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VIA ELECTRONIC SUBMISSION

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

CITIZEN PETITION

Sandoz Inc. ("Sandoz") hereby submits this citizen petition pursuant to 21 C.F.R. §§ 10.25, 10.30 and Sections 505(j) and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 355(j), (q). For the scientific reasons discussed herein, Sandoz respectfully requests that the Food and Drug Administration ("FDA") refrain from approving any abbreviated new drug application ("ANDA") that references Advair Diskus 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg inhalation powder) as the reference listed drug ("RLD") unless it contains the results of a pharmacokinetic ("PK") bioequivalence study that meets the necessary study design parameters described below in order to ensure the safety and efficacy of all ANDA products referencing this RLD.

I. ACTIONS REQUESTED

Sandoz is one of the largest generic pharmaceutical manufacturers in the United States. In 2010, Sandoz acquired Oriel Therapeutics, Inc., gaining additional technology and experience in the development of generic orally inhaled drug products ("OIDPs"), including ongoing research and development of a fluticasone propionate/salmeterol combination product. Based on its extensive in-house research, Sandoz has a highly informed perspective on the development of generic versions of Advair Diskus.

GlaxoSmithKline ("GSK") is the developer and manufacturer of Advair Diskus. Although the final patent listed for Advair Diskus in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") expired on August 23, 2016 (with six-month pediatric exclusivity), there are still no FDA-approved generics. This is largely due to the fact that, until relatively recently in 2013, FDA had not articulated the type and quantum of data it would require for approval of generic OIDPs. Among other issues, the PK batch-to-batch

variability of OIDPs has been a consistent concern for both regulators and industry in the context of generic development for several years.[1]

In September 2013, FDA released its bioequivalence recommendations for generic versions of Advair Diskus.[2] FDA's recommendations provide specific guidance on the design of bioequivalence studies that the agency expects to see in ANDAs referencing Advair Diskus as the RLD. However, as discussed below, FDA's draft guidance lacks the study design requirements that are necessary to address certain drug-specific characteristics of the Advair Diskus 100/50 RLD—namely, the degree of PK batch-to-batch variability and the rapid onset of peak plasma concentration for both active ingredients. As a result of these RLD characteristics, targeted study design requirements are needed to accurately demonstrate PK bioequivalence for generic versions of Advair Diskus 100/50.

Sandoz is aware that FDA has accepted for review ANDAs that reference Advair Diskus as the RLD. However, to the extent that these ANDA applicants relied solely on FDA's draft guidance in conducting their PK bioequivalence studies, Sandoz is concerned that the applications may fail to contain accurate and generalizable evidence of PK bioequivalence for their low-strength (100/50) products. Accordingly, Sandoz requests that FDA refrain from approving any ANDA for a generic version of Advair Diskus 100/50 unless the agency ensures that:

(1) Type I error rate is adequately controlled in PK 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 plasma concentration of both active ingredients at the marketed dose of the RLD.

As discussed below, Sandoz's research confirms that the above PK bioequivalence study design requirements are essential to ensuring: (i) an accurate and generalizable bioequivalence conclusion with adequate Type I error rate control in light of the inherent RLD batch-to-batch variability, and (ii) an adequate capture, and thereby accurate comparison, of maximum plasma concentrations in light of the rapid absorption of the RLD product. These requirements are

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[1] *See, e.g.*, Günther Hochhaus, et al., *Generics for Oral Inhaled Drugs: Knowledge Gaps for Streamlining Bioequivalence Approval*, Presentation at the FDA Generic Drug User Fee Amendments of 2012 Regulatory Science Initiatives Part 15 Public Hearing (June 21, 2013) (Attachment A); Robert Lionberger, *Interpreting Pharmacokinetics for Inhalation Bioequivalence*, Presentation at the International Pharmaceutical Aerosol Consortium on Regulatory Science / University of Florida Orlando Inhalation Conference (Mar. 19, 2014) (Attachment B).

[2] Draft Guidance for Industry on Bioequivalence Recommendations for Fluticasone Propionate; Salmeterol Xinafoate; Availability, 78 Fed. Reg. 55,263 (Sept. 10, 2013); FDA, *Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate* (Recommended Sept. 2013).

therefore crucial to ensuring the safety and effectiveness of any generic version of Advair Diskus 100/50.

II. STATEMENT OF GROUNDS

A. The Advair Diskus RLD

Advair Diskus is a combination product containing fluticasone propionate (a corticosteroid) and salmeterol (a long-acting beta$_2$-adrenergic agonist ("LABA")) 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 ("COPD"). GSK first obtained approval for Advair Diskus on August 24, 2000 and currently markets three strengths of the product: low-strength (100/50 mcg), mid-strength (250/50 mcg), and high-strength (500/50 mcg).[3]

In July 2012, Congress passed the Generic Drug User Fee Amendments of 2012 ("GDUFA") as part of the Food and Drug Administration Safety and Innovation Act ("FDASIA"). In its GDUFA Performance Goals letter, FDA agreed to begin work on several specific regulatory science initiatives.[4] These initiatives addressed, as the first item, the bioequivalence of locally acting OIDPs, which currently lack generic competition. FDA promised to continue to develop "new and improved" study designs or establish "alternative approaches" to ensure the bioequivalence of locally delivered OIDPs in order to facilitate more efficient development of generic products in this sector.[5] FDA held a public meeting on its initiatives a year later in June 2013, where representatives of both industry and academia emphasized the need for reliable, high-quality generic versions of respiratory drug-device combination products.[6]

FDA's regulatory science initiatives played a key role in its published recommendations for demonstrating the bioequivalence of generic OIDPs. In September 2013, FDA released its draft guidance on bioequivalence recommendations for generic versions of Advair Diskus, which represented only FDA's second such guidance in this space.[7] The resulting fluticasone propionate/salmeterol draft guidance provides specific recommendations on bioequivalence

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[3] The approved dosages are as follows:

- Treatment of asthma in patients 12 years and older: 1 inhalation of Advair Diskus 100/50, 250/50, or 500/50 twice daily.
- Treatment of asthma in patients ages 4 to 11 years: 1 inhalation of Advair Diskus 100/50 twice daily.
- Maintenance treatment of COPD: 1 inhalation of Advair Diskus 250/50 twice daily.

Advair Diskus Prescribing Information & Medication Guide, at 1 (Rev. Apr. 2016) (Attachment C).

[4] FDA, *Generic Drug User Fee Act Performance Goals and Procedures* (2012).

[5] *Id.* at 18.

[6] *See generally* FDA, FY 2013 Regulatory Science Initiatives Part 15 Public Meeting Presentations (June 21, 2013), http://www.fda.gov/Drugs/NewsEvents/ucm399495.htm.

[7] The first guidance was released only a few months before in April 2013. *See* FDA, *Draft Guidance on Albuterol Sulfate* (Recommended Apr. 2013, Revised June 2013).

studies for generic versions of the Advair Diskus 100/50 RLD, including an in vitro bioequivalence study, a PK bioequivalence study, and a large clinical endpoint study. However, as discussed below, Sandoz's data demonstrate that FDA's PK study recommendations, if followed, could result in inaccurate bioequivalence conclusions.

B. The Bioequivalence Standard

Under Section 505(j) of the FDCA, an ANDA must contain "information to show that the new drug is bioequivalent to the [RLD]," and FDA may refuse to approve an ANDA if, among other things, "information submitted in the application is insufficient to show that the drug is bioequivalent to the [RLD]."[8] A generic drug is considered to be bioequivalent to an RLD 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 [RLD] when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses."[9] Notably, FDA's regulations make clear that this bioequivalence standard may only be met "*in an appropriately designed study*."[10]

As part of the requirement that there not be a "significant difference" in the rate and extent of absorption (i.e., the bioavailability[11]) of a generic drug when compared to that of the RLD, FDA has generally adopted an 80-125% limit of acceptance for bioequivalence testing results. Specifically, FDA guidance provides that, in order to establish bioequivalence, "the calculated confidence interval should fall within a [bioequivalence] limit," and this limit is "usually 80-125%… based on a clinical judgment that a test product with [bioavailability] measures outside this range should be denied market access."[12] Nonetheless, it is critical that any study obtaining bioequivalence results to be judged within the 80-125% limit be *appropriately designed* to provide a valid comparison.

In addition, Type I error rate control is fundamental to bioequivalence testing, as it is the standard for statistical hypothesis tests that form the basis of FDA drug approval decisions. In the bioequivalence context, the Type I error rate is defined as the probability of concluding that the Test and Reference product averages are equivalent when, in fact, they differ enough to be considered non-equivalent.[13] In most situations, a two one-sided tests procedure controls the Type I error rate at the nominal significance level of 5%, a fact that substantially contributed to FDA's acceptance of the two one-sided tests procedure for most bioequivalence testing.[14] Prior

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[8] 21 U.S.C. 355(j)(2)(A)(iv), (4)(F); *see also* 21 C.F.R. §§ 314.94(a)(7)(i), 314.127(a)(6)(i).

[9] 21 U.S.C. § 355(j)(8)(B)(i); *see also* 21 C.F.R. § 320.23(b).

[10] 21 C.F.R. §320.1(e) (emphasis added).

[11] 21 C.F.R. § 320.1(a); *see also* FDA, *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence*, at 2 (Jan. 2001) (defining bioequivalence as "relative [bioavailability]").

[12] FDA, *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence*, at 2, fn. 2 ("Although BA and BE are closely related, BE comparisons normally rely on (1) a criterion, (2) a confidence interval for the criterion, and (3) a predetermined BE limit…. To establish BE, the calculated confidence interval should fall within a BE limit, usually 80-125% for the ratio of the product averages.")

[13] *Id.* at 3, 15.

[14] *Id.* at 2-3.

to the two one-sided tests procedure, use of the "power approach" allowed a Type I error rate that rose above 5% as the error degrees of freedom increased, for example, to approximately 12% for a two-way crossover design with approximately 100 subjects.[15] FDA concluded that this was undesirable, and the agency subsequently abandoned the power approach for bioequivalence testing.

Within this framework, FDA routinely releases recommendations on the design of bioequivalence studies for specific products that meet the agency's bioequivalence standards for generic drug approval. However, as with all FDA guidance documents, product-specific bioequivalence recommendations represent only the agency's current thinking on the topic, and guidance revisions are common. Indeed, FDA has stated that its published bioequivalence recommendations "will be revised as appropriate to ensure that the most up-to-date [bioequivalence] information is available to the public."[16] Moreover, FDA has made clear that it is not bound to its published recommendations in assessing whether an ANDA contains adequate evidence of bioequivalence. Rather, in its review of proposed generic products, FDA considers all available relevant information, "which may include information submitted by the public to dockets for citizen petitions."[17]

Under the statute, once a generic product is approved, it is listed in the Orange Book with a therapeutic equivalence code.[18] An "AB" code signifies that the generic drug is therapeutically equivalent to the RLD and, as such, "can be substituted [for the RLD] with the full expectation that the substituted product will produce the same clinical effect and safety profile as the [RLD]."[19] This substitutability is based on the guarantee that a "therapeutically equivalent" drug "can be expected to have the same clinical effect and safety profile [as the RLD] when administered to patients under the conditions specified in the labeling."[20] The substitutability of AB-rated generic drugs underscores the public health importance of ensuring accurate bioequivalence evaluations for purposes of product approval. In the case of ANDAs referencing Advair Diskus 100/50, reliable approval decisions require PK comparisons with a firm basis in the actual performance characteristics of the RLD, including the demonstrated and substantial batch-to-batch PK variability and rapid onset of peak plasma concentration observed for both active ingredients in Advair Diskus 100/50.

C. Batch-to-Batch Variability of Advair Diskus 100/50

In public meetings on OIDPs, FDA discussed the study design that would be necessary to characterize PK batch-to-batch variability for a product. In particular, FDA stated that a comparison of one batch of the Test product with two batches of the Reference product, with one

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[15] Donald J. Schuirmann, *A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability*, 15 J. Pharmacokinetics & Biopharmaceutics 657, 668 (1987) (Attachment D).

[16] FDA, *Guidance for Industry: Bioequivalence Recommendations for Specific Products*, at 3 (June 2010).

[17] *Id.*

[18] 21 U.S.C. § 355(j)(7).

[19] FDA, Orange Book Preface §§ 1.2, 1.7 (2016).

[20] *Id.*

Reference batch repeated, could adequately characterize both the intra-subject batch-to-batch variability and the intra-subject residual variability of the Reference product.[21] In addition, FDA has specifically defined the concept of bio-*in*equivalence. Demonstrating bio-inequivalence requires special FDA-prescribed testing considerations, and the agency has made clear that "a study failing to show bioequivalence cannot be used to claim bio-inequivalence."[22] Sandoz conducted a study satisfying all of FDA's bio-inequivalence design criteria with multiple batches of Advair Diskus 100/50, and the recently published results demonstrate that Advair Diskus 100/50 PK batch-to-batch variability is: (i) a significant variance component additional to, and separate from, residual error variance, and (ii) larger in magnitude than is consistent with the bioequivalence standard.[23] Batch-to-batch PK variability of this RLD is, therefore, both existent and substantial.

As shown in **Figure 1**, Advair Diskus 100/50 failed to meet FDA's 80-125% standard for bioequivalence in all three of the study's pairwise batch-to-batch comparisons, and in some cases, the substantial PK differences between the marketed RLD batches demonstrated bio-inequivalence. For example, in the batch 1-*vs*-batch 2 comparison, the 90% confidence interval around the geometric mean ratios ("GMRs") for the maximum plasma concentration (C_{max}) of fluticasone propionate was 59-72%, fully outside the 80-125% bioequivalence window. Similarly, the corresponding salmeterol C_{max} 90% confidence interval was 56-72%. In contrast, the replicated Advair Diskus 100/50 batch (batch 1) met the 80-125% bioequivalence requirement on every PK metric, confirming that the observed differences between batches were not the consequence of inadequate study size or poor execution.

[21] Günther Hochhaus, et al., *Meeting Report: Pharmacokinetics of Orally Inhaled Drug Products*, 17 Am. Ass'n of Pharmaceutical Scientists J. 769, 773 (2015) (Attachment E); *see also* Robert Lionberger, *supra* note 1.

[22] FDA, *Background for Advisory Committee for Pharmaceutical Science: Concept and Criteria of BioINequivalence* (Oct. 20, 2004) (Attachment F).

[23] Elise Burmeister Getz, et al., *Batch-to-Batch Pharmacokinetic Variability Confounds Current Bioequivalence Regulations: A Dry Powder Inhaler Randomized Clinical Trial*, Clinical Pharmacology & Therapeutics (Advance Online Publication 2016) (Attachment G).

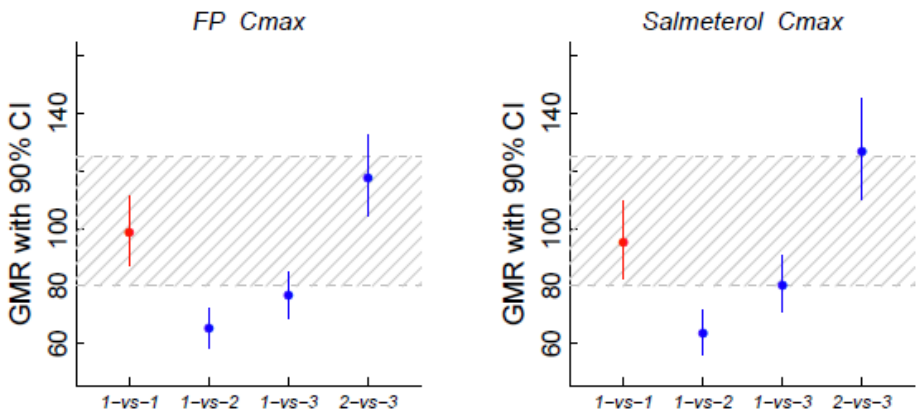

Figure 1. Advair Diskus 100/50 PK Bioequivalence Comparison Within and Between Batches

Geometric mean ratio (GMR) and 90% confidence interval (CI) for comparisons of maximum plasma concentration (C_{max}) of fluticasone propionate and salmeterol among three manufacturing batches of Advair Diskus 100/50. Batches are identified numerically as batch 1, batch 2, and batch 3. Batch 1 was replicated across two treatment periods; the comparison of the two replicates of batch 1 is indicated in red. Comparisons between different batches are indicated in blue. Thirty healthy adult male and female subjects were administered 100 mcg fluticasone propionate in combination with 50 mcg salmeterol by oral inhalation in a randomized crossover trial with seven-day washout between doses. PK blood samples were collected pre-dose and 3, 4, 5, 6, 8, 10, 15, 20, 30 and 45 minutes and 1, 2, 4, 8, 12, 16, 20, 24, 28, 32 and 36 hours after dosing. Concentrations of fluticasone propionate and salmeterol were determined by HPLC-MS/MS with a lower limit of quantitation of 1.00 pg/mL for both analytes. Shaded region indicates the bioequivalence zone of 80-125%.

The significant Advair Diskus 100/50 batch-to-batch variability was independently confirmed in a second Sandoz PK study, as shown in **Figure 2**. In this study, three different batches of the RLD were again compared, and again all three pairwise batch-to-batch comparisons failed to meet FDA's 80-125% standard for bioequivalence. As in the published study discussed above, batch-to-batch PK differences were large enough to demonstrate bio-inequivalence. A manuscript reporting this randomized clinical trial has been accepted for publication.[24]

[24] Elise Burmeister Getz, et al., *Between-Batch Pharmacokinetic Variability Inflates Type I Error Rate in Conventional Bioequivalence Trials: A Randomized Advair Diskus Clinical Trial*, Clinical Pharmacology & Therapeutics (pending publication).

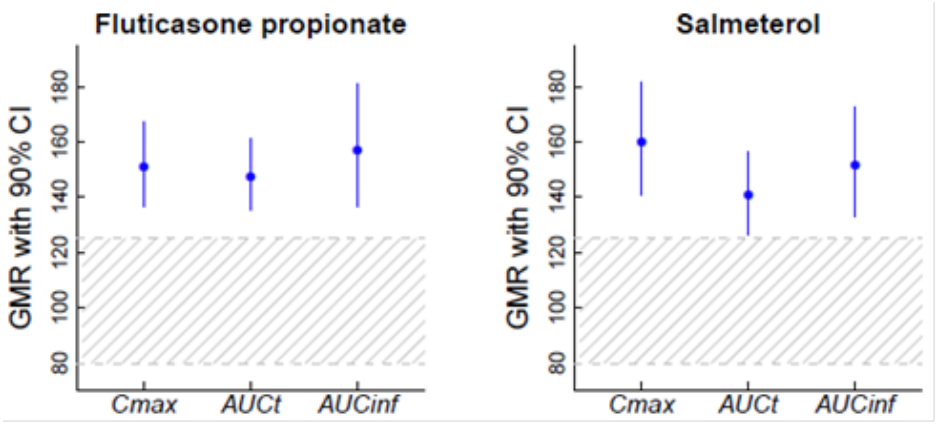

Figure 2. Advair Diskus 100/50 PK Bioequivalence Comparison Across Batches

Geometric mean ratios (GMRs) with associated 90% confidence intervals (CIs) for the comparison of two manufacturing batches of Advair Diskus 100/50. Twenty-four healthy adult male and female subjects were administered 100 mcg fluticasone propionate in combination with 50 mcg salmeterol by oral inhalation in a randomized crossover trial with seven-day washout between doses. PK blood samples were collected pre-dose and 3, 4, 5, 6, 8, 10, 15, 20, 30 and 45 minutes and 1, 2, 4, 8, 12, 16, 24, 32, 40, 48 and 56 hours after dosing. Concentrations of fluticasone propionate and salmeterol were determined by HPLC-MS/MS with a lower limit of quantitation of 1.00 pg/mL for both analytes. Shaded region indicates the bioequivalence zone of 80-125%.

Importantly, the research conducted by Sandoz shows that, for Advair Diskus 100/50, batch-to-batch PK variability is: (i) larger than is consistent with FDA's definition of bioequivalence, (ii) reproducible, and (iii) not isolated to the occasional outlying batch. The implications of this emerging knowledge on Advair Diskus performance cannot be ignored in ANDA PK bioequivalence comparisons for this RLD.

D. Fluticasone Propionate Absorption Kinetics Following Administration as Advair Diskus 100/50

The vast majority of the existing literature on fluticasone propionate PK following oral inhalation has focused on doses well above that of the Advair Diskus 100/50 RLD—typically 500 to 3,000 mcg—presumably in response to previous bioanalytical limitations.[25] Indeed, the

[25] *See generally* H. Möllmann, et al., *Pharmacokinetic and Pharmacodynamic Evaluation of Fluticasone Propionate After Inhaled Administration*, 53 Eur. J. Clinical Pharmacology 459 (1998) (Attachment H); R. Kunka, et al., *Dose Proportionality of Fluticasone Propionate from Hydrofluoroalkane Pressurized Petered Dose Inhalers (pMDIs) and Comparability with Chlorofluorocarbon pMDIs*, 94 Supp. B Respiratory Medicine S-10 (2000) (Attachment I); Lars Thorsson, et al., *Pharmacokinetics and Systemic Activity of Fluticasone Via Diskus® and pMDI, and of Budesonide via Thurbuhaler®*, 52 British J. Clinical Pharmacology 529 (2001) (Attachment J); Charles Brindley, et al., *Absorption Kintetics After Inhalation of Fluticasone Propionate via the Diskahler®, Diskus®, and Metered-Dose Inhaler in Healthy Volunteers*, 39 Supp. 1 Clinical Pharmacokinetics 1 (2000) (Attachment K); S. Kirby, et al., *Salmeterol and Fluticasone*

PK of 100 mcg fluticasone propionate and 50 mcg salmeterol from Advair Diskus 100/50 following a single dose to healthy subjects are not present in the literature, outside of the recent Sandoz publication.[26] As a consequence, the conventional assumption is that the time to maximum fluticasone propionate plasma concentration (T_{max}) following oral inhalation is approximately one hour, as has been consistently reported for the higher dose levels. GSK's own comments to FDA's draft bioequivalence guidance exemplify this common opinion, stating: "peak salmeterol plasma concentrations are achieved in approximately five minutes" and "peak plasma concentrations for fluticasone propionate, in contrast, are achieved in about one to two hours."[27]

However, Sandoz data confirm a much more rapid absorption of fluticasone propionate following administration as Advair Diskus 100/50. **Figure 3** illustrates plasma concentration-*vs*-time profiles for fluticasone propionate and salmeterol from 31 individual manufacturing batches across the three marketed strengths of Advair Diskus, where concentration values (y-axis) are normalized by the nominal dose (100 mcg, 250 mcg, or 500 mcg for fluticasone propionate; 50 mcg for salmeterol) to better visualize the kinetic comparison among the dose levels. While the 250/50 and 500/50 products yield a fluticasone propionate T_{max} of approximately 30 minutes to one hour, T_{max} of the 100/50 product is typically less than 10 minutes. The distribution of fluticasone propionate T_{max} values from individual Advair Diskus manufacturing batches is illustrated in **Figure 4**, showing an average T_{max} for the 100/50 product to be approximately 8 minutes. As expected, the shorter T_{max} values for Advair Diskus 100/50 relative to the higher dose levels correspond to a relatively higher maximum concentration. The early T_{max} (less than 10 minutes) of the 100 mcg fluticasone propionate dose from Advair Diskus 100/50 reported here is consistent with that recently reported by GSK.[28] These emerging data allow—and require—consideration of the more rapid absorption of the 100 mcg dose in bioequivalence study PK sampling schedules for the low-strength Advair Diskus RLD.

Propionate Given as a Combination: Lack of Systemic Pharmacodynamic and Pharmacokinetic Interactions, 56 European J. Clinical Pharmacology 781 (2001) (Attachment L).

[26] Elise Burmeister Getz, et al., *supra* note 23.

[27] GSK Comments Submitted to Docket No. FDA-2007-D-0369, at 7-8 (Nov. 12, 2013) (Attachment M).

[28] Rashmi Mehta, et al., *Comparison of the Pharmacokinetics of Salmeterol and Fluticasone Propionate 50/100 ug Delivered in Combination as a Dry Powder Via a Capsule-Based Inhaler and a Multi-Dose Inhaler*, 35 Clinical Drug Investigation 319, 322 (2015) (Attachment N).

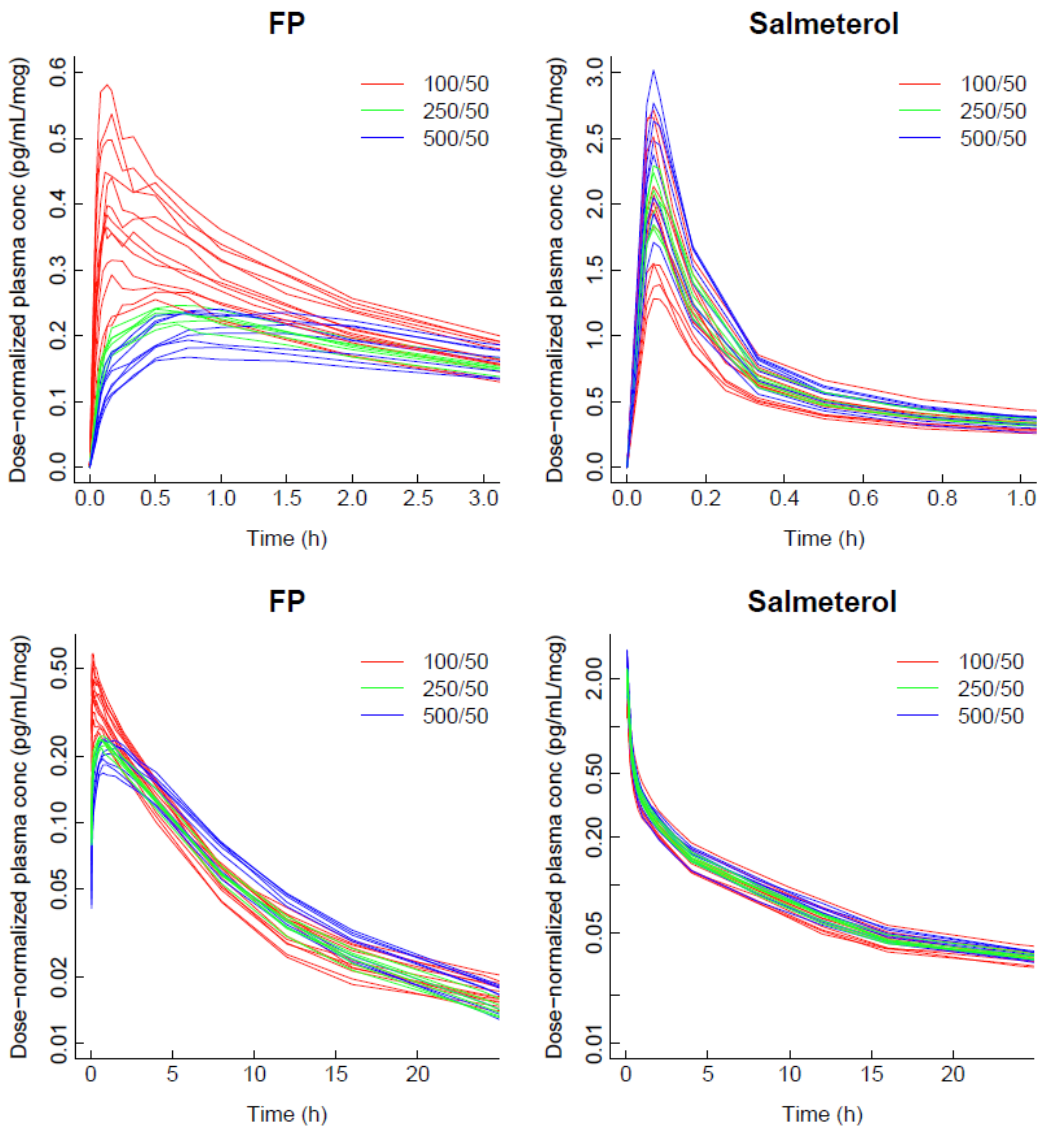

Figure 3. Plasma Concentration-*vs*-Time Profiles for Fluticasone Propionate (100, 250, and 500 mcg) and Salmeterol (50 mcg) Following Single-Dose Oral Inhalation from Advair Diskus to Healthy Adult Subjects

Top: linear scale. Bottom: semi-log scale. Fluticasone propionate (FP) dose was 100 mcg (red), 250 mcg (green), or 500 mcg (blue). In all cases, a single inhalation of the corresponding Advair Diskus strength was administered. The geometric mean concentration is shown at each nominal time point. Each profile represents a single Advair Diskus manufacturing batch.

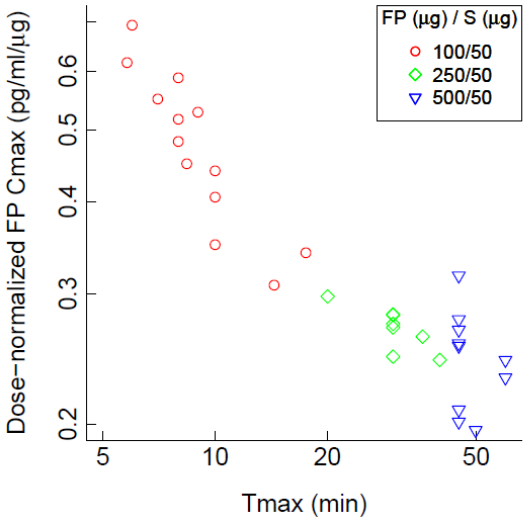

Figure 4. Fluticasone Propionate C_{max}/Dose Compared to T_{max} for Advair Diskus

A single inhalation of the indicated Advair Diskus strength was administered to healthy adult subjects. Each symbol represents the least-squares geometric mean C_{max} (on a log scale) versus the median T_{max} (also on a log scale) from a single Advair Diskus manufacturing batch.

The T_{max} of a dose from Advair Diskus 100/50 that exceeds the clinical recommendation (via multiple actuations per dose) may occur later than reported here for a single actuation. However, as discussed below, the PK of Advair Diskus 100/50 can be well characterized at the clinically recommended dose (i.e., following a single inhalation) using current bioanalytical technology. With a lower limit of quantitation ("LLOQ") of 1.00 pg/mL for both fluticasone propionate and salmeterol,[29] more than 90% of PK profiles allow determination of AUC extrapolated to infinite time (AUC_{inf}) following a single actuation of the Advair Diskus 100/50 product.

E. Requirements for Demonstrating PK Bioequivalence to the Advair Diskus 100/50 RLD

Sandoz's clinical data demonstrate that PK differences between marketed batches of Advair Diskus 100/50 exceed the definition of bioequivalence, and that the absorption rate of fluticasone propionate is rapid following inhalation of the low-strength 100 mcg product. Yet FDA's current bioequivalence recommendations include PK study design parameters that fail to account for these important properties of the RLD. As a result, PK bioequivalence studies based on the draft guidance and existing literature are at high risk of producing false bioequivalence conclusions. It is essential that ANDAs referencing the Advair Diskus 100/50 RLD address these issues in PK bioequivalence testing prior to approval.

At the same time, FDA must be careful not to permit approaches that overcome one issue while creating another. With respect to batch-to-batch variability, the estimated GMR and

[29] Covance, Inc., *Analytical Methods for Bioanalysis*, at 29 (2015) (Attachment O).

associated confidence interval in a conventional single-batch bioequivalence study design are highly susceptible to inaccuracy when Advair Diskus 100/50 is the Reference product. While the impact on the GMR might be alleviated by evidence that the selected batch of Test and Reference each represents the respective product average, a confidence interval derived without knowledge of batch-to-batch variability will *always* underestimate the standard error of the treatment difference and, hence, will *always* underestimate the true confidence interval width. Likewise, increasing the number of study subjects cannot address the Type I error rate inflation or inaccuracy of the GMR because the source of these errors is variability between batches, not variability between subjects. Utilization of multiple inhalations in a single-dose study may also desensitize the study by assessing bioequivalence at a dosage that exceeds the *approved* dosage (single inhalation), inconsistent with clinical practice, all without justification, since current analytical methods are adequate to characterize the PK profile following administration of the approved, marketed dose.

In light of these issues, Sandoz requests that FDA ensure that any PK bioequivalence studies relied upon for approval in ANDAs referencing the Advair Diskus 100/50 RLD are *generalizable across product batches*, consistent with FDA's standards for Type I error rate control, and are *sensitive to product differences in the rate of active ingredient absorption at the marketed dose*. In order to do this, as discussed further below, FDA should require PK bioequivalence studies to include a multiple-batch design, a single inhalation dosing regimen, and an early time point sampling regimen to address the unique variability and kinetic issues of the Advair Diskus 100/50 RLD. These study parameters are warranted to provide an accurate and sensitive PK bioequivalence comparison and, in turn, reliable ANDA approvals.

1. FDA Should 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

FDA's draft guidance on generic fluticasone propionate/salmeterol products proposes a two-way crossover study design for PK bioequivalence comparisons using a single batch each of the Test and Reference products. However, for generic versions of Advair Diskus 100/50, a PK bioequivalence study using a single RLD batch—either strategically selected or randomly chosen—could lead to an unrealized expansion in the variation of absolute systemic exposure beyond that which was designed into the conventional 80-125% bioequivalence limits. Ultimately, FDA may determine that the PK variability in the RLD justifies expansion of the 80-125% limits for generic versions of this product (so that the RLD-*vs*-RLD comparison no longer fails the PK bioequivalence test). However, to date, FDA has not publicly adopted this approach. Accordingly, FDA should ensure that PK testing with Advair Diskus 100/50 is performed in a way that accurately characterizes the results judged within the 80-125% standard.

When batches of an RLD are shown to be substantially different from one another—which, as discussed in Section C, has been reproducibly demonstrated for Advair Diskus 100/50—reliance on a conventional single-batch bioequivalence study design may misrepresent the true relationship between the Test and Reference products. Indeed, such a study design cannot provide an accurate estimate of the Test/Reference ratio (GMR) and associated confidence interval. Instead, the confidence interval constructed from such a study design,

although correct for the single specific batch of Test and Reference that happened to be selected for that particular study, is always incorrect with regard to the overall product comparison when there is true batch-to-batch variability. When batch-to-batch variability is present but ignored (by virtue of a study design that cannot estimate it), the standard error of the Test/Reference ratio is underestimated and the calculated confidence interval is artificially narrow, thus inflating the Type I error rate and increasing the risk of erroneous determinations of generic product equivalence. Analyses conducted by Sandoz and accepted for publication demonstrate that, for most two-way crossover bioequivalence study designs, Type I error rate will be inflated *to approximately 25%* when between-batch variability is nonzero.[30] This risk of a false bioequivalence conclusion is substantially higher than the 5% Type I error rate that FDA consistently deems to be the maximum acceptable limit.

When between-batch variability is nonzero, the additional variability widens the Test/Reference ratio distribution. In other words, the Test/Reference ratio can be expected to fluctuate more widely because the comparison will be influenced by measurement noise (which is already acknowledged by current statistical bioequivalence methods) as well as by the variation between individual batches of the product. This wider fluctuation gives rise to Test/Reference ratios that can be close to 100% *by chance alone*, when the actual product averages fall outside FDA's 80-125% limits. This issue arises when the confidence interval around the estimated Test/Reference ratio does not acknowledge the additional variability in the underlying distribution. In this scenario, an observed Test/Reference ratio near 100% can be incorrectly assumed to be associated with high confidence, when in fact the variability in the Test/Reference ratio leads to low confidence when it is based on a single batch of each product. The current FDA-recommended two-way crossover study design for PK bioequivalence cannot estimate between-batch variability and, therefore, assumes it to be zero. Inevitably, this too-narrow confidence interval overestimates confidence in the observed Test/Reference ratio estimate, allowing bioequivalence to be concluded in error.

As noted above, using clinically relevant variance estimates (error and between-batch variance estimates derived from Advair Diskus 100/50 PK data), the Type I error rate from the FDA-recommended two-way crossover design rises *to approximately 25%*. Thus, the conventional PK bioequivalence study design, in which a single batch of Test is compared to a single batch of Reference, is not appropriate when Advair Diskus 100/50 is the RLD. Instead, a correctly constructed confidence interval is one that incorporates estimates of both residual and between-batch variability through use of *multiple batches of each product*. Such a confidence interval will naturally be wider than the incorrect confidence interval of the two-way crossover design. Whereas drugs that have highly variable PK dispositional characteristics face bioequivalence power issues associated with *the number of PK observations* (i.e., the number of subjects tested), a bioequivalence assessment for products with high batch-to-batch variability faces bioequivalence power issues associated with *the number of product batches*. As always, it is the responsibility of the sponsor to ensure that the clinical trial is properly powered in light of all known sources of variability.

Here, in the presence of significant RLD variability, it is essential that a PK bioequivalence assessment include appropriate measures to address the observed variability,

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[30] Elise Burmeister Getz, et al., *supra* note 24.

such as multiple Test and Reference batches.[31] This approach protects against bioequivalence conclusions that are highly dependent on the particular Reference and Test batch selected for a given study, and ensures that the results are more generalizable and representative of the *actual* product characteristics. The approach also ensures correct estimations for the product averages and the standard error of the treatment difference. In other words, a multiple-batch study is necessary to correctly estimate the confidence interval around the GMR with 90% confidence. Indeed, Sandoz's research has demonstrated that this is the only manner in which the Type I error rate can be controlled at the requisite 5%. Ultimately, FDA policy and precedent supports the rejection of any ANDA PK bioequivalence study that fails to adequately control for Type I error inflation caused by the demonstrated batch-to-batch variability of the RLD, because Type I error rate inflation calls into question the safety and efficacy of the generic product. FDA and industry must be aligned in the effort to ensure that AB-rated generic products meet therapeutic equivalence expectations and, accordingly, should address batch-to-batch variability with a multiple-batch PK design in the context of the Advair Diskus 100/50 RLD.

2. 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

FDA's draft guidance for fluticasone propionate/salmeterol products provides that PK bioequivalence studies should be conducted with the "[m]inimum number of inhalations that is sufficient to characterize a PK profile by using a sensitive analytical method."[32] The objective of this requirement is to ensure that the bioequivalence assessment is performed in a manner consistent with clinical use (i.e., at a dose level that matches, to the extent possible, the dose level experienced by patients), which the Advair Diskus Prescribing Information describes as "1 inhalation twice daily."[33] The approved Medication Guide likewise instructs patients to: "Use 1 inhalation… 2 times each day… about 12 hours apart."[34] Thus, a patient's intended exposure to Advair Diskus is—without deviation—that following a *single inhalation*. In addition, the 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.

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[31] Sandoz notes that FDA's draft guidance already requires a minimum of 3 batches for in vitro testing, and reference scaling is permitted according to the variability of the combined dataset (i.e., the variability between Reference batches). The only reason not to implement a similar approach for PK testing is because of a concern that it will lead to too-large clinical studies, but this seems hardly relevant in light of the draft guidance's additional requirement for an 800+ patient clinical endpoint trial. Moreover, the concern for too-large clinical trials cannot serve as a basis for refusing to explore PK trial design options that can incorporate multiple batches without increasing the number of subjects beyond a reasonable level. The key may lie in the expansion of reference scaling methodology, as this would reduce study sizes in the between-batch variability context, just as it has for drugs with high dispositional variability.

[32] FDA, *Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate*, at 2.

[33] Advair Diskus Prescribing Information & Medication Guide, at 4.

[34] *Id.* at 57.

Current analytical methodologies provide a LLOQ of 1.00 pg/mL or less for fluticasone propionate and salmeterol with an acceptable volume per sample (6 mL).[35] This LLOQ is approximately 50-fold below the typical maximum observed concentration of fluticasone propionate (C_{max} ~50 pg/mL) and approximately 100-fold below that of salmeterol (C_{max} ~100 pg/mL). Analysis of Advair Diskus 100/50 PK data demonstrates that AUC_{inf} (the area under the concentration-*vs*-time curve extrapolated beyond the last quantifiable concentration (T_{last})) is less than 20% for approximately 90% of PK profiles following a single inhalation of the marketed dose (100 mcg fluticasone propionate, 50 mcg salmeterol), confirming that the PK profile can be adequately captured at the lowest marketed dose of the low-strength RLD product. Accordingly, at this LLOQ, a single inhalation of 100 mcg fluticasone propionate with 50 mcg salmeterol allows characterization of the PK profile as recommended by the FDA guidance.

As discussed above in Section D, since the 100 mcg product exhibits rapid absorption relative to higher doses, applicants must pay careful attention to dosing in PK comparisons using the low-strength Advair Diskus RLD. Ultimately, such dosing should replicate consumer use of the RLD product to ensure accurate bioequivalence conclusions. Given the adequacy of a single inhalation for PK characterizations, FDA should require a single inhalation study design for bioequivalence testing with Advair Diskus 100/50 absent adequate scientific justification that a bioequivalence conclusion based on results from a higher-than-clinically-recommended dose are relevant to the marketed dose level.

3. 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

Figures 3 and 4 illustrate that as the fluticasone propionate dose increases from 100 mcg to 250 mcg to 500 mcg, the T_{max} increases from approximately 8 minutes to 30 minutes to 45 minutes, respectively. A substantial portion of fluticasone propionate PK results following administration of Advair Diskus 100/50 show T_{max} only 3 minutes after a single inhalation. In turn, salmeterol T_{max} routinely occurs approximately 4 minutes after a single inhalation. As a result, the time to maximal concentration of both active ingredients in Advair Diskus 100/50 occurs very quickly after administration of the marketed dose. It is, therefore, critical that very early time points are 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.

Until recently, the PK properties of Advair Diskus 100/50 have not appeared in published literature. Indeed, as noted above, GSK's own comments to FDA's draft bioequivalence guidance, although reasonable for the highest strength of Advair Diskus (500/50), are highly inaccurate with regard to the kinetics of the low-strength Advair Diskus product. GSK's comments state that "peak salmeterol plasma concentrations are achieved in approximately five minutes" and "peak plasma concentrations for fluticasone propionate, in contrast, are achieved in

[35] Covance, Inc., *supra* note 29.

about one to two hours."[36] However, as noted above, 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.

If ANDA applicants rely on FDA's draft bioequivalence guidance and the published literature alone in shaping their sampling regimes, their PK bioequivalence results may fail to accurately capture the desired testing parameters. FDA has previously expressed particular concern for precise time point sampling, and has stated that "[f]ailure to include early (5-15 minute) sampling times leading to first time-point C_{max} values may result in FDA not considering the data for affected subjects from the analysis."[37] This level of concern should be heightened here, where the accurate time point for measurement after administration of the marketed dose is even sooner than the traditional "early" 5-15 minute threshold.

Accordingly, FDA should require that any ANDA bioequivalence study using Advair Diskus 100/50 as the RLD begin PK sampling for both active ingredients 3 minutes after a single inhalation and continue with intensive sampling through 10 minutes post-inhalation. Such a requirement can ensure the accuracy and specificity of bioequivalence conclusions based on these measurements.

F. Conclusion

Sandoz recognizes the substantial healthcare burden that exists in the United States due to the lack of generic options for the control and treatment of asthma. Sandoz is dedicated to conducting the scientific and clinical research necessary to identifying the appropriate pathway to approval of reliable generics in the OIDP space. While many generic drugs are highly predictable and pose little consumer risk with standard two-way crossover PK bioequivalence study designs, Sandoz's research has identified specific inadequacies with this approach when used in the context of the Advair Diskus 100/50 RLD. Fortunately, these inadequacies can be overcome through use of multiple batches in PK bioequivalence testing with a design and statistical methodology that incorporates RLD variability and rapid absorption kinetics into the determination of generic equivalence.

With the information outlined in this citizen petition, Sandoz seeks to inform FDA and the healthcare community that the current fluticasone propionate/salmeterol bioequivalence recommendations do not adequately address the distinct and unique PK properties associated with the Advair Diskus 100/50 RLD. Sandoz identified the emerging concerns described above during its own development program, and these issues could result in patient-relevant and recognizable differences among AB-rated generics. It is, therefore, critical that FDA address these PK bioequivalence concerns prior to approving any generic products for the treatment of asthma patients.

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[36] GSK, *supra* note 27.

[37] FDA, *Draft Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*, at 13 (Dec. 2013).

As with all OIDPs, FDA must aim to approve high quality products that satisfy not only the need for public access, but also public confidence. Accordingly, Sandoz requests that FDA require all ANDAs referencing the Advair Diskus 100/50 RLD to ensure that Type I error rate is adequately controlled in bioequivalence testing, that the dose used in such testing retains adequate sensitivity to product differences existing at the marketed dose of the RLD, and that the sampling schedule in such testing is centered around the actual time to maximum concentration of both active ingredients when administered at the marketed dose. To satisfy these essential bioequivalence criteria, ANDAs should include a thorough evaluation of the batch-to-batch variability of the reference product in relation to the ANDA candidate, as well as a PK assessment that is based on multiple batches of the RLD; a single inhalation dosing regimen, as identified in the current product labeling and simulated in patient experience; and very early (3-10 minutes) sampling time points that adequately capture and evaluate the time to maximum concentration of both active ingredients at the marketed dose. For ANDAs referencing Advair Diskus 100/50 as the RLD, these study parameters ensure the continued reliability of AB-rated generic drugs and uphold the promise that such drugs will be safe and effective.

Sandoz notes that the FDA bioequivalence standard and methodology for highly variable drugs and certain modified-release drugs were achieved neither quickly nor in the absence of data, but instead through the thoughtful search for statistical and clinical approaches which incorporated quality-forward decision making. Similarly, Sandoz has proposed solutions that, based on the available data, present an adoptable means to addressing the PK bioequivalence issues associated with Advair Diskus 100/50. Sandoz requests that the agency recognize the need for further scrutiny in the PK bioequivalence comparison before approving generic versions of this RLD.

III. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to a categorical exclusion pursuant to 21 C.F.R. § 25.31(a).

IV. ECONOMIC IMPACT

Sandoz will submit economic impact information if requested by the Commissioner following review of the petition pursuant to 21 C.F.R. § 10.30(b).

V. CERTIFICATION

Pursuant to 21 C.F.R. § 10.30(b), the undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Pursuant to Section 505(q)(1)(H) of the FDCA, 21 U.S.C. § 355(q)(1)(H), I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action

requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: April 5, 2012 (PK study results demonstrating early peak plasma concentration of fluticasone propionate in Advair Diskus 100/50); September 10, 2013 (publication of draft bioequivalence guidance for generic versions of Advair Diskus); December 23, 2013 (PK study results demonstrating batch-to-batch variability of Advair Diskus 100/50); February 19, 2016 (information that an ANDA referencing Advair Diskus as the RLD had been accepted for filing by FDA). 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 organizations: Sandoz Inc. 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,

Anthony Maffia
Vice President, Regulatory Affairs
Sandoz Inc.

Maffia III Antho ny

Digitally signed by Maffia III Anthony
DN: SERIALNUMBER=1838378 + CN=Maffia III Anthony, OU=GX, OU=people, DC=novartis, DC=com
Reason: I am approving this document.
Date: 2016.10.13 10:20:42 --4:00

Attachments

Attachment A — Günther Hochhaus, et al., *Generics for Oral Inhaled Drugs: Knowledge Gaps for Streamlining Bioequivalence Approval*, Presentation at the FDA Generic Drug User Fee Amendments of 2012 Regulatory Science Initiatives Part 15 Public Hearing (June 21, 2013)

Attachment B — Robert Lionberger, *Interpreting Pharmacokinetics for Inhalation Bioequivalence*, Presentation at the International Pharmaceutical Aerosol Consortium on Regulatory Science / University of Florida Orlando Inhalation Conference (Mar. 19, 2014)

Attachment C — Advair Diskus Prescribing Information & Medication Guide (Rev. Apr. 2016)

Attachment D — Donald J. Schuirmann, *A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability*, 15 J. Pharmacokinetics & Biopharmaceutics 657 (1987)

Attachment E — Günther Hochhaus, et al., *Meeting Report: Pharmacokinetics of Orally Inhaled Drug Products*, 17 Am. Ass'n of Pharmaceutical Scientists J. 769, 773 (2015)

Attachment F — FDA, *Background for Advisory Committee for Pharmaceutical Science: Concept and Criteria of BioINequivalence* (Oct. 20, 2004)

Attachment G — Elise Burmeister Getz, et al., *Batch-to-Batch Pharmacokinetic Variability Confounds Current Bioequivalence Regulations: A Dry Powder Inhaler Randomized Clinical Trial*, Clinical Pharmacology & Therapeutics (Advance Online Publication 2016)

Attachment H — H. Möllmann, et al., *Pharmacokinetic and Pharmacodynamic Evaluation of Fluticasone Propionate After Inhaled Administration*, 53 European J. Clinical Pharmacology 459 (1998)

Attachment I — R. Kunka, et al., *Dose Proportionality of Fluticasone Propionate from Hydrofluoroalkane Pressurized Petered Dose Inhalers (pMDIs) and Comparability with Chlorofluorocarbon pMDIs*, 94 Supp. B Respiratory Medicine S-10 (2000)

Attachment J — Lars Thorsson, et al., *Pharmacokinetics and Systemic Activity of Fluticasone Via Diskus® and pMDI, and of Budesonide via Thurbuhaler®*, 52 British J. Clinical Pharmacology 529 (2001)

Attachment K — Charles Brindley, et al., *Absorption Kintetics After Inhalation of Fluticasone Propionate via the Diskahler®, Diskus®, and Metered-Dose Inhaler in Healthy Volunteers*, 39 Supp. 1 Clinical Pharmacokinetics 1 (2000)

Attachment L — S. Kirby, et al., *Salmeterol and Fluticasone Propionate Given as a Combination: Lack of Systemic Pharmacodynamic and Pharmacokinetic Interactions,* 56 European J. Clinical Pharmacology 781 (2001)

Attachment M — GSK, Comments Submitted to Docket No. FDA-2007-D-0369 (Nov. 12, 2013)

Attachment N — Rashmi Mehta, et al., *Comparison of the Pharmacokinetics of Salmeterol and Fluticasone Propionate 50/100 ug Delivered in Combination as a Dry Powder Via a Capsule-Based Inhaler and a Multi-Dose Inhaler*, 35 Clinical Drug Investigation 319 (2015)

Attachment O — Covance, Inc., *Analytical Methods for Bioanalysis* (2015)