



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Frederick H. Branding
McGuireWoods LLP
77 West Wacker Drive
Suite 4100
Chicago, IL 60601-1815

FEB 22 2006

C. Elaine Jones, Ph.D.
Vice President, US Regulatory Affairs
William M. Zoffer
Vice President, Assistant General Counsel
GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Charles J. Raubicheck
Frommer Lawrence & Haug, LLP
745 Fifth Avenue
New York, NY 10151

Re: Docket Nos. 2004P-0206/CP1; 2004P-0239/CP1, SUP 1, SUP 2 & PSA 1; 2004P-0348/CP1 & SUP 1; and 2004P-0523/CP1 & PSA1

Dear Petitioners:

This letter is a consolidated response to multiple citizen petitions submitted to the Food and Drug Administration (FDA) concerning review and approval standards for abbreviated new drug applications (ANDAs) for fluticasone propionate nasal spray suspension products. This letter responds to the following petitions.

- Bell, Boyd & Lloyd, LLC (Bell) submitted petition 2004P-0206/CP1 dated May 1, 2004 (Bell Petition).
- GlaxoSmithKline (GSK) submitted petition 2004P-0239/CP1 dated May 19, 2004, that includes comments on Bell's Petition (GSK May Petition).¹ GSK submitted a

¹ GSK submitted a supplement dated January 6, 2005, to its May Petition (2004P-0239/SUP1) requesting that FDA refrain from approving any ANDAs for beclomethasone dipropionate nasal spray product until final guidance establishing a bioequivalence methodology for nasal spray products has been issued. GSK summarily concludes, without further explanation, that the arguments advanced in support of its petition on fluticasone propionate are applicable to any ANDAs for beclomethasone dipropionate (Beconase). As explained in section III.A of this response, neither the Federal Food, Drug, and Cosmetic Act (the Act) nor FDA regulations require the Agency to publish a final guidance before approving any ANDAs for such products. Based on our current knowledge, FDA has no reason to believe that the same approach used to review ANDAs for fluticasone propionate products could not be used to review ANDAs for beclomethasone dipropionate products. Therefore, this request is denied.

supplement dated June 16, 2005, to its petition (2004P-0239/SUP2) (GSK Second Supplement).

- Frommer Lawrence & Haug, LLP (Frommer) submitted petition 2004P-0348/CP1 dated July 26, 2004, that includes comments on the first two petitions referenced above (Frommer Petition).²
- GSK submitted petition 2004P-0523/CP1 dated November 23, 2004 (GSK November Petition).
- GSK submitted a combined petition for stay of action 2004P-0239/PSA1 and 2004P-0523/PSA1 dated March 25, 2005 (GSK PSA).

In their petitions, Bell and Frommer request that FDA:

- Receive for substantive review and make the determination that an ANDA seeking approval of fluticasone propionate nasal spray suspensions be granted final approval, provided such an ANDA contains successful results of bioavailability and bioequivalence studies conducted under the methodologies set forth in FDA's draft guidance entitled *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, April 2003 (2003 draft BA/BE guidance).

In its May petition, GSK requests that FDA:

- Issue a final and complete guidance document setting forth a scientifically valid methodology for determining bioequivalence for nasal spray products, including resolution of outstanding technical issues with respect to bioequivalence methodology, including:
 - (1) *a priori* derived statistical criteria for analyzing in vitro and in vivo comparisons between a proposed generic³ product and the reference listed drug (RLD),
 - (2) direction to conduct in vivo clinical studies in “the most difficult to treat” indication for each related group of indications,

² Frommer submitted a supplement dated May 13, 2005, to its petition (2004P-0239/SUP1) to emphasize that in vivo studies that have demonstrated bioequivalence to the listed drug using the maximum labeled dose should be approved without awaiting finalization of guidance and to assert that use of the maximum labeled dose should be mandatory. As discussed in section II.A.3 (including n. 21) of this response, while we have not mandated its use, we recommend use of the maximum labeled dose for study purposes.

³ The term *generic* is used in this response to refer to drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act.

- (3) direction to assess systemic exposure by pharmacokinetic studies as the preferred method, and clear and appropriate standards for sampling times when conducting such studies, and
 - (4) certain criteria, including complete statistical standards for establishing device equivalence.
- Refrain from approving any ANDAs for fluticasone propionate nasal spray until the guidance development process, including sufficient opportunity for public review and comment on the 2003 draft BA/BE guidance, has been completed and a final guidance has been issued. GSK also notes that nasal suspension formulations pose heightened bioequivalence challenges.

In its November petition, GSK requests that FDA:

- Refrain from approving any ANDAs for fluticasone propionate nasal spray unless the proposed generic product is shown to meet the same standards of product quality (i.e., specifications for droplet size distribution and spray pattern) and consistency (i.e., low variability) as those approved for Flonase in October 2004 (supplement S-019 to NDA 20-121).

In its Second Supplement, GSK reasserts its request that:

- FDA complete the guidance process based on GSK's review of FDA documents that support approved generic nasal *solution* products. In an attached declaration from a GSK statistician (Declaration), GSK challenges the statistical methods used to analyze the results of comparative in vitro tests in the bioequivalence reviews.

For the reasons that follow, the petitions submitted by GSK are denied and the petitions submitted by Bell and Frommer are denied in part.⁴

I. BACKGROUND

Flonase is a nasal spray product used to treat the nasal symptoms of both allergic and non-allergic rhinitis. Its active ingredient is the corticosteroid, fluticasone propionate. Flonase consists of an aqueous suspension of microfine fluticasone propionate intended

⁴ Bell's and Frommer's petitions are denied in so far as they suggest that FDA *must* approve any ANDA that successfully demonstrates bioequivalence using recommended methodologies. FDA may have other reasons for denying an ANDA final approval. FDA also disagrees with Frommer's and Bell's argument that in vitro tests must be evaluated using a geometric mean methodology (see section II.A.1.c of this response). In addition, FDA disagrees with Frommer's claim regarding whether or not a specific test is essential to demonstrate safety (see discussion regarding hypothalamic-pituitary-adrenal axis suppression studies in section II.A.3 of this response). Finally, as discussed in n. 2, FDA disagrees with Bell's and Frommer's petitions to the extent that they request FDA make mandatory the recommendations in the 2003 draft BA/BE guidance.

for topical administration to the nasal mucosa through a metered atomized spray pump; therefore, Flonase is classified as a nasal spray suspension. FDA approved GSK's new drug application (NDA) for Flonase (NDA 20-121) in 1994 and subsequently approved several supplements to the NDA to, among other things, add new labeling information, including new indications for use. The performance of a nasal spray product is determined by the formulation (both active and inactive ingredients) and the spray device. Usually the device is made up of a container, a pump, and an actuator.

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the Act). In addition, an ANDA must contain, with certain exceptions not relevant here, information to show that the proposed drug has the same active ingredient(s), indications for use, route of administration, dosage form, strength, and labeling as the RLD (sections 505(j)(2)(A) and (j)(4) of the Act). The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that contain identical amounts of the same active ingredient(s) in the same route of administration and dosage form, meet applicable standards of strength, quality, purity and identity, are manufactured in compliance with current good manufacturing practices regulations, and are adequately labeled, are therapeutically equivalent, and may be substituted for each other.

II. DISCUSSION OF SCIENTIFIC STANDARDS

Bell and Frommer petition FDA to review and approve, while GSK petitions FDA to refrain from approving, any new or pending ANDAs for fluticasone propionate nasal spray that demonstrate successful results of bioavailability and bioequivalence studies conducted under the methodologies set forth in FDA's 2003 draft BA/BE guidance.

A. Bioequivalence Methodology

The Act generally requires an ANDA applicant to provide, among other things, information to show that the generic drug is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the Act). Section 505(j)(8)(B) of the Act provides that a generic drug shall be considered to be bioequivalent to the RLD if:

- (i) 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.

Further, section 505(j)(8)(C) of the Act provides:

For 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.

FDA's statutory duty to evaluate generic drugs for approval requires the Agency to use its scientific judgment when analyzing bioequivalence data to determine whether there is a "significant difference" in the rate and extent of absorption of the drug. FDA regulations establish the general parameters, requirements, and appropriate evidence for the design of bioequivalence studies (e.g., 21 CFR 320.24 and 320.26). The courts have expressly upheld FDA's regulatory implementation of the Act's bioequivalence requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 397-400 (3d Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994)).

Nasal spray drug products deliver the active ingredient topically, directly to the site of action (nasal cavity). The drug is then absorbed and becomes available to the nasal sites of action before reaching the systemic circulation. While the nasal spray product has the potential to produce systemic activity, blood (plasma) levels do not in general reflect the amount of drug reaching the nasal cavity only. Therefore, the preferred method for determining bioequivalence, i.e., comparing concentrations of the active ingredient in the blood, is generally not appropriate by itself. FDA has spent many years developing appropriate scientifically valid methods that are able to demonstrate bioequivalence in both local delivery and systemic exposure for this class of products.

FDA's recommended approach to establish bioequivalence for locally acting nasal suspension spray drug products relies on (1) qualitative and quantitative sameness of formulation of test and reference products, (2) comparability in container and closure systems, and (3) in vitro and in vivo methods that demonstrate equivalent product performance (2003 draft BA/BE guidance at 5). More specifically, FDA's general approach for establishing equivalent product performance includes:

- Equivalent device performance with regard to the amount of drug per actuation, droplet size distribution, and plume shape
- Equivalent local delivery of active ingredient
- Equivalent systemic exposure to the active ingredient

Because it is very difficult to evaluate local delivery directly, FDA concludes equivalent local delivery for nasal suspension spray products when two products demonstrate equivalent effectiveness in a comparative in vivo clinical trial of test and reference products and equivalent in vitro performance measures of test spray devices. Because the clinical studies alone may not be sensitive enough to detect small differences in product performance, FDA relies on demonstrations of equivalence in both the clinical study and device performance. For fluticasone propionate nasal spray, systemic exposure to the active ingredient has known risks, so FDA also evaluates in vivo pharmacokinetic studies to ensure that there is not a significant difference between test and reference products

with respect to systemic exposure. Products that demonstrate equivalence in all of the in vitro and in vivo equivalence tests requested of ANDA applicants are deemed equivalent.

FDA developed this approach through a process that involved many Agency committee meetings, advisory committee input, public meetings, “technical papers,” the publication of draft guidances in 1999 and 2003, and receipt and review of comments on the draft guidances.⁵ As discussed in section III.A of this response, FDA draft guidances are made public to provide the Agency’s current thinking on a topic and to solicit public comment. Guidance documents do not restrict FDA’s ability to consider methodologies other than those articulated, nor do they restrict or replace the Agency’s obligation to make a determination as to whether individual applications meet statutory requirements.⁶

1. *Statistical Criteria*

The 2003 draft BA/BE guidance did not specify certain aspects of the statistical criteria for determining when in vivo and in vitro tests demonstrate equivalence. GSK requests that FDA finalize *a priori* derived statistical criteria for analyzing in vitro and in vivo comparisons between a proposed generic product and an approved RLD (GSK May Petition at 9-10). To this end, GSK states that it is “crucial” for the Agency to publish statistical appendices in draft form (for comment), and refrain from reviewing any data submitted by ANDA applicants until completion of the guidance development process (Id.).

As discussed below, it is not necessary for the Agency to issue a final version of the 2003 draft BA/BE guidance (including statistical appendices) before approving ANDAs for fluticasone propionate nasal spray products. For example, although it is desirable for the statistical analysis and acceptance intervals to be defined in advance of studies, occasionally because of the lack of data on the variability and precision of particular studies, it is not possible to define certain criteria in advance of analysis of the data from actual bioequivalence studies. Under such circumstances, FDA considers and analyzes submitted data in order to define and specify the appropriate statistical standard.⁷ The

⁵ Draft guidance entitled *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, June 1999 (1999 draft BA/BE guidance), 2003 draft BA/BE guidance, and comments (FDA docket 99D-1738); November 1999, April 2000, November 2000, and July 2001 meetings of the Orally Inhaled and Nasal Drug Products (OINDP) Subcommittee of the Advisory Committee for Pharmaceutical Science (ACPS) (<http://www.fda.gov/ohrms/dockets/ac/cder00.htm#Pharmaceutical%20Science>), including technical reports (http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_reports.htm).

⁶ See generally 21 CFR 10.115(d).

⁷ It is not unusual for FDA to evaluate submitted studies without *a priori* derived statistical criteria. Most clinical bioequivalence studies entail product-specific study designs and are conducted without guidance on statistical criteria published by the Agency; in such cases, FDA bases the details of statistical review on the data. Other examples of non-oral dosage form studies for which FDA determined details of statistical analyses based on data submitted include, but are not limited to: certain skin irritation, sensitization, and adhesion studies and certain studies submitted for approval of generic acne products.

ANDA approval process ensures that approved generic fluticasone propionate nasal products meet applicable statutory and regulatory requirements.

a. In Vivo Bioequivalence Studies Assessing Local Delivery

FDA recommends appropriate in vivo bioequivalence study design, clinical endpoints, and inclusion criteria (2003 draft BA/BE guidance at 21-25) for equivalence comparison of local delivery of test and reference nasal aerosol and spray products. The draft guidance recommends:

- traditional treatment study (i.e., randomized, double blind, placebo-controlled, parallel group) in which test and reference products are assessed for a two-week duration, preceded by a seven-day placebo run-in period to establish a baseline and identify placebo responders
- equivalence and efficacy analyses with the clinical endpoint based on total nasal symptom score (TNSS) (a composite score of patient self-rated symptoms), expressed as a mean change from baseline of the TNSS

Bell and Frommer recommend that FDA require “statistical equivalence criteria (90% confidence interval) for the specified endpoints... within the acceptable bioequivalence limits. The bioequivalence limits for the 90% confidence interval for the test/reference ratio of the change from baseline in the untransformed^[8] TNSS should be within 80% to 125%” (Frommer Petition at 4, Bell Petition at 3). In addition, Bell and Frommer recommend that “both the test and reference products should be superior to placebo ($p < 0.05$) to demonstrate that the study is sensitive enough to show potential differences between products, if they exist” (Frommer Petition at 4, Bell Petition at 3).

FDA considers two fluticasone propionate nasal spray products equivalent in local delivery when the 90 percent confidence interval for the point estimate (mean ratio between test and reference products for the change in TNSS relative to baseline) is within an 80 to 125 percent acceptance interval. The acceptance interval (also referred to as acceptance limits) is expressed as two numbers that provide upper and lower limits on the confidence interval. The acceptance interval is a fixed standard, while the confidence interval is determined from the data in the particular study. If the confidence interval is contained within this acceptance interval, the Agency concludes that the study demonstrates equivalence.

FDA determined that this acceptance interval is appropriate for fluticasone propionate nasal spray products based on an assessment as to whether comparisons between two reference products would meet the standard.⁹ FDA determined the baseline value for its

⁸ Because the clinical endpoint for bioequivalence studies of local delivery is not a pharmacokinetic parameter, the data were not log transformed.

⁹ Bioequivalence studies are not only performed as part of the ANDA process, but also conducted by innovators to confirm equivalence between formulations. The bioequivalence studies that generic

analysis based on a scientific assessment of the data submitted in the ANDAs. We could not determine this baseline value, however, until there was sufficient data to define a bioequivalence comparison. Finally, FDA compares the test and reference products against placebo.

b. In Vivo Bioequivalence Studies Assessing Systemic Exposure

In addition to a comparative clinical study for local delivery, FDA recommends the use of standard pharmacokinetic bioequivalence studies to compare test and reference nasal aerosol and spray products (2003 draft BA/BE guidance at 25-27). More specifically, the guidance recommends, among other things, measurement of the area under the plasma concentration vs. time curve (AUC) calculated to the last measured concentration time (AUC_{0-t}), which represents a measure of total exposure and the peak exposure or maximum drug concentration (C_{max}) (Id. at 27).

FDA generally considers two products to be bioequivalent when the 90 percent confidence intervals for the ratios of the pharmacokinetic parameters (AUC and C_{max}) are entirely within an 80 to 125 percent acceptance interval. The 80 to 125 percent acceptance interval is a scientific judgment about the best statistical practices to use in bioequivalence determinations and reflects decades of scientific data on the variability of product characteristics within and between batches, as well as biological variability in patients. Because the mean of the study data lies in the center of the 90 percent confidence interval, the mean of the data is usually close to 100 percent (a test/reference ratio of 1).¹⁰

Although the 2003 draft BA/BE guidance does not describe in detail these statistical criteria, by virtue of applying, and incorporating by reference, its general acceptance limit (80 to 125 percent) to the in vivo bioequivalence studies, FDA is applying its standard statistical criteria for in vivo bioequivalence determinations.¹¹

We conclude from the in vivo bioequivalence studies that the variability in pharmacokinetic values within this acceptance interval is not expected to adversely affect clinical outcomes because this variability is within the range of differences that can already arise due to other product specific and biological factors.¹² Further, based on currently available, relevant information, and our experience and expertise, we conclude

companies conduct to support an ANDA are the same as the bioequivalence studies that innovator companies submit to an NDA to support formulation or manufacturing changes.

¹⁰ Guidance for industry on *Statistical Approaches to Establishing Bioequivalence*, January 2001; *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), 24th Ed., at ix.

¹¹ FDA clarified in the 2003 draft BA/BE guidance at 3 that “[t]his guidance should be used with other, more general CMC and BA and BE guidances available from CDER.”

¹² Dighe, S.V., and W.P. Adams, “Bioequivalence: A United States Regulatory Perspective,” in *Pharmaceutical Bioequivalence* (P.G. Welling et al., eds.), 1991, pp. 347-380.

that this approach is appropriate for reviewing ANDAs for fluticasone propionate nasal spray suspension products.

c. In Vitro Studies

FDA identifies six measurable properties for use in comparing the device performance of two nasal spray (including suspension) products¹³ (2003 draft BA/BE guidance at 10-21 and Table 1):

- Single actuation content through container life
- Droplet size distribution by laser diffraction
- Drugs in small particles/droplets, or particle/droplets size distribution by cascade impactor
- Spray pattern
- Plume geometry
- Priming and repriming

Frommer states (and Bell similarly maintains) that it “is essential that these in vitro tests are evaluated on the basis of point estimates (90%-111%), the comparative variability (range) of the test and reference product” (Frommer Petition at 3, Bell Petition at 2).

Frommer and Bell describe the *geometric mean* method, in which review of in vitro studies on nasal spray products is based on reviewers’ examination of the comparative variability of the data between test and reference products and the ratios of geometric means of the test and reference products falling between 90 and 111 percent.¹⁴

Based on our experience and expertise, we have concluded that the *Population Bioequivalence* (PBE) method is appropriate for reviewing ANDAs for fluticasone propionate nasal spray suspension products. A description of the PBE method for evaluation of comparative in vitro performance studies on aerosols and nasal spray products, using a confidence interval approach was included in the information reposted in April 2003 entitled, *Statistical Information from the June 1999 Draft Guidance* and the *Statistical Information for In Vitro Bioequivalence Data* (originally posted in August 1999) (<http://www.fda.gov/cder/guidance/5383stats.pdf>).

Under the PBE method, for each comparative in vitro test described in the 2003 draft BA/BE guidance, FDA calculated a 95 percent confidence interval as a measure of equivalence between the test and reference products that includes the ratio of the

¹³ Note that statistical acceptance criteria are not applied to the Drug Particle Size Distribution by Microscopy Measurement because these data are not used for comparative bioequivalence evaluations (2003 draft BA/BE guidance at 17).

¹⁴ This criterion was indicated as the average bioequivalence limit in the information reposted in April 2003 entitled, *Statistical Information from the June 1999 Draft Guidance* (<http://www.fda.gov/cder/guidance/5383stats.pdf>).

geometric means of the two products and the difference in variability between test and reference products.¹⁵ The confidence interval is compared to an acceptance limit that is based on fixed statistical parameters (i.e., the regulatory constants, Sigma_{T0} and Epsilon (see n. 16 of this response)) and takes into consideration the observed within-study variability of the test and reference products. Inherent in the PBE method is the principle that the acceptance limits for the confidence interval depend on the relative variability of the test and reference products observed in the study. In the case of low variability data for the reference product, the acceptance limits narrow toward the 90-111 percent criteria used in the geometric mean method, enabling only test products with comparable variability to meet the criteria. Conversely, in the case of high variability data for the reference product, the acceptance limits might be slightly wider.¹⁶ This permits approval of generic products that are comparably or less variable than the reference product (even if the ratio of the geometric means falls slightly outside of the 90-111 criteria) and guards against approval of generic products that are more variable than the reference product (even if the ratio of the geometric means falls within the 90-111 percent criteria).

We disagree with Frommer's and Bell's statement that it is essential to use the geometric mean method to review fluticasone propionate nasal spray suspension products. FDA has determined that the PBE method is appropriate for determinations of bioequivalence for fluticasone propionate nasal spray suspension products.¹⁷ By using a confidence interval that incorporates sample size, fixed statistical parameters, and variability of the observed test and reference products into the analysis, rather than relying on an individual reviewer's examination of the comparative variability, the PBE method provides greater consistency in in vitro bioequivalence evaluations for ANDAs for generic fluticasone propionate nasal spray suspensions.

In its Second Supplement, GSK submits a declaration from a GSK-employed statistician. The declaration summarily reviews publicly available in vitro study data from FDA

¹⁵ Although the 2003 draft BA/BE guidance refers to use of the geometric mean method for a couple of the in vitro tests (e.g., discussion of plume geometry, at 20), based on the Agency's experience and expertise FDA currently recommends the PBE method for evaluation of all comparative in vitro study data for fluticasone propionate nasal spray products. In the analysis of the cascade impactor data for nasal spray products, any test to reference ratio of less than or equal to the upper PBE limit is acceptable. As explained in the 2003 draft BA/BE guidance at 15, the test is designed to ensure that the amount of small particles is less than or equivalent to the reference product.

¹⁶ The regulatory constant Sigma_{T0} represents the scaling variance (Sigma_{T0}^2), which determines the value at which the acceptance limits are scaled to the within-study variability of the reference product. When the reference product variance is greater than the scaling variance, the acceptance limits are widened. When the reference product variance is less than the scaling variance, the acceptance limits are held constant. Epsilon represents the variance offset term, which allows for some differences that may be inconsequential between the total variances of the test and reference products.

¹⁷ It is important to note, however, that the geometric mean method is also conventional statistical practice within government and industry and is an appropriate method of statistical analysis when the assay variability is expected to be low, as may be the case with the approved nasal spray *solution* products. Under the PBE method, when there is low variability for the reference product, the acceptance criteria narrow toward the 90-111 percent acceptance limits used under the geometric mean method.

bioequivalence reviews of some approved generic nasal *solution* products based on the geometric mean method and concludes that the FDA reviewers did not apply statistical methods and criteria that are clear and consistent and that are aligned with conventional equivalence standards (GSK Second Supplement at 2).¹⁸

GSK's arguments against use of the geometric mean method are not relevant to the fluticasone propionate nasal spray suspension products evaluated under the PBE method; therefore, although we disagree with these arguments, we will not respond to them in this response. However, we will respond to one of GSK's arguments because it reflects a misunderstanding of FDA's bioequivalence testing in general. GSK argues that FDA ignored statistically significant differences between products, referring to examples in the Declaration at 12-15.

When we review the data from in vitro bioequivalence studies, we seek to detect whether there is a significant difference in in vitro performance between the test and reference product, not a significant difference in a statistical sense. For example, GSK criticizes FDA for dismissing a relative difference between test and reference product "as being only 1.7 %," a difference that was found to be a statistically significant based on the "p value" (Declaration at 13). However, there is no evidence that a difference of 1.7 percent would have any clinical consequence. In fact, our current standards (applicable to both ANDAs and NDAs) for spray content uniformity permit much greater spray-to-spray differences within the reference product.¹⁹

2. *Patient Population in Which the Test and Reference Products Are Studied*

We recommend that clinical bioequivalence studies be performed in patients with seasonal allergic rhinitis (SAR) and a finding of bioequivalence may extend to all labeled indications for locally acting nasal corticosteroids (2003 draft BA/BE guidance at 23). GSK requests that the Agency require applicants to perform clinical bioequivalence studies in patients with perennial allergic rhinitis (PAR) and perennial non-allergic rhinitis (PNAR), instead of only SAR (GSK May Petition at 11-13). GSK argues that bioequivalence testing on the "most difficult to treat" indication is a matter of sound science and FDA policy (Id.).

While FDA often recommends bioequivalence testing in the more difficult to treat indication because it often results in a more efficient study design (i.e., demonstrating equivalence to reference and superiority to placebo), this is not always the case. FDA

¹⁸ GSK notes that its reviews were of nasal *solution* products, whereas Flonase is a *suspension*, which poses "even greater bioequivalence challenges than products formulated as solutions" (GSK Second Supplement at 1). FDA agrees that nasal suspensions pose additional challenges; therefore, we recommend in vivo tests with suspensions.

¹⁹ The mean amount of active ingredient per determination is expected to be within 85 to 115 percent of label claim (see page 13 of the guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation*, July 2002 (2002 CMC guidance)).

disagrees that the “most difficult to treat” indication is always preferred for bioequivalence testing. A more difficult to treat indication does not necessarily lead to a more sensitive bioequivalence test. The choice of endpoint for a bioequivalence study should be one that is an appropriate test of formulation performance. If two endpoints are both acceptable choices for a bioequivalence test (as is the case for SAR and PAR), FDA does not believe that the difficulty of treatment of the indication provides a reason to choose one indication over the other. SAR has advantages over PAR (e.g., easier recruitment of subjects, shorter study duration, PAR patients are also prone to SAR). FDA consistently has stated that SAR is an appropriate endpoint for in vivo bioequivalence studies for nasal spray products and published its position in multiple draft guidances.²⁰ In the case of fluticasone propionate nasal spray suspensions, FDA has determined that a study in SAR is appropriate to determine bioequivalence generally for the product category because of the very close similarity between the two indications. For example, FDA has stated:

The pathophysiology of SAR and PAR are very similar in terms of the chemical mediators produced and end-organ manifestations, with differences between the two entities primarily based on the causes and duration of the disease. . . . [T]he same groups of chemical mediators appear to be regulators of the responses in seasonal and perennial allergic rhinitis.

(FDA draft guidance, *Allergic Rhinitis: Clinical Development Programs for Drug Products*, April 2000, at 1). As indicated in the draft guidance, equivalence for one indication is valid for both and for any other indications because the single indication provides evidence that the formulations perform similarly (Id. at 4-5). Therefore, we deny GSK’s request that we require bioequivalence studies in patients with PAR.

GSK requests that FDA require bioequivalence studies for the PNAR indication because it does not have the same pathophysiology as SAR and PAR (IgE antibodies are not involved in PNAR (GSK May Petition at 12-13). Because the goal of bioequivalence studies is to test the equivalence of in vivo formulation performance, it is redundant to test each indication separately. If the test and reference products deliver the same drug at the same rate and to the same extent as demonstrated in the SAR patient study, there is no evidence, or reason to believe, that the drug delivery performance will not be the same in PNAR patients and that products will not have equal effectiveness for other indications that have the same site of action (i.e., nasal cavity). Therefore, FDA currently does not intend to require ANDA applicants for fluticasone propionate nasal spray suspension products to submit separate bioequivalence studies for the PNAR indication.

²⁰ In its 2003 draft BA/BE Guidance (and in its 1999 draft BA/BE guidance), FDA recommended studies of patients with SAR and states that a conclusion of bioequivalence may extend to all indications. Moreover, an industry consortium (ITFG/IPAC (Inhalation Technology Focus Group and International Aerosol Consortium)) supported this conclusion in technical papers filed with the Agency (www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_rpt4.pdf).

GSK asserts that because the pathophysiology of PNAR is distinct, extrapolation from SAR or PAR studies is not sufficient evidence for a new drug product to be approved and requests that FDA require generic applicants to conduct clinical studies to support the PNAR indication (GSK May Petition at 13). The fact that a separate PNAR study is required for a new drug product is not relevant to a bioequivalence determination. The bioequivalence studies do not extrapolate clinical evidence from patients with SAR and PAR to those with PNAR, rather they use one indication to assess formulation performance of the generic product relative to that of the reference product. The combination of in vitro and in vivo tests ensures product equivalence under all conditions of use prescribed, recommended, or suggested in the labeling.

3. *Pharmacokinetic Studies of Systemic Exposure to the Active Ingredient*

FDA generally recommends that plasma concentration-time profiles from in vivo bioavailability and bioequivalence studies be used to evaluate systemic exposure (2003 draft BA/BE guidance at 25-27). We recommend the following study design, study measures, and inclusion criteria for comparison of test and reference products:

- single-dose treatment, crossover study design, whereby single doses of test and reference drug products are administered to healthy volunteers, and the blood, plasma, or serum levels of the drug are measured over time
- study conducted using maximum labeled adult dose to maximize plasma drug levels
- standard pharmacokinetic parameters as study measures, as follows: area under the plasma concentration vs. time curve (AUC) calculated to the last measured concentration time (AUC_{0-t}), which represents a measure of total exposure of the drug; and (C_{max}) the peak exposure or maximum drug concentration

Frommer and Bell recommend studies be “conducted at a dose not exceeding the daily recommended dose,” with estimated AUC and measured C_{max} “from the plasma concentrations versus time profile or from at least four consecutive sampling times that show drug concentrations above the validated lowest quantifiable concentration (LOQ)” (Frommer Petition at 4-5, Bell at 3). Although GSK agrees that pharmacokinetic studies are appropriate to assess systemic exposure, GSK questions one aspect of Frommer and Bell's requested approach, stating that four consecutive sampling times would be inadequate and requests that FDA provide further guidance specifying that detectable samples be collected over the entire dose interval (GSK May Petition at 14-15). GSK further states that “[t]he detection and quantification of fluticasone propionate (FP) in the plasma following the administration of Flonase at the maximum clinical dose requires a highly sensitive assay” (Id).

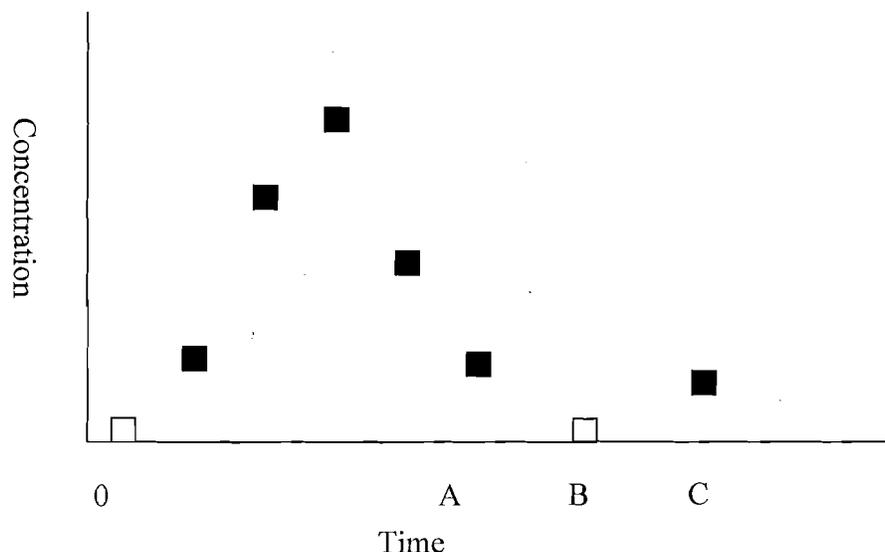
If full plasma concentration profiles are available for both the test and reference products, the AUC and C_{max} values are derived from those full profiles. However, if they are not available, FDA believes that four consecutive sampling times using the maximum clinical

dose²¹ is sufficient to detect whether two fluticasone propionate nasal spray suspension products provide significantly different systemic exposure (as measured by both C_{max} and AUC). As part of the ANDA review process, FDA evaluates the individual data within a pharmacokinetic study and includes in the final analysis only those subjects in which the test and reference product result in at least four consecutive plasma concentrations that contain peak drug concentration (C_{max}). By selecting sampling times that contain C_{max} values, FDA ensures that there is no significant difference in the C_{max} obtained from at least four samples.

For AUC, FDA would terminate the computation at the last quantifiable plasma concentration before the first zero value following these four or more values. Figure 1 illustrates a hypothetical profile of measured plasma concentrations. The black squares represent quantifiable levels and the white squares represent sample times where plasma concentrations could not be detected. This is a valid profile because it contains five measurable points that include the maximum concentration. The AUC would be calculated from time zero to time A. The data point at C would not be included in the AUC because there is a zero concentration measured at time B.

²¹ The labeled clinical dose is 200 μm . In the past, FDA recommended an 800- μm test dose to make it easier to detect plasma concentrations. However, FDA changed this recommendation in the 2003 draft BA/BE guidance because it was concerned that delivery of that volume of liquid could result in loss of drug due to drainage into the nasopharynx or externally from the nasal cavity. Sponsors that had already conducted studies using 800- μm doses were not requested to conduct new studies. These studies are still considered appropriate because test and reference formulations have identical amounts of active ingredients and the test and reference products were determined to have the same viscosity (which measures how easily a liquid flows), resulting in the same amount of run-off for the test and reference product. GSK demonstrated the limited effect of run-off in a pharmacokinetic study in which they gave subjects 800- μm doses, finding a one-minute separation between sprays was sufficient to minimize run-off (Daley-Yates et al., "Bioavailability of Fluticasone Propionate and Mometasone Furoate Aqueous Nasal Sprays," *European Journal of Clinical Pharmacology*, 60(4):265-268, 2004). FDA recommends the 200- μm test dose because there is minimal systemic absorption of the drug and the systemic exposure tests are designed to assess comparative safety between test and reference products. Even if the lower dose challenges the assay's limit of detection, this would inform FDA as to the test and reference products' comparative performance.

Figure 1. FDA Sampling Method (Plasma Concentration over Time)



When the AUC is calculated in this manner, it is actually more difficult statistically for an applicant to show equivalence than if more sample points were assessed over the entire dose interval because a difference near the peak could be counteracted by a difference in the other direction earlier or later in the profile.

Frommer claims that a comparative hypothalamic-pituitary-adrenal (HPA) axis suppression study to demonstrate that exposure following use of the test drug is not higher than that in the reference product is essential to support safety of the test product (Frommer Petition at 5). FDA disagrees. An HPA axis suppression study²² is the primary alternative safety assay for inhaled corticosteroids but is only recommended to be used for nasal spray suspension products when pharmacokinetic profiles cannot be measured at all. FDA recommends pharmacokinetic studies if at all possible (2003 draft BA/BE guidance at 27-28). It is difficult to design HPA axis suppression studies sensitive enough to detect the small differences that result from corticosteroid exposure from the labeled doses, making them less informative than pharmacokinetic data indicative of systemic exposure. For example, an HPA axis suppression study in which both test and reference show no HPA axis suppression would not provide persuasive evidence that the safety profiles are equivalent in long-term exposure. Therefore, we do

²² An HPA axis suppression study is used to determine if exposure to a corticosteroid drug will result in significant reduction in the normal levels of hormones, such as cortisol. In the study, subjects are exposed to the drug for a prolonged period of time. Over the course of the study, plasma and urinary levels of cortisol and the increase in cortisol in response to stimulation are measured to determine if exposure to the drug caused significant reductions in cortisol.

not recommend that ANDA applicants perform HPA axis suppression studies in instances where pharmacokinetic studies are feasible.²³

4. *Performance Measures to Test Spray Devices*

GSK claims that the 2003 draft BA/BE guidance is incomplete and requests that FDA address a number of issues regarding each of the recommended in vitro tests of the spray device before approving an ANDA for fluticasone propionate nasal spray (GSK May Petition at 15-17). As explained in detail below, we disagree with GSK's concerns and believe that the 2003 draft BA/BE guidance adequately addresses the recommended in vitro tests. To the extent that GSK recommends specific changes to the guidance (e.g., clarification on key terminology and inclusion of a glossary) (Id. at 17), we will consider these suggestions during the guidance development process.²⁴

a. *Single Actuation Content (SAC) Through Container Life*

FDA recommends single actuation content (SAC) through container life testing to measure delivery of the drug discharged from the actuator of the device to ensure that the test product delivers an equivalent amount of the drug relative to the reference product over the labeled number of actuations (2003 draft BA/BE guidance at 12-13). GSK requests that SAC apply throughout the shelf life of test and reference products at equivalent ages because physical age of the suspension can influence the test (GSK May Petition at 17).

During the regular course of the ANDA review process, the Agency evaluates whether the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve its identity, strength, quality, and purity (section 505(j)(4)(A) of the Act). FDA requires stability data for proposed products to establish the labeled shelf life, also ensuring product equivalence over the products' lifetime (21 CFR 314.94(a)(9)(i)). For nasal spray suspensions, FDA also provides recommendations for stability testing that include tests for spray content uniformity (guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation*, July 2002 (2002 CMC guidance)). We believe that these requirements and recommendations

²³ FDA has not requested HPA axis suppression studies in a related context, topical corticosteroids delivered through the skin, when the generic product has demonstrated equivalence in delivery of the corticosteroid to the site of action (guidance for industry on *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence*, June 1995).

²⁴ Included in the list of clarifications in GSK's comments on the 2003 draft BA/BE guidance was a request to clarify why the requirements for priming comparison are tighter than those for dose uniformity (GSK May Petition at 17). This comment does not raise a scientific issue that precludes or otherwise complicates ANDA review for fluticasone propionate nasal spray suspensions. For purposes of this response, it is worth noting that FDA evaluates priming comparisons between reference and test products by comparing the SAC (single actuation content) data collected at the beginning of the product lifetime. These data are evaluated with the same PBE method used to assess all comparative in vitro bioequivalence tests for fluticasone propionate nasal spray suspension products.

are adequate to ensure that generic versions of the fluticasone propionate nasal spray product preserve identity, strength, quality, and purity over their shelf life.

b. Droplet Size and Particle Size Distribution

FDA recommends determining droplet size and particle size distribution by laser diffraction, or an appropriately validated alternate methodology, and cascade impactor to measure deposition of the drug in the nasal passages (2003 draft BA/BE guidance at 13-17). GSK requests that FDA clarify how data for droplet size distribution by laser diffraction should be evaluated and suggests revisions to aspects of the description of the test for a drug in small particles/droplets (GSK May Petition at 17).

FDA evaluates droplet size distribution (DSD) bioequivalence based on the mean droplet size (D50) and the width of the DSD (span) data obtained via laser diffraction from the fully formed plume. A D50 of 50 μm means that 50 percent of the volume of the spray is in droplets smaller than 50 μm . Similarly, 10 percent of the spray is smaller than D10 and 90 percent is smaller than D90. The span $((D90 - D10) / D50)$ is a measure of difference between the largest and smallest droplets.²⁵ To conclude equivalence, the PBE method is used for evaluation of both the D50 and span data.²⁶

FDA recommends tests of particle/droplet size by cascade impactor to provide evidence that the test product will not deliver greater amounts of excipient beyond the nose than does the reference product (2003 draft BA/BE guidance at 15). In their comments on the 2003 draft BA/BE guidance, GSK requests FDA to explain the choice of cascade impactor as the only method recommended to measure the small particle fraction (GSK May Petition, Tab 8 at 12). At the time the guidance was drafted, FDA was not aware of any other method, nor has GSK recommended an alternative, that would be appropriate for measuring the small particle fraction.²⁷ Although GSK's comments on droplet size and particle size distribution will be considered during the guidance development process, the comments do not raise scientific issues that necessitate a change in the ANDA review process for fluticasone propionate nasal spray suspensions.

²⁵ The 2003 draft BA/BE guidance (at 13-14) recommends that sponsors submit D10, D50, D90, and span data. Because the span is a combination of D10, D50, and D90, the comparison of D50 and span is more efficient than comparing D10, D50, and D90 individually.

²⁶ GSK requests clarification of the distinction between “comparable” and “equivalent” particle size distribution (GSK May Petition at 16-17). GSK maintains that particle size distribution for suspension products should be equivalent, not just comparable, to the reference product (Id. at 16). Because all of the parameters in the in vitro bioequivalence tests are evaluated with equivalence defined using the PBE method, there is no meaningful distinction between the terms in this context.

²⁷ In their comments on the 2003 draft BA/BE guidance, GSK also suggested that the definition of small particles be changed from 9 μm to 6 μm (GSK May Petition, Tab 8 at 12). GSK did not provide any justification for this change, however. In addition, GSK suggested revisions to aspects of the description of the test for drug in small particles/droplets (Id). FDA believes this description in the 2003 draft BA/BE guidance currently is satisfactory, but will consider the suggestions when finalizing the guidance.

c. Plume Geometry

FDA recommends plume geometry analysis to describe a side view of the droplet cloud parallel to the axis of the plume (2003 draft BA/BE guidance at 20-21). GSK requests that FDA provide scientific support for the suggested analysis procedure for plume geometry (GSK May Petition at 17). In their comments on the 2003 draft BA/BE guidance, GSK also asks for a justification of why plume geometry should be used for bioequivalence since with the normal product use a free plume is not formed inside the nasal cavity (Id., Tab 8 at 14).

FDA recommends that plume geometry be characterized by the plume length (height), plume width, and plume angle (spray cone angle) visualized from the side of a fully developed plume still in contact with the actuator tip (2003 draft BA/BE guidance at 20-21). FDA recommends this test, as well as the other tests listed in the draft guidance, based on the results of many public meetings that discussed the question of which in vitro tests are appropriate. Studies in the literature have indicated that the spray angle is one aspect of product performance that determines where in the nasal cavity drug is deposited (e.g., Cheng, Y.S., et al., "Characterization of Nasal Spray Pumps and Deposition Pattern in a Replica of the Human Nasal Airway," *Journal of Aerosol Medicine*, 14(2):267-80, 2001). Finally, GSK has not submitted evidence to indicate that plume geometry is uncorrelated with device performance in vitro. Nor has GSK submitted evidence to suggest an alternative test may be more appropriate.

B. Product Quality and Chemistry, Manufacturing, and Controls (CMC)

GSK requests that the Agency refrain from approving an ANDA for fluticasone propionate nasal spray that does not meet the same standards of product quality as the approved specifications for droplet size distribution (DSD) and spray pattern (SP) for Flonase products (GSK November Petition at 2). GSK further argues that in the absence of United States Pharmacopeia (USP) standards for product quality, FDA "has no choice but to apply the standards set within the applicable NDA to assure the identity, strength, quality, and purity of any proposed generic product" (Id. at 18).

Flonase nasal spray was originally approved in 1994 without specifications for DSD and SP. In 1997, FDA began to recommend that applicants include DSD and SP specifications to ensure that the quality of nasal spray products is maintained through the expiration dating period (2002 CMC guidance, 2003 draft BA/BE guidance and its earlier 1999 draft). As part of a 1999 supplement, GSK submitted specifications for DSD and SP. In response, FDA requested that GSK, in the form of a phase-4 commitment, adjust acceptance limits and reduce variation (measured by percent relative standard deviation) in the DSD data and that GSK test the DSD and SP of every batch. In October 2004, FDA approved final DSD and SP specifications for Flonase based on GSK's reduction in variation and revised acceptance limits (GSK November Petition at 5-12).

The purpose of CMC review is to ensure that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug product are

adequate to assure and preserve its identity, strength, purity, and quality (21 CFR 314.127(a)(1); section 505(j)(4)(A) of the Act). ANDA applicants must submit, with one exception not relevant here, the same type of CMC information as required in an NDA (21 CFR 314.94(a)(9)(i)). The required CMC information includes, among other things, "...a description of the manufacturing and packaging procedures and in-process controls for the drug product" and "the specifications necessary to ensure the identity, strength, quality, [and] purity... of the drug product. . . ." (21 CFR 314.50(d)(1)(ii)(a), 314.94(a)(9)).²⁸

GSK argues that because in vitro tests of product quality are different from in vitro comparative bioequivalence studies, "separate and apart from BE testing, product quality must be evaluated on an absolute basis, to assess whether applicable quality standards are being met with acceptably low variation" (GSK November Petition at 6-7). GSK argues that the FDA-approved reductions in relative standard deviations for DSD and SP (between 6.6 and 8 percent for DSD and between 6.5 and 11.3 percent for SP) should set the specifications for ANDA applicants (GSK November Petition at 11-12).²⁹ GSK cites *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997) for the proposition that FDA must apply the applicable legal standard for product quality consistently to generic and innovator applicants (GSK November Petition at 12-17). GSK argues that the "same principles would apply with equal force here, were FDA to approve generic fluticasone propionate nasal spray products that have not been shown to meet specifications for DSD and SP comparable to those that were required for Flonase under S-019" (Id. at 16).

The CMC review of a proposed product includes the review of the manufacturing process and results in a set of specifications (a combination of test and acceptance criteria for a

²⁸ FDA affirms the following characterization of product quality:

Although no unified FDA definition of drug quality for regulatory purposes has been articulated, an operational definition can be discerned from an understanding of FDA practices. Much of FDA regulation of pharmaceuticals is centered around statements in the drug label-the label claims. These claims are based, to a great extent, on data from clinical studies submitted by the product manufacturer and verified by FDA review. When evaluating proposed specifications and in-process controls for a new drug product, FDA compares these metrics to the values obtained from the clinical trial material and may request a narrowing of the specifications or limits based on the findings from the study materials. This practice is intended to ensure that subsequent production batches deliver the same clinical performance as the investigational batches-the dosing, safety, and efficacy as described in the label. So one aspect of the FDA drug quality definition might be: delivers clinical performance per label claims. A corollary to this statement is: does not introduce additional risks due to unexpected contaminants.

(Janet Woodcock, "The Concept of Pharmaceutical Quality," *American Pharmaceutical Review*, Nov/Dec 2004.)

²⁹ Contrary to GSK's assertion, it should be noted that relative standard deviation is not an absolute measure of product quality (GSK November Petition at 6). DSD and SP data results may be inconsistent not only because of product inconsistencies, but also because of test inconsistencies. Moreover, a lower relative standard deviation does not always mean higher quality. Data may have a low relative standard deviation, indicating low variability, but fall outside of the acceptable range.

drug product) that the product must meet when it is released to the market. All products are evaluated on an “absolute basis” (to use GSK’s terminology) for drug quality that is the same for ANDAs and NDAs: to consistently manufacture product that delivers clinical performance per label claims.

For nasal spray products, the 2002 CMC guidance recommends that both NDA and ANDA applicants provide specifications for SP and DSD (2002 CMC guidance at 14-15). As GSK acknowledges in its November Petition at 16, the actual specifications used may differ between different ANDA applicants and between ANDA applicants and the manufacturers of the reference product. Thus, although the actual specifications for drug quality between ANDA and reference products may differ, FDA requires generic and innovator applicants, including applicants for fluticasone propionate nasal spray products, to meet the same standard for product quality.³⁰ ANDA applicants may meet standards of quality using different specifications (tests and acceptance criteria) than those used by the innovator sponsor.³¹ Each firm develops its own proprietary product quality tests (e.g., to measure DSD and SP) that may use different equipment under different conditions. Because GSK’s DSD and SP product quality tests and methodologies are proprietary, it is virtually impossible for a generic manufacturer to perform the exact same tests that GSK used for Flonase approval to compare test and reference products. In its petition, GSK does not provide the actual methods and specifications for DSD and SP, and these specifications have not been adopted by the USP. ANDA applicants are not expected to have exactly the same product quality specifications as the RLD.³²

FDA does not rely on bioequivalence tests as a surrogate for product quality standards as GSK implies. Although in vitro bioequivalence and CMC tests may measure the same parameters, the analysis and determination as to whether a product passes the tests is very different. All bioequivalence tests compare two products to each other, while CMC tests compare one product to defined limits. For example, a bioequivalence test of DSD is passed if test and reference products are determined to be the same (within acceptance limits), whereas a CMC test for DSD is passed if the droplet size is within a specified range. Unlike bioequivalence testing, which is a one-time comparison of the test to a

³⁰ Postmarketing monitoring of product quality also is similar for NDAs and ANDAs. For any approved generic fluticasone propionate nasal spray product, FDA will examine DSD and SP data for production batches. If FDA has concerns about the variability observed for these batches, then it will ask for reductions in variability to ensure product quality, just as was done with Flonase.

³¹ For further discussion on this point, see comment 88 in the preamble of *Supplements and Other Changes to an Approved Application; Final Rule*, 69 FR 18728, 18748-18749 (April 8, 2004).

³² GSK notes that FDA often has difficulty approving generics that have very tight specifications (GSK November Petition at 18, n. 8). GSK references FDA comments in those situations when specifications are public (e.g., USP) or the test methodology is not complex (e.g., impurities for solid dosage forms). In this case, where specifications for complex methods (e.g., DSD) are in question and there are no publicly available specifications, FDA may accept differences in specifications from the reference product, as long as the specifications on the ANDA product are sufficient to meet quality standards and as long as the product that meets these specifications (the test product) has been demonstrated to be bioequivalent to the reference product.

reference product, many CMC tests are applied to each batch of product produced (for release testing to determine if the batch should be released to the market) and to units of product used for stability testing.³³

Bioequivalence tests are critical to the establishment of appropriate specifications for drug quality (e.g., DSD) that each test product must meet. FDA reviews and approves CMC specifications for generic products by examining product quality test results for batches of test product that have been demonstrated to be equivalent to the reference drug. This provides a conservative basis for setting a CMC specification that should result in future batches also being bioequivalent. Bioequivalence tests provide the link between the test product and the pivotal clinical trials establishing safety and efficacy for the reference product. Product quality tests link each batch to the batch used to demonstrate bioequivalence. As a result, the specifications ensure that each production batch of generic fluticasone propionate nasal spray meets the standards for drug quality (i.e., delivers clinical performance per label claims), based on batches that have been demonstrated to be bioequivalent with Flonase.

III. DISCUSSION OF PROCEDURAL ISSUES

A. Issuance of Final Guidance Before Approval of ANDAs

GSK requests that FDA issue a final guidance to establish a complete and valid bioequivalence methodology for fluticasone propionate nasal spray products before approving an ANDA (GSK May Petition at 17-19). GSK states that FDA is now expressly authorized to establish scientifically valid alternative bioequivalence methodologies for nonsystemic drugs (section 505(j)(8) of the Act), and such methods must be scientifically valid (Id). GSK argues that Agency action on an ANDA prior to completion of the guidance process would belie “reasoned agency decisionmaking” (Id).

Neither the Act nor FDA regulations require FDA to issue final guidance prior to approving an ANDA. As in the new drug approval process, FDA is required to make decisions based on the information provided by individual applicants and evaluate the scientific content of ANDAs to determine if the application meets the statutory and regulatory requirements (section 505(j) of the Act). GSK has cited no authority to support its position that the Agency must complete a guidance document prior to approving an ANDA for a fluticasone propionate nasal spray product. The Agency has engaged in “reasoned agency decisionmaking” at the point at which it has examined the relevant data and “articulated a satisfactory explanation for its action including ‘a rational connection between the facts found and the choice made’” (*Motor Vehicle Manufacturers Ass’n v. State Farm Mut. Ins. Co.*, 463 U.S. 29, 43 (1983)). Whether or not FDA issues final guidance does not speak to the scientific validity of FDA’s bioequivalence

³³ Stability testing ensures that product quality is maintained throughout the shelf life. In a stability test, units of the product are stored for defined periods of time and then the CMC tests are performed. If the stability tests that were passed at release now fail, the product may be recalled from the market or the labeled shelf life reduced (2002 CMC guidance at 28).

methodology, scientific evaluation, and approval of generic fluticasone propionate nasal spray products.³⁴

As discussed, FDA has spent many years developing appropriate methods that are able to demonstrate bioequivalence for nasal spray products (section II.A of this response, including n. 5). Over the past eight or more years, based on industry and public input, FDA has developed a scientifically valid methodology capable of detecting a significant difference between test and reference fluticasone propionate nasal spray products. As GSK notes, FDA decided to revise and reissue the 1999 draft BA/BE guidance as the 2003 draft BA/BE guidance to solicit additional comments on the approaches outlined.

In the intervening years, FDA has had many exchanges with sponsors with respect to methods appropriate for particular products. Direct communication with potential generic drug applicants, rather than issuance of guidance documents, is a routine part of FDA's business. In 2002, the Office of Generic Drugs received 744 written communications with questions related to ANDA submission (e.g., bioequivalence, chemistry, labeling). In 2003, it received 971 requests. In 2004, it received 1,210 requests. If FDA were required to answer questions from potential generic drug applicants by issuing guidance documents, it would be impossible for the Agency to fulfill its responsibility under the Act to approve every generic drug that meets the statutory standards.

As discussed in section II.A.1 of this response, although it is desirable to provide assurance to sponsors and applicants in the form of final guidance, it is not always possible for FDA to define certain criteria in advance of analysis of the data from actual studies. As FDA states in many of its guidances, "FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited." Guidance documents are issued for the convenience of applicants and to facilitate the review process. Thus, guidance does not rule out or limit scientific methods that satisfy the statutory and regulatory requirements.

B. Petition for Stay of Action

GSK requests a stay "of just three business days — beyond the point in time when GSK is first notified of FDA's decision to grant final approval — of the effective date of any approvals FDA may decide to grant" of ANDAs for generic versions of Flonase or Beconase (GSK PSA at 1). GSK asserts that it is making its request to "avoid irreparable injury to its litigating and commercial position," describing the grant of its petition as necessary "to consider and pursue its right to judicial review without being undermined by unnecessary shifts in the underlying circumstances" (Id.).

³⁴ FDA has denied other requests for additional guidance issuance prior to ANDA approval. For example, FDA denied requests to defer action on labeling of generic ribavirin products until a public guidance development process was completed (April 6, 2004, FDA Response, Docket No. 2003P-0321).

FDA's regulation at 21 CFR 10.35(e) sets out the standard for review of a petition for stay of action:

The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition. The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:

- (1) The petitioner will otherwise suffer irreparable injury.
- (2) The petitioner's case is not frivolous and is being pursued in good faith.
- (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
- (4) The delay resulting from the stay is not outweighed by public health or other public interests.

The Commissioner shall grant a stay if all four of the above criteria apply. FDA need not address GSK's irreparable injury argument or whether or not GSK's petition has been filed in good faith and is not frivolous because FDA has determined that GSK has failed to demonstrate public policy grounds for the stay or that the delay would not be outweighed by public health or other public interests.

GSK has not articulated sound public policy grounds for supporting a stay. In addition, GSK has not demonstrated that the delay resulting from the stay is not outweighed by public health or other public interests. The only argument that GSK offers is that the "balance of equities" or "*status quo*" will shift to "GSK's detriment" once generics are approved for marketing (GSK PSA at 4, 5). GSK specifically argues that the public interest of "meticulous compliance with law by public officials" or "meaningful judicial review" is served by ensuring that the "balance of equities" remains in its favor until it can successfully obtain injunctive relief of longer duration through the court system (*Id.* at 5).

The Agency disagrees. Once FDA has reviewed all of the data, addressed all of the scientific questions, completed application review, and decided that approval is appropriate, it has meticulously complied with the law. An assumption underlying GSK's argument is that the Agency's approval standards will, upon further examination, be found inadequate. This assumption is too speculative and too unlikely to form the basis of a public policy argument for grant of a stay. As explained above, FDA has analyzed and developed appropriate standards and specifications for approval of generic Flonase products. Because the merits of GSK's challenge are unpersuasive, there is no legitimate public policy ground to stay the approval of ANDAs for fluticasone propionate nasal spray products.

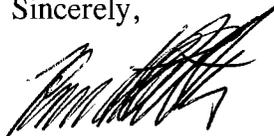
Moreover, even assuming GSK's "meaningful judicial review" argument was a valid public policy reason to grant a stay, the adverse effects on applicants and

consumers associated with a delay resulting from a stay are not outweighed by this reason. Meaningful judicial review is not served by delaying approval to maintain the *status quo*. One of the purposes of the Hatch-Waxman Amendments is to foster the availability of low-cost generic drugs. This important public policy would be frustrated if FDA were to grant the stay GSK requests. As GSK admits, granting a stay of just three days could alter the “balance of equities” in its favor before a reviewing court (Id. at 3). The policies behind Hatch-Waxman dictate that GSK not be permitted to shield its market share when the Agency has reasonably determined that competing generic drug products may be approved under section 505(j) of the Act.

IV. CONCLUSION

For the reasons stated above, the petitions submitted by Bell and Frommer are denied in so far as they suggest that FDA *must* approve any ANDA that successfully demonstrates bioequivalence using recommended methodologies. Also, for the reasons stated above, GSK’s petitions are denied.

Sincerely,



Randall W. Lutter, Ph.D.
Acting Associate Commissioner
for Policy and Planning