.[15] 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 the MDI beyond the labeled number of actuations.[16] 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 MDI sprays, but the counter does not advance).[17]

FDA's 2013 draft guidance on *Albuterol Sulfate* (Aerosol) provides recommendations on studies to establish bioequivalence in support of ANDAs for albuterol sulfate MDIs (Albuterol Draft Guidance).[18] In addition, the Albuterol Draft Guidance includes a section on the 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. This section also states that in vitro and in-use studies should be conducted to support the functionality, accuracy, and robustness of the proposed dose counter of the test product.[19]

II. DISCUSSION

You request that FDA refrain from approving any ANDA or 505(b)(2) application that relies on ProAir HFA as the listed drug unless 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. You also request that FDA refrain from approving any ANDA or 505(b)(2) application that relies on ProAir HFA as the RLD unless the applicant successfully mitigates the risk of a canister and actuator mismatch. Below, we address the arguments you have made in support of your requests.

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[14] 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.
[15] Dose Counter Guidance at 3.
[16] Id.
[17] Id.
[18] 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).
[19] Albuterol Draft Guidance at 7.

A. Integrated Dose Counters

1. Applications Relying on ProAir HFA

You state that "[s]ince 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 that does not incorporate a dose counter."[20]

You state that failure to include a dose counter would result in impermissible design differences between ProAir HFA and the proposed generic product.[21] Quoting FDA's 2009 response to a citizen petition filed by King Pharmaceuticals, Inc., about FDA approval of drug products containing autoinjectors (King citizen petition), you state that design differences will be permitted only if "they do not significantly alter product performance or operating principles and do not result in impermissible differences in labeling" and that FDA "considers whether any difference in materials, design, or operating principles introduces a new risk. . . ."[22] You state that, in this case, 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.

You also assert that failure to include a dose counter would result in impermissible labeling differences between ProAir HFA and the proposed generic product. You argue that labeling changes that introduce new or increased risks or that otherwise render the proposed generic less safe or effective than the RLD are not permitted. You state that because the approved labeling for ProAir HFA provides detailed instructions with respect to the dose counter, a generic product without a dose counter would have impermissibly different labeling instructions. Specifically, you state that the labeling either would need to remain silent or recommend that patients track each actuation and such labeling differences necessitated by the absence of a dose counter would render the proposed generic product less safe than ProAir HFA.[23]

Finally, you state that FDA should require that any dose counter in the proposed generic product function in the same manner and have the same labeled instructions for use as the dose counter in ProAir HFA to avoid confusion upon generic substitution.[24]

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[20] Petition at 10.
[21] Petition at 8-10.
[22] Petition at 8-9, quoting FDA's July 29, 2009, response to the King citizen petition(Docket Nos. FDA-2009-P-0040 and FDA-2007-P-0128) at 6, available at http://www.regulations.gov.
[23] Petition at 10-11.
[24] Petition at 11-12.

The Albuterol Draft Guidance recommends that a test product (generic albuterol sulfate MDI) should have a dose counter if the RLD has a dose counter.[25] Consistent with these recommendations, generally we would expect a proposed generic albuterol sulfate MDI to have a dose counter if the RLD has a dose counter.[26]

When reviewing an ANDA for a generic version of ProAir HFA (a drug-device combination product), FDA evaluates the device 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. However, as you acknowledge[27] and as noted in our response to the King citizen petition on autoinjectors, this does not mean that all design features of the device in the ANDA and its RLD must be exactly the same. Some design differences in devices may be acceptable as long as they do not significantly alter product performance or operating principles and do not result in impermissible differences in labeling.[28] Whether the device proposed in an ANDA for a generic version of ProAir HFA involves significant differences in design, operating principles, or labeling that introduce new or heightened risks would be considered as part of the normal course of the ANDA review process.

We do not necessarily expect a dose counter for a generic version of ProAir HFA to function in exactly the same manner and have the same labeled instructions for use as the dose counter in ProAir HFA. Acceptable design differences in devices may result in permissible differences between the generic product and ProAir HFA labeling. For products produced or distributed by different manufacturers, certain labeling differences are permissible within the meaning of section 505(j)(2)(A)(v) and 505(j)(4)(G) of the FD&C Act and implementing regulations including § 314.94(a)(8)(iv), and permissibility of any labeling differences between a generic version of ProAir HFA and ProAir HFA would be assessed during the normal course of ANDA review.

2. In Vitro and In-Use Testing

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[25] Albuterol Draft Guidance at 7.

[26] You also make certain assertions with respect to 505(b)(2) applications that rely on ProAir HFA. Although the Dose Counter Guidance recommends that manufacturers of MDIs for oral inhalation integrate a dose-counting mechanism into their MDI drug product, 505(b)(2) applications can differ from the listed drugs in a variety of ways, and we cannot speculate here as to what demonstrations would be needed for a 505(b)(2) application citing ProAir HFA as a listed drug. Therefore, this response focuses on your request with respect to ANDAs and does not address your individual assertions with respect to 505(b)(2) applications. In addition, 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.

[27] Petition at 8.

[28] See FDA's July 29, 2009, response to the King citizen petition on (Docket Nos. FDA-2009-P-0040 and FDA-2007-P-0128) at 6, available at http://www.regulations.gov.

For any proposed generic or 505(b)(2) version of ProAir HFA that incorporates a dose counter, you assert that FDA should require the applicant to establish the functionality, reliability, and accuracy of its dose counter in real world settings. In addition you state that the generic applicant should be required to address reliability issues specific to its particular dose counters, including ergonomics, ruggedness, and accuracy in clinical settings, through appropriate in vitro and clinical testing. Specifically, you state that the dose counter should be engineered to track actuations reliably and should be designed to be as close to 100 percent reliable as possible. You cite to the Albuterol Draft Guidance to support this request. You further request that such testing include a "reasonable representation of special populations likely to use the drug" and the "clinical testing should include a sufficient number of subjects to reach statistically significant conclusions regarding dose counter performance.[29]

The Albuterol Draft Guidance states that "[i]n vitro testing and in-use studies should be conducted to support the functionality, accuracy, and robustness of the proposed dose counter.[30] In general, we agree that for a generic version of ProAir HFA, in vitro and in use studies can support the functionality, accuracy, and robustness of the proposed dose counter.[31] The adequacy of information to support approval of any particular ANDA for a generic version of ProAir HFA would be assessed during the normal course of ANDA review.

B. Canister and Actuator Mismatch

You state that there is a possible risk of canister and actuator mismatch and request that FDA require ANDA and 505(b)(2) applicants to incorporate one or more design features into the components of their proposed products to dissuade or prevent their actual or attempted use with either the ProAir HFA canister or its actuator mouthpiece. You request that FDA require, at a minimum, a competitor's actuator mouthpiece to have an appearance that clearly distinguishes it from ProAir HFA's actuator mouthpiece to prevent a patient from pairing the wrong canister with the wrong mouthpiece. You also request that FDA require that the competitor's actuator have a different color scheme from any previously approved MDI's color scheme, a contrasting label or embossed element, and a proprietary name to provide additional protection against mismatches.[32]

Typically for metered dose inhalation aerosol products, the labeling includes information conveying that the canister and actuators are specific to a product and should not be interchanged with those of other products. These statements are found in the labeling for

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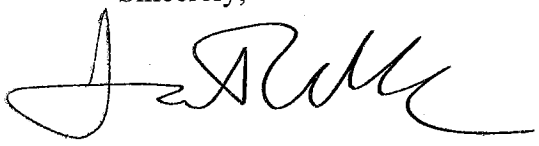
[29] Petition at 13-14.
[30] Albuterol Draft Guidance at 7.
[31] In the context of an ANDA for a generic version of ProAir HFA, these studies support the quality of the product. See e.g., section 505(j)(4)(A) of the FD&C Act; see also section 505(j)(2)(A).
[32] Petition at 14-18.

ProAir HFA. We would expect that a generic version of ProAir HFA would include the same type of labeling statements as ProAir HFA's labeling. We believe these statements are sufficient to protect against canister and actuator mismatch and therefore decline to require ANDA or 505(b)(2) applicants relying on ProAir HFA to incorporate these design features into the components of their proposed products.

III. CONCLUSION

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

Sincerely,



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