U.S. FOOD & DRUG ADMINISTRATION

MAR 10 2017

Anthony Maffia
Vice President, Regulatory Affairs
Sandoz Inc.
100 College Road West
Princeton, NJ 08540

Re: Docket No. FDA-2016-P-3356

Dear Mr. Maffia:

This letter responds to your citizen petition received on October 13, 2016 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or Agency) refrain from approving any abbreviated new drug application (ANDA) for a generic version of Advair Diskus 100/50 (fluticasone propionate 100 microgram (mcg) and salmeterol 50 mcg inhalation powder); (hereafter Advair Diskus 100/50 or Advair Diskus) unless the Agency ensures that:

> (1) Type I error rate is adequately controlled in [pharmacokinetic (PK)] bioequivalence testing, including accounting for Type I error rate inflation caused by batch-to-batch variability of the [reference listed drug (RLD)];
>
> (2) [T]he dose used in PK bioequivalence testing retains the necessary sensitivity to product differences existing at the marketed single inhalation dose of the RLD; and
>
> (3) [T]he sampling schedule used in PK bioequivalence testing is robust and centered around the actual time to maximum plasma concentration of both active ingredients at the marketed dose of the RLD.

(Petition at 2).

We have carefully reviewed your Petition, and for the reasons stated below, your Petition is denied without comment on whether we will take the actions you request.

I. BACKGROUND

A. Advair Diskus

Advair Diskus is a combination product containing fluticasone propionate (a corticosteroid) and salmeterol (a long-acting beta$_2$-adrenergic agonist) in a powder formulation for oral inhalation. The product is indicated for long-term, twice-daily use for treatment of asthma in patients ages 4 years and older and for maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease.

FDA approved Advair Diskus on August 24, 2000 (new drug application (NDA)

021077).[1] Advair is currently marketed by GlaxoSmithKline in three strengths: 100 mcg fluticasone propionate/50 mcg salmeterol, 250 mcg fluticasone propionate/50 mcg salmeterol, and 500 mcg fluticasone propionate/50 mcg salmeterol.

FDA issued a draft product-specific guidance for Fluticasone Propionate; Salmeterol Xinafoate in September 2013.[2]

B. Section 505(q) of the Federal Food, Drug, and Cosmetic Act

Section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(q)) was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144, 126 Stat. 993), which was signed into law on July 9, 2012. Section 505(q) of the FD&C Act, as originally added by the FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act (21 U.S.C. 355(b)(2) or (j)) and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on a petition no later than 150 days after the date on which the petition is submitted. The 150-day period is not to be extended for any reason.

II. DISCUSSION

You assert that "unique variability and kinetic issues" related to Advair Diskus 100/50 require the application of the bioequivalence study design elements you enumerate in the Petition (Petition at 12). Your Petition acknowledges FDA's *Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate* (September 2013), but contends that it "lacks the study design requirements [i.e., those enumerated in the Petition] that are necessary to address certain drug-specific characteristics" (Petition at 2).

Consequently, your Petition requests that FDA "refrain from approving any ANDA for a generic version of Advair Diskus 100/50 unless the agency ensures that that (1) Type I error rate is adequately controlled in bioequivalence testing, including accounting for Type I error rate inflation caused by batch-to-batch variability of the RLD; (2) the dose used in PK bioequivalence testing retains the necessary sensitivity to product differences existing at the marketed single inhalation dose of the RLD; and (3) the sampling schedule used in PK bioequivalence testing is robust and centered around the actual time to maximum concentration of both active ingredients

[1] The 2000 Advair Diskus approval letter is available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21077_Advair%20Diskus_Approv.pdf

[2] See the *Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. When final, this guidance will represent FDA's current thinking on this topic.

at the marketed dose of the RLD (Petition at 2, 17).

In support of your request that "FDA require that PK bioequivalence studies for generic versions of Advair Diskus 100/50 adequately control for Type I Error, including accounting for Type I Error Rate Inflation caused by batch-to-batch variability of the RLD," you assert that reliance on conventional single-batch bioequivalence study design may misrepresent the true relationship between Test and Reference products when batches of an RLD are shown to be substantially different from one another. Your petition includes a discussion of the asserted limitations with conventional single-batch bioequivalence study design where there is substantial batch-to-batch variability in the RLD (Petition at 2, 5-8, 12). You specifically state that any PK bioequivalence assessment should therefore include appropriate measures to address the observed variability, such as employing multiple Test and Reference batches (Petition at 13-14).

You also assert that "FDA should require that PK bioequivalence studies for generic versions of Advair Diskus 100/50 use a dose that retains the necessary sensitivity to product differences in rate of absorption that exist at the marketed single-inhalation dose of the RLD" (Petition at 14). You specifically state that the PK profile of any proposed ANDA product should be based on a single-inhalation testing regimen to retain adequate sensitivity to the actual product characteristics. In support of your request, you state:

> [T]he available data demonstrate that a single inhalation is sufficient to provide an appropriate bioequivalence profile for fluticasone propionate/salmeterol products. Based on this fact, and the consistency of the labeled dose and patient exposure to this highly variable RLD, the PK profile of any proposed ANDA product should be based on a single-inhalation testing regimen to retain adequate sensitivity to the actual product characteristics.

(Petition at 14).

Finally, you assert that "FDA should require that PK bioequivalence studies for generic versions of Advair Diskus 100/50 employ a robust sampling schedule that centers around the actual time to maximum concentration of the active ingredients at the marketed dose" (Petition at 15). As grounds for this request, you assert that the time to maximal concentration of both active ingredients in Adviar Diskus 100/50 occurs very quickly after administration of the marketed dose (Petition at 15). As a result, you state that very early time points should be targeted for PK sampling in a single inhalation dosing paradigm to ensure an accurate assessment of bioequivalence between a generic product and the Advair Diskus 100/50 RLD (Petition at 15).

You further state that:

> Sandoz's research clearly shows that maximum concentration for fluticasone propionate can occur in minutes, not hours. This data underscores the need for robust PK blood sampling in the 3 to 10 minutes immediately following inhalation to capture the peak plasma concentration associated with the marketed dose of the low-strength RLD.

(Petition at 16).

As described in section I.B of this response, section 505(q)(1)(F) of the FD&C Act requires FDA to take final Agency action on the Petition within 150 days of submission. Therefore, we must take action on the Petition at this time. For the reasons explained below, we deny without comment the specific requests in your Petition regarding the approvability of any specific ANDA referencing Advair Diskus 100/50 as its RLD.

FDA has made no final determination on whether to approve or not approve any ANDA referencing Advair Diskus 100/50 as its RLD. In the case of ANDAs referencing Advair Diskus 100/50, FDA's consideration of one or more applications will necessarily inform our decisions on the nature of the data and information regarding the approvability of such applications (and also whether any revisions to the draft guidance are appropriate). Therefore, FDA must determine whether it would be appropriate to take final Agency action on the approvability of a specific aspect of an ANDA before taking final action on the approvability of the ANDA as a whole. To make this determination, we believe it is appropriate to evaluate the statutory and regulatory provisions governing the content and review of ANDAs in connection with the statutory provision of section 505(q) of the FD&C Act governing the time frame for action on the Petition.

The FD&C Act and FDA regulations establish procedural protections for applicants in the context of application review. Section 505 of the FD&C Act and FDA's regulations in part 314 (21 CFR part 314) describe certain procedures by which the Agency reviews an NDA or ANDA and notifies an applicant if it determines that an application is approved (§ 314.105) or may not be approved (section 505(c) and (j) of the FD&C Act; §§ 314.125 and 314.127), or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies (§ 314.110). In addition, the statute and regulations describe a specific process through which an applicant whose application the Agency has found does not meet the requirements for approval may challenge the Agency's determination (section 505(c)(1)(B) and (d) of the FD&C Act; § 314.200). Under this process, the Agency will give the applicant notice of an opportunity for a hearing on whether the application is approvable, with a specific time frame and process if the applicant requests such a hearing (id.). These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

There is no evidence that in enacting section 505(q) of the FD&C Act, Congress intended to bypass the application review process or to lessen an ANDA applicant's procedural rights by requiring that the Agency make decisions that constitute final Agency action regarding the approvability of certain aspects of pending applications on a piecemeal basis outside of the process established under the FD&C Act and FDA regulations.[3] Therefore, we do not interpret

[3] In other citizen petition responses, we have responded to requests related to general standards for approval (e.g., bioequivalence criteria for generic drug products) that may pertain to one or more pending drug applications without commenting on the approvability of any particular aspect of a specific pending application. We believe that this approach of describing our general policies or standards for approval of a drug application (beyond the descriptions provided in this response) would not be appropriate in this case because, as stated, our review of a given ANDA would inform our decisions regarding the sufficiency of the specific data and information needed for approval. We

section 505(q) of the FD&C Act to require that the Agency render a final Agency decision within the statutory deadline on the approvability of a specific aspect of an ANDA when a final decision on the approvability of any such ANDA has not yet been made.[4] Accordingly, we are denying without comment your requests on the specific requirements for approval of any ANDA referencing Advair Diskus 100/50 as its RLD.

III. CONCLUSION

For the reasons described above, the Petition is denied.

Sincerely,

Robert Temple for

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

will continue to evaluate each citizen petition on a case-by-case basis on the appropriateness of responding to requests regarding any pending application.

[4] Under applicable statutory and regulatory provisions, we are generally prohibited from disclosing any determinations regarding the receipt or approvability of any pending NDA or ANDA before we have reached a final decision on whether to approve or not approve the ANDA or NDA.