



GlaxoSmithKline

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CITIZEN PETITION

The undersigned, on behalf of GlaxoSmithKline ("GSK"), submits this petition under 21 CFR 10.30, 21 USC 355, and 21 USC 371(h), among other provisions of applicable law.

By this petition, GSK requests that the Commissioner of Food and Drugs (the "Commissioner") expeditiously issue a final and complete guidance document setting forth a scientifically valid methodology for determining bioequivalence ("BE") for nasal spray products. Further, GSK requests that the Agency refrain from approving any further abbreviated new drug applications ("ANDAs") for such products and, in particular, for nasal suspension formulations which pose heightened BE challenges, until a final guidance document has been issued. As shown below, until a valid scientific methodology has been established, including valid statistical criteria, it is premature for the Agency to consider reviewing ANDAs for specific nasal suspension products.

GSK markets the nasal suspension product Flonase® (fluticasone propionate) Nasal Spray, 50 mcg. Since 1999, GSK has engaged fully and constructively in the Agency's development of the document titled *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*. The document, however, remains in draft form and numerous comments submitted by GSK and others have yet to be addressed.

GSK's focus to date has been on the process initiated by the Agency in 1999 for establishing (the science permitting) valid *in vitro* and *in vivo* BE methods for nasal spray products. It has been GSK's expectation that until the Agency has

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established a valid methodology, it would not and could not begin to assess individual ANDAs, particularly for nasal suspension products.

Two weeks ago, on May 3, 2004, FDA acknowledged receipt of a citizen petition submitted by the law firm of Bell, Boyd & Lloyd ("BBL") on behalf of an unnamed client. ^{1/} See Tab 1, FDA Docket No. 2004P-0206/CP1 and ACK1 (May 3, 2004). BBL argues that FDA should immediately begin to apply the *Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (Apr. 2003) ("2003 Draft BA/BE Guidance") to ANDA products. (The 2003 Draft BA/BE Guidance is attached as Tab 2.) The BBL petition suggests to GSK that the Agency may be nearing an approval decision on an ANDA *before* the Agency has developed a final, valid methodology. ^{2/}

Given the uncertainty about whether FDA will complete the guidance process prior to taking action on individual ANDAs, GSK is compelled to submit this petition on the grounds set forth below.

I. ACTIONS REQUESTED

The undersigned hereby requests that the Commissioner take the following actions:

- A. Expeditiously complete the ongoing guidance development process, including appropriate resolution of outstanding technical issues with respect to BE methods for nasal suspension formulations. The final guidance document should set forth a scientifically valid BE methodology for purposes of section 505(j)(8) of the Food, Drug, and Cosmetic Act, including (among other things):
 - (1) *a priori* derived statistical criteria for analyzing *in vitro* and *in vivo* comparisons between a proposed generic product and an approved reference product;

^{1/} The petition is dated May 1, 2004. The Agency acknowledged receipt and filing of the petition on May 3, 2004. However, the petition was not made available to the public until May 10, 2004.

^{2/} Flonase® was the subject of one patent listed in FDA's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (known as *The Orange Book*). The patent expired on November 14, 2003, but was the subject of a pediatric exclusivity extension that expired on May 14, 2004. GSK disagrees with BBL's position that FDA should use the approach outlined in the 2003 Draft BA/BE Guidance for generic versions of Flonase®, and GSK intends to submit a copy of this petition to FDA Docket No. 2004P-0206 in opposition to the BBL petition.

- (2) direction to conduct *in vivo* clinical studies in “the most difficult to treat” indication for *each* related group of indications;
 - (3) specific and emphatic direction to assess systemic exposure by PK studies as the preferred method, and clear and appropriate standards for sampling times when conducting such studies; and
 - (4) fully developed criteria – including complete statistical standards – for establishing device equivalence.
- B. Refrain from approving any ANDAs for fluticasone propionate nasal spray products until the guidance development process, including a sufficient opportunity for public review and comment, has been completed and a final guidance has issued.

II. STATEMENT OF GROUNDS

A. Factual Background

1. Flonase®

Flonase® (fluticasone propionate) is a corticosteroid nasal spray used to treat the nasal symptoms of seasonal and year-around allergies, as well as nonallergic rhinitis. It consists of an aqueous suspension of microfine fluticasone propionate intended for topical administration to the nasal mucosa through a metered atomized spray pump. Tab 3, Flonase® Prescribing Info. (Mar. 2004) at 1.

FDA approved a new drug application (“NDA”) for Flonase® on October 19, 1994, and subsequently approved several supplemental NDAs to add new labeling information, including new indications for use. Currently, Flonase® is indicated “for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.” *Id.* at 5. ^{3/}

The active ingredient, fluticasone propionate, is a synthetic, trifluorinated corticosteroid. It is a potent glucocorticoid with anti-inflammatory

^{3/} These indications are often referred to in practice, and in this petition, as “SAR” for seasonal allergic rhinitis, “PAR” for perennial allergic rhinitis, and “PNAR” for perennial nonallergic rhinitis.

properties; however, the precise mechanism of action through which it affects seasonal and perennial allergic rhinitis symptoms (“SAR” and “PAR”) is unknown. *Id.* at 2. The mechanism of action and the precise site of action through which fluticasone propionate affects perennial nonallergic rhinitis (“PNAR”) is also unknown and may be different from the mechanism and site of action for SAR and PAR.

2. The Draft BA/BE Guidance Document

In June 1999, FDA initiated a guidance development process to establish a recommended approach for measuring the bioavailability (“BA”), and establishing the bioequivalence (“BE”), of nasal aerosol and nasal spray products intended for local action (e.g., Flonase®). See Tab 4, *Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (June 1999) (the “1999 Draft BA/BE Guidance”); 64 FR 33869 (June 24, 1999) (announcing the availability of the guidance). ^{4/}

The 1999 Draft BA/BE Guidance was developed by a constellation of Agency committees, including the Oral Inhalation and Nasal Drug Products Technical Committee, the Locally Acting Drug Products Steering Committee, the Biopharmaceutics Coordinating Committee, the Inhalation Drug Products Working Group, and the Agency’s Chemistry, Manufacturing, and Controls Coordinating Committee. See Tab 4 at 1, note 1.

Among other things, the 1999 Draft BA/BE Guidance recommended that sponsors of proposed generic products use “qualitatively and quantitatively” the same formulation as the pioneer product. Further, the draft guidance described a series of *in vitro* performance studies, along with a “systemic exposure” or “systemic absorption” study, to establish equivalence between a proposed generic and the pioneer product. *Id.* at 19.

The Agency, however, also included in the draft guidance an important reservation; the Agency acknowledged that the *in vitro* studies described in the draft could not assure equivalence in particle size in nasal spray suspension formulations between the generic and the pioneer, and that differences in particle size could cause clinically different effects. See *id.* at 3-4. As the Agency explained to a subcommittee of its Advisory Committee for Pharmaceutical Science, “[b]ecause particle size differences between test and reference products have the potential to alter the rate and extent of delivery of drug to local sites of action in the nose,

^{4/} Portions of the 1999 Draft BA/BE Guidance were not made available for comment until August 16, 1999.

differences in clinical effectiveness could result.” See Tab 5, Questions to the Committee, Orally Inhaled and Nasal Drug Products (“OINDP”) Subcommittee of the Advisory Committee for Pharmaceutical Science (“ACPS”) (July 21, 2001). Therefore, the Agency also included in the draft guidance a recommendation that sponsors of suspension products conduct a clinical study in patients with allergic rhinitis “to confirm equivalent local delivery.” *Id.*

In the following years, the Agency convened a series of public meetings on the draft guidance, solicited several rounds of public comments, and received at least three “technical papers” on the subject of BE standards for locally acting nasal products, ^{5/} including:

- An OINDP Expert Panel Planning Meeting (Nov. 1999)
- An OINDP Subcommittee Meeting (Apr. 2000)
- The Receipt of Technical Papers (Aug. 2000)
- An ACPS Meeting (Nov. 2000)
- An OINDP Subcommittee Meeting (July 2001)

Despite these efforts, the Agency still was unable to recommend a validated BE methodology for nasal spray products. Instead, in April 2003, the Agency decided to issue a superseding draft guidance and acknowledged that a great deal of additional work remained undone. As the Agency explained:

Because of changes made as a result of comments received to the docket, internal discussions, and deliberations of the Advisory Committee for Pharmaceutical Science, we have decided to issue the guidance once again in draft. A

^{5/} GSK, among others, submitted detailed comments to the 1999 Draft BA/BE Guidance. See Tab 6, Comments of GlaxoWellcome Re: Docket No. 99D-1738 (Sept. 9, 1999). In addition, GSK participated in the preparation of comments and technical papers submitted by The International Pharmaceutical Aerosol Consortium (“IPAC”), who also made several presentations before the OINDP Subcommittee. See Tab 7, Comments of The International Pharmaceutical Aerosol Consortium re: Re: Docket No. 99D-1738 (Sept. 30, 1999); Initial Assessments, Slide Presentations, and Testimony of the ITFG/IPAC Collaboration to the OINDP Subcommittee (Apr. 26, 2000), Transcript at 151-78, 261-81; Statement to Advisory Committee for Pharmaceutical Science (Nov. 15, 2000), Transcript at 100-127; Statement to Advisory Committee for Pharmaceutical Science and OINDP Subcommittee (July 10, 2001); Slide Presentations and Testimony of Cynthia Glynn and Joel Sequeira on behalf of ITFG/IPAC-RS Collaboration at OINDP Subcommittee Meeting (July 17, 2001).

series of attachments are being developed and will be posted with this draft guidance as stand alone documents on the Internet as soon as they have been completed.

Tab 2, at 3. As further evidence of the tentative nature of the approach outlined in the new draft, FDA specifically encouraged applicants “to submit any evidence that supports or refutes the approaches outlined in this guidance . . .” 68 FR 16293 (Apr. 3, 2003) (announcing availability of the draft guidance). 6/

As of the date of this petition, the Agency has not issued a final guidance setting forth a valid BE methodology for locally acting nasal products. In fact, the Agency has yet to complete or make available for comment the “series of attachments” that were supposed to have accompanied the 2003 Draft BA/BE Guidance. See Tab 2, at 3. These “stand alone documents” were to include essential statistical criteria for analyzing the data developed in each of the recommended *in vitro* and *in vivo* studies described in the guidance. None of the participants in the five-year long process has had any opportunity to comment on these still missing pieces. 7/

B. Statutory and Regulatory Background

Under the Food, Drug, and Cosmetic Act (the “FDCA”), a sponsor seeking premarket approval of a generic drug must demonstrate, among other things, that the proposed drug is bioequivalent to a pioneer or “listed drug.” See 21 USC 355(j)(2)(A)(iv). 8/ “Bioequivalence” under section 505(j) of the FDCA generally means that the “rate and extent of absorption of the [proposed] drug do not show a

6/ A guidance document represents the Agency’s “current thinking” on a given subject. When the Agency issues a guidance document in “draft” form, it means that the Agency has not yet developed a coherent or valid approach to the subject. For example, as the Agency stated when it issued the April 2003 draft guidance, “The draft guidance, *when finalized, will represent the agency’s current thinking* on BA and BE product quality information related to nasal inhalation aerosols and nasal metered-dose spray pumps.” 68 FR at 16293 (emphasis added).

7/ GSK submitted extensive comments on those parts of the 2003 Draft BA/BE Guidance that have been made public. See Tab 8, Comments of GSK Re: Docket No. 99D-1738 (June 26, 2003); see also Tab 9, Comments of The International Pharmaceutical Aerosol Consortium Re: Docket No. 99D-1738 (July 7, 2003).

8/ Drug products that are determined to be bioequivalent and pharmaceutically equivalent (*i.e.*, they contain the identical active ingredient in the identical amount and dosage form, 21 CFR 320.1(c)) are eligible to be classified by FDA as “therapeutically equivalent.” Therapeutically equivalent products, according to FDA, “can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.” *The Orange Book* at viii.

significant difference from the rate and extent of absorption of the listed drug when administered . . . under similar experimental conditions . . .” *Id.* at 355(j)(8)(B)(i); see 21 CFR 320.1.

On December 8, 2003, President Bush signed into law the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (the “MMA”), Pub. L. No. 108-173. Title XI of the MMA amended the FDCA to address, among other things, bioequivalence standards for drugs that are not intended to be absorbed into the bloodstream. ^{9/} In particular, Congress added a new statutory provision that allows FDA to assess the bioavailability of non-systemic drug products by using “scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action.” See Pub. L. 108-173 (amending section 505(j)(8) of the FDCA). Congress also added that, with respect to bioequivalence, FDA (by delegation of authority from 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.

21 USC 355(j)(8)(C).

Thus, while the new statutory standard provides the Agency with flexibility in making BE determinations, it also limits the FDA to the use of “*scientifically valid*” methods and measurements to assess the BA and BE of non-systemic drug products. These methods and measurements, once established, must be able to accurately measure the rate and extent of absorption of the active ingredient at the local site of action, and they must be able to detect differences between the test and reference product with respect to both safety and efficacy. ^{10/}

^{9/} As explained by one of the sponsors, “Under the current statute, the primary method by which the FDA determines whether a generic is equivalent to a brand drug (“bioequivalence”) is by measuring the rate and absorption of the drug into the bloodstream. For certain drugs which are not absorbed into the bloodstream, such as topicals and inhalers, the FDA uses different tests to determine bioequivalence, which are defined in their regulations Gregg-Schumer would clarify that the FDA does have the authority to establish separate tests for determining the bioequivalence of drugs which are not absorbed into the bloodstream - *as long as those tests are scientifically valid and meet rigorous standards.*” Press Release by Senator Charles E. Schumer (D-N.Y.), Schumer Generic Drug Legislation Passes Full Senate (June 19, 2003) (emphasis added) *at* http://www.senate.gov/~schumer/SchumerWebsite/pressroom/press_releases /PR01804.html.

^{10/} On March 3, 2004, FDA published in the *Federal Register* a notice and request for comments on this and other changes to the FDCA, as amended by the MMA. “Generic Drug Issues; Request for

A methodology that cannot detect significant differences between the test and the reference products necessarily fails to meet the requirement of scientific validity. *See* 21 USC 355(j)(8).

Finally, in addressing the issue of BE methodologies for a class of products, FDA is required by law to issue a public “guidance document” to communicate recommendations on the “testing of regulated products,” except where the communication is directed to individual firms or persons. 21 CFR 10.115(b)(2), (b)(3). If the guidance involves “complex scientific issues,” then the Agency must publish a draft version of the guidance and seek public comment before finalizing its recommendations. *Id.* at 10.115(g); *see* 21 USC 371(h)(C). The Agency may, as part of this process, hold one or more public meetings to facilitate the development of the guidance. *See* 21 CFR 10.115(g). FDA is prohibited by law, however, from using any means – other than a guidance document – to communicate new or different regulatory expectations to a broad public audience. *See id.* at 10.115(e).

III. ARGUMENT

The burden of proof under section 505(j) of the FDCA rests on the generic drug applicant to demonstrate that the proposed drug product is bioequivalent to a “reference listed drug.” 21 USC 355(j)(2)(A)(iv); 21 CFR 320.21(a). At the same time, the burden is on FDA to assure that the data presented by the applicant are based on valid methods and measures, and have been analyzed using appropriate and sensitive statistical techniques. 21 CFR 320.23(a)(1) and (2). Finally, for products that are not intended to be absorbed into the bloodstream, bioequivalence may be assessed by measurements that reflect the rate and extent to which the active ingredient becomes available at the site of action. *Id.* Such measurements, however, must be “scientifically valid.” 21 USC 355(j)(8)(C).

After more than five years of proceedings concerning these complex scientific matters, FDA has yet to articulate a valid BE methodology for assessing nasal spray products. To take action on approving an ANDA at this time, particularly for a nasal suspension product, would be to risk approval of generic products that would not be assured of delivering the same therapeutic results as Flonase®, or as to one another. Among the issues that have yet to be resolved are: (1) the statistical criteria that will be applied to the *in vitro* and *in vivo* comparisons of the test and reference products; (2) the patient populations in which the test and reference products must be studied; (3) the shortcomings of methods (other than PK studies) for assessing systemic exposure to the active ingredient, and the need for

adequate sampling times needed to establish a valid assessment in PK studies; and (4) a final array of performance measures to assure equivalent performance, from first to last use, of the test and reference spray devices. 11/

To the Agency's credit, it has used a public process to try to address these and other fundamental scientific issues. The Agency has invited wide public participation and has consulted numerous experts and expert panels to assist in this process. Nevertheless, a final recommended BE methodology has yet to be issued. It is, therefore, GSK's considered view that the Agency should expeditiously complete that process before moving to the next step of reviewing sponsor-specific data packages purporting to show bioequivalence submitted under ANDAs.

A. FDA Should Establish a Scientifically Valid BE Methodology Before Approving ANDAs that Reference Nasal Suspension Products Such As Flonase®

1. A Valid BE Methodology Should Include A Priori Derived Statistical Criteria

A valid BE methodology must include statistical techniques of sufficient sensitivity to detect clinically relevant differences between a test and reference drug. 21 USC 355(j)(8)(C); 21 CFR 320.23(a)(2). Prior to initiating any valid BE study, the person conducting the study must establish *in advance* parameters such as the sample size, power, confidence interval, and acceptance limits. These parameters should be justified and should be calibrated to the clinical demands of the products being studied. See, e.g., *FDA Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001) (International Conference on Harmonisation (ICH)) at 10 (stating that an acceptable equivalence margin should be defined in advance, "taking into account the historical data and relevant clinical and statistical considerations"). As required by statute, the analysis must be able to confirm the proposition that there is no significant difference – between the test and the reference product – in the

11/ While FDA has approved ANDAs for certain nasal spray products (e.g. Ipratropium Bromide Nasal Spray, Cromolyn Sodium Nasal Solution, and Flunisolide Nasal Solution), these products are *formulated as solutions*. Nasal products like Flonase® that are *formulated as suspensions*, which have far different physico-chemical properties than solutions, pose greater technical challenges for purposes of establishing valid BE standards to assure equivalent therapeutic results. FDA has specifically acknowledged these differences. See, e.g., Tab 4, at 3-4 (differences in suspension particle size – which *in vitro* studies described in the 1999 BA/BE Draft Guidance can not adequately detect – can result in variable clinical performance); Tab 5 (advising a subcommittee of FDA's Advisory Committee for Pharmaceutical Science that "[b]ecause particle size differences between test and reference products have the potential to alter the rate and extent of delivery of drug to local sites of action in the nose, differences in clinical effectiveness could result").

rate and extent to which the active ingredient becomes available at the site of drug action. 21 USC 355(j)(8)(A).

The importance of the statistical analysis for assessing the BA and BE of nasal spray products – particularly those in suspension formulations – cannot be overstated. Such products raise a unique set of issues related to *in vitro* and *in vivo* measurements, sample sizes, patient populations, and intra-subject variability, for which statistical criteria must be carefully derived. The centerpiece of the Agency's effort to design a statistical analysis plan for nasal spray products can be found in separate appendices to the 1999 and 2003 Draft BA/BE Guidance Documents. With the 1999 Draft Guidance, the Agency delayed the release of these appendices by two months; with the 2003 Draft Guidance, the Agency has yet to make them public. Because these Appendices, particularly Appendix F to the 2003 Draft Guidance (*Statistics for Allergic Rhinitis Studies*) have not been made available for comment, a full understanding of the risk to the public (type I error) and risk to sponsors (type II error) cannot be made in an informed manner.

It is, therefore, crucial that the Agency follow through on its commitment to publish the statistical appendices in draft form (for comment), and refrain from reviewing any data submitted by ANDA sponsors purporting to show BE until it has completed the guidance process. The scientific rationale behind the statistical analysis will be corrupted if the "goal posts" and other key elements of the analysis are established only after the Agency has seen the data.

Even more, it is important to the integrity and validity of the generic drug approval process not to risk the appearance of a "results oriented" approach to setting generic drug approval standards. For example, in 1995 the Agency engaged in what some considered to be a retrospective analysis when it widened the standard for bioequivalence acceptance limits for generic albuterol metered dose inhaler products to 67% - 150%, in contrast to the range of 80% - 125% that is generally applied. By all appearances, these "interim" acceptance limits were set after the generic applicant had conducted its studies and after the Agency had begun reviewing the application. See Tab 10, "FDA Generic Albuterol MDI Interim Bioequivalence Interval is 67% to 150%; Ivax Albuterol MDI Falls Within Range Calculated by 'Bootstrap' Approach," *The Pink Sheet* (Feb. 19, 1996).

The statistical methods and limits should be defined prior to the review of any ANDAs, to ensure scientific integrity. In this instance, the Agency should complete its thinking on appropriate statistical methods for assessing nasal spray products, and propose its criteria through the pending guidance development

process. ^{12/} The Agency should derive and define, *a priori*, the limits of equivalence on an absolute scale in order to maintain statistical validity. The failure to establish *a priori* equivalence margins in this context will raise fundamental questions about the validity and integrity of the generic drug review process.

2. A Valid BE Methodology For Proposed Generic Versions of Flonase® Must Include Clinical Studies in PAR and PNAR Patients

As explained in the 2003 Draft BA/BE Guidance, a sponsor seeking to show BE of a nasal suspension product (such as Flonase®) will need to conduct *in vivo* studies with a clinical endpoint “because of an inability at the present time to adequately characterize drug particle size distribution (PSD) in aerosols and sprays (reference omitted).” Tab 2, at 5. ^{13/}

While GSK agrees with this conclusion, we disagree with the draft recommendation for nasal corticosteroid products that such a study may be conducted in seasonal allergic rhinitis patients only. According to the 2003 Draft BA/BE Guidance, “[a] study population consisting of seasonal allergic rhinitis (SAR) patients will allow documentation of BE, which may extend to all indications in product labeling for locally acting nasal corticosteroids.” *Id.* at 23. As stated in GSK’s June 2003 comments, a study in perennial allergic rhinitis (PAR) patients must be required for a showing of BE to Flonase®. *See* Tab 8, at 2, 15. PAR is the more severe and sustained form of the disease condition and is the more difficult to treat. *Id.* at 15. Furthermore, as explained below, a separate study in PNAR is also essential because of the different pathophysiology of that disease.

For a topical or locally acting drug product with multiple related indications, FDA has determined that a showing of equivalence in one indication may suffice, provided it is “the one that is most difficult to treat (references

^{12/} The Agency must also address other methodological concerns that have been raised. For example, as GSK has noted previously in its comments, the Agency appears to be recommending log transformation of the data. However, the recommended endpoint for analysis of equivalence and efficacy of nasal corticosteroids – absolute change in patient self-rated total nasal symptom score (“TNSS”) – is likely to be normally distributed on the absolute scale and does not require transformation.

^{13/} The 2003 Draft BA/BE Guidance discusses in detail the complex relationship between particle size and distribution patterns, on the one side, and availability of the active drug substance to the local site of action, on the other. *See generally* Tab 2, at 4-6. It is sufficient for purposes of this petition to recognize that FDA has set forth a scientific rationale that essentially requires nasal suspension ANDA applicants to conduct one or more clinical studies as part of an overall showing of bioequivalence.

omitted).” See Tab 11, FDA Response to Citizen Petition of Westwood Squibb Pharmaceuticals, Inc., Docket No. 95P-0379/CP1 (May 22, 2002) at 2 (the “Westwood Squibb Response”). While SAR and PAR are related indications, PAR is the more difficult to treat and, therefore, must be used as the basis for the BE demonstration. PAR sufferers experience more severe and sustained nasal congestion due to the intensity and persistence of the late-phase inflammatory response promoted by chronic, unrelenting exposure to primarily indoor allergens such as house dust mite and animal dander. ^{14/} As a result, PAR generally is more difficult to treat and, as a matter of science and stated Agency policy, must be used as the basis for establishing BE to Flonase® for the allergic rhinitis indications. Tab 11, at 4 (BE testing based on clinical studies should be done in the “most difficult to treat” indication).

In addition, GSK believes that a separate study is needed in PNAR patients. According to the Westwood Squibb Response, a demonstration of BE in one indication may establish BE “for all related indications with the same site of action.” *Id.* While SAR and PAR are known to be mediated by specific IgE antibodies, the etiology and pathophysiology of PNAR is not well defined. Although nasal mucosal inflammation and hyperreactivity are associated with the disease condition, PNAR is not mediated through specific IgE antibodies. ^{15/} Indeed, PNAR is considered a diagnosis of exclusion after SAR and PAR are ruled out. A diagnosis of PNAR includes negative allergen skin tests or *in vitro* tests of specific IgE antibodies to aeroallergens and a history of non-seasonal nasal symptoms, often exacerbated by various non-allergen environmental triggers. ^{16/}

^{14/} See Tab 12 (scientific articles organized alphabetically by author), including The American Academy of Allergy, Asthma, and Immunology, *The Allergy Report Volume 2: Diseases of the Atopic Diatheses* (2000) at 2-3, available at http://www.theallergyreport.org/report_index.html (last visited May 13, 2004); Mark S. Dykewicz & Stanley Fineman, eds., “Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology,” 81 ANN. ALLERGY ASTHMA & IMMUNOL. 478, 484 (1998) (hereinafter *Dykewicz & Fineman*).

^{15/} See Tab 12, Wytske J. Fokkens, “Thoughts on the Pathophysiology of Nonallergic Rhinitis,” 2 CURR. ALLERGY ASTHMA REP. 203-209 (2002) (hereinafter *Fokkens*); Timothy L. Smith, “Vasomotor Rhinitis is Not a Wastebasket Diagnosis,” 129 ARCH. OTOLARYNGOLOGY HEAD NECK SURG. 584, 586 (2003); James A. Hadley, “Vasomotor Rhinitis Remains a True Clinical Problem,” 129 ARCH. OTOLARYNGOLOGY HEAD NECK SURG. 587-588 (2003); Jacquelynne P. Corey, “Vasomotor Rhinitis Should Not be a Wastebasket Diagnosis,” 129 ARCH. OTOLARYNGOLOGY HEAD NECK SURG. 588-589 (2003)(hereinafter *Corey*); Russell A. Settipane & Philip Lieberman, “Update on Nonallergic Rhinitis,” 86 ANN. ALLERGY ASTHMA & IMMUNOL. 494, 496-97 (2001)(hereinafter *Settipane & Lieberman*); *Dykewicz & Fineman, supra*, at 484.

^{16/} See Tab 12, *Fokkens, supra*, at 203-04; *Settipane & Lieberman, supra*, at 494, 496-97; *Dykewicz & Fineman, supra*, at 484-85, 492.

Further, the nasal symptom complex associated with PNAR differs from SAR and PAR and usually includes nasal congestion, rhinorrhea and post-nasal drainage. ^{17/} Unlike SAR and PAR, nasal itching is not a nasal symptom typically associated with PNAR. Non-allergen environmental triggers such as smoke, strong odors, chemical fumes, and weather changes are well documented in the medical literature and are agreed on by allergy specialists as being associated with PNAR. ^{18/} FDA's position (as GSK understands it) that two replicate studies are necessary to establish the efficacy of new drugs being developed for PNAR – as opposed to one study combined with extrapolation of results in allergic rhinitis – is consistent with the medical literature that PNAR is physiologically distinct. Thus, because PNAR's pathophysiology is different and unique from that of SAR and PAR, a 2-week SAR clinical trial is not sufficient as an *in vivo* means of assessing equivalence.

In short, the burden of proof is on the generic applicant to show that PNAR relies on the same mechanism of action and same site of action as SAR and PAR. *See, e.g.*, 62 FR 42562, 42565 (Aug. 7, 1997) (stating that the burden of proof is on the generic applicant to establish each element of equivalence). Absent such a showing, it would be inappropriate – as a matter of science and precedent – to apply a finding of equivalence in SAR/PAR to PNAR. ^{19/} The draft guidance should be amended accordingly. Moreover, the Agency must refrain from approving any ANDAs that reference nasal suspension drugs like Flonase® where the application lacks separate *in vivo* studies in PAR and PNAR patients; to do otherwise would be inconsistent with the statute and would risk inequivalent therapeutic results in all relevant patient populations.

^{17/} See Tab 12, D. Robert Webb, *et al.*, "Intranasal Fluticasone Propionate is Effective for Perennial Nonallergic Rhinitis With or Without Eosinophilia," 88 ANN. ALLERGY ASTHMA IMMUNOL. 385-390 (2002).

^{18/} See Tab 12, *Fokkens, supra*, at 204; *Settipane & Lieberman, supra* note 13, at 497, 504; *Dykewicz & Fineman, supra*, at 485.

^{19/} Nor may a generic applicant seek to omit the PNAR indication from the labeling of its product to avoid having to do a clinical study in PNAR patients. The PNAR study is needed to meet the generic applicant's burden of demonstrating bioequivalence to the reference listed drug product; a generic applicant cannot elect to show BE in some indications but not others, where clinical studies are needed to show BE of the proposed generic product, as a whole, to the reference listed drug. Second, generic products are required to carry the same labeling as the reference listed drug, except in certain limited circumstances. 21 CFR 314.94(a)(8)(iv). A "labeling carve out" based on refusal to show BE in all approved indications is not a recognized basis for omitting an indication. *See id.*

3. A Valid BE Methodology for Proposed Generic Versions of Flonase® Should Include PK Studies (With Adequate Sampling Times) of Systemic Exposure to the Active Ingredient

Nasal spray products such as Flonase® are intended for local delivery to achieve local effects. Nevertheless, some amount of systemic absorption may occur and, as a result, the safety risks associated with systemic absorption of the active ingredient, as well as any impurities in or on the drug product, must be assessed.

In the 2003 Draft BA/BE Guidance, the Agency endorses as the preferred measure a pharmacokinetic (PK) study to assess systemic exposure where measurable plasma levels can be obtained. Tab 2, at 6, 25-27. In its comments on the 2003 Draft BA/BE Guidance, GSK expressed its strong agreement with the need for a PK study because it is the most sensitive, reliable method of detecting differences between formulations. We reiterate that concern now. The dissolution of fluticasone propionate particles in the nose is the critical step in determining nasal absorption and systemic exposure. Therefore, differences in drug substance between generic and innovator product could result in differences in systemic exposure. The only robust method of detecting such differences is to conduct a pharmacokinetic study.

Even in the context of the current stated preference for PK studies, however, the draft guidance is incomplete, as is evident from at least one “podium pronouncement” made after the most recent edition of the draft guidance was published. According to a November 3, 2003, report in the trade press, an FDA official has been providing unofficial guidance that, in the case of Flonase® Nasal Spray: “If you are able to evaluate patients with at least four consecutive plasma concentrations, we would consider that an acceptable profile for this drug.” See Tab 13, “USP Monographs Will Follow International Format for Drug Impurities,” *The Pink Sheet* (Nov. 3, 2003).

We are concerned that this opinion, which has not been subject to public comment, is open to differing interpretation and may result in data of poor quality being generated to address the safety equivalence of generic products. This is no small matter; indeed, in the BBL petition, BBL specifically recognized the “four consecutive sampling times” standard as one of the elements of BE that FDA should require of all ANDA sponsors. See Tab 1, at 3.

The detection and quantitation of fluticasone propionate (FP) in the plasma following the administration of Flonase® at the maximum clinical dose

requires a highly sensitive assay. Allowing the use of only four consecutive plasma samples with detectable FP concentrations could result in unreliable data. For example, if all four samples were taken over a short time interval around C_{max} this would provide no assurance that the bioavailability of the formulation matched the innovator product for purposes of adequate assessment of comparative safety. The systemic effects of corticosteroids are related to the total systemic exposure over the day (AUC), not C_{max} . The guidance needs to specify that plasma concentrations should be collected over the entire dose interval with a minimal portion of the AUC being extrapolated. ^{20/} Moreover, the guidance must be more emphatic in insisting on PK studies as the preferred method of assessing systemic absorption, as noted above.

4. A Valid BE Methodology Must Ensure Equivalence Between the Test and Reference Devices

The 2003 Draft BA/BE Guidance emphasizes the need to assess bioequivalence of the test product (T) to the reference product (R) based in part on showing equivalent performance of the device characteristics using validated analytical methods. Tab 2, at 4-5, 7, 22. For example, FDA notes that greatest assurance of equivalence occurs when the test product uses the same brand and model of device as the reference product. *Id.* at 7. The 2003 Draft BA/BE Guidance also recommends that all *in vitro* tests be validated prior to the study to ensure accuracy and precision, and that analytical methods used to evaluate product samples be validated. *Id.* at 11.

These themes resonate throughout the Agency's discussion of *in vitro* tests useful in characterizing BA and BE:

- *Single Actuation Content (SAC) through container life* – measures delivery of drug discharged from the actuator of the device to ensure that “the T product delivers an equivalent amount of drug relative to the R product over the labeled number of actuations.” *Id.* at 12.
- *Droplet size and particle size distribution* – influence deposition of drug in the nasal passages, and should be thoroughly characterized using validated analytical methods. *Id.* at 13-15. In particular, “Nasal spray formulations frequently contain suspended drug substance in the

^{20/} The history of assay development for the detection of FP in plasma has been one of continuous improvements, starting with a detection limit of 50pg/ml and currently validated by GSK at 5pg/ml. Technical issues, including further assay development, should not therefore be a valid reason for omitting adequate pharmacokinetic data from ANDAs.

presence of insoluble suspending agent, which complicates the particle size characterization.” *Id.* at 17.

- *Spray pattern* – important to characterize and quantify using validated analytical methods that will determine whether the size and shape of the spray patterns are equivalent. *Id.* at 17-19.
- *Plume geometry* – the angle, width, and height of the fully developed plume of the spray after it exits the actuator should be documented using the same analytical method. *Id.* at 20-21.
- *Priming and repriming* – data showing comparable number of actuations to prime the product on initial use and to reprime the product after periods of nonuse are critical “to document that each product delivers the labeled dose within the number of actuations stated in the R [reference] product labeling . . .” *Id.* at 21.

Nevertheless, the discussion in the Draft Guidance of standards for assessing the BA and BE of the formulation and device delivery system is incomplete. For example, the Draft Guidance recommends that ANDAs for a suspension formulation include data demonstrating “comparable” particle size distribution. *Id.* at 6. Nowhere, however, is comparability defined in the document. ^{21/} As stated in our comments of June 2003, the particle size distribution for suspension products should be *equivalent* to the reference product, not just comparable. *See* Tab 8, at 7. A working group was formed within the Product Quality Research Institute to investigate a particular statistical methodology for determining equivalence of particle size distributions and the Working Group submitted its Work Plan in the summer of 2002. ^{22/} GSK has participated within this working group and, as of this date, the research objectives of this group have not been completed.

In addition, GSK has previously filed extensive comments – including requests for clarification and suggested revisions – to the discussion of the *in vitro*

^{21/} *See* Tab 14, Comments of the Generic Pharmaceutical Association (GPhA) Re: Docket No. 99D-1738 (July 7, 2003) at 3 (“It is not clear how it can be verified that the same particle size is used in the reference and in the ANDA test product if no validated technology exists at this time.”).

^{22/} *See* Tab 15, Product Quality Research Institute, *Work Plan: Investigation of an Optimized Chi-square Method for Comparing Particle Size Distribution Profiles Obtained by Cascade Impactors with Specific Reference to Equivalence Testing of Orally Inhaled and Pressurized Nasal Drug Products* (Summer 2002).

BA and BE tests described in the Draft Guidance. See Tab 8, at 10-14. For example, our comments:

- Note that SAC can be influenced by the physical age of the suspension, and thus that SAC should be applied throughout the shelf life of R and T products at equivalent ages. *Id.* at 10.
- Request clarification on how data for droplet size distribution by laser diffraction should be evaluated. *Id.* at 11.
- Suggest revisions to aspects of the description of the test for drug in small particles/droplets. *Id.* at 12.
- Request scientific support for the suggested analysis procedure for plume geometry. *Id.* at 14.
- Request clarification on why the requirements for priming comparison are tighter than the requirements for dose uniformity. *Id.*
- Request clarification on key terminology and suggest inclusion of a glossary. *Id.* at 13.

The performance of the device delivery system is critical to the safety and efficacy of nasal drug products such as Flonase®. The Agency must complete the process for developing validated *in vitro* performance measures and standards for comparison of test and reference products, taking into account the numerous comments received from interested parties, and finalize the guidance document to clarify those standards for industry. Until these steps are taken, it would be premature for FDA to take action on ANDAs for these products.

B. FDA Should Complete its Guidance Process and Provide Interested Persons an Opportunity to Review the Final Guidance in Advance of Any ANDA Approvals

FDA set out in advance to describe a set of *in vitro* and *in vivo* studies that would, when finalized, represent a valid methodology for ensuring the equivalence of locally acting generic and pioneer nasal spray products. The more than five years that have ensued, including several public meetings and the issuance of two draft guidance documents, reflect the complexity of the scientific

challenges that are presented. At this point, the Agency does not even have a proposed statistical analysis plan “on the table” for review and comment. 23/

The Agency itself has conceded that the development of valid standards in this area has been a struggle. 24/ In light of these concerns, and the incomplete stage of the guidance development process, it should be clear that the Agency has not yet arrived at a complete and valid methodology or paradigm for assessing the BE of locally acting nasal spray products – and, in particular, suspension products – for purposes of section 505(j) of the FDCA. GSK requests that the Agency move expeditiously to do so, and remains committed to supporting the effort.

Finally, there has been an important change in the law that confirms the need for FDA to complete this guidance process before reaching any final decisions on ANDAs. Congress has now expressly authorized FDA to use “alternative” BE methods for non-systemic drugs. See 21 USC 355(j)(8)(C), as amended by the MMA. However, if FDA chooses to do so, Congress has required that such methods be established as “scientifically valid” and have the capability “to detect a significant difference between the [proposed] drug and the listed drug in safety and therapeutic effect.” 21 USC 355(j)(8)(C).

Agency action on individual ANDAs prior to completion of the guidance development process would, in this instance, raise a significant issue under traditional standards of reasoned agency decisionmaking. See 5 USC 706(2)(A); *Motor Vehicle Manufacturers Ass'n v. State Farm Mut. Ins. Co.*, 463 U.S. 29, 43 (1983). Here, FDA has sought to develop a valid analytical approach to assessing the BE of nasal spray products. However, after more than five years of process, the Agency has been unable to move beyond the “draft” guidance stage and, even more, has yet to issue key components of the methodology for public review and comment. For FDA to take action on an ANDA under these circumstances, particularly with respect to the more challenging nasal suspension products, would call into question

23/ The generic manufacturers, as well, have recognized the incomplete state of the Agency’s draft guidance. See Tab 14, Comments of the Generic Pharmaceutical Association (GPhA) Re: Docket No. 99D-1738 (July 7, 2003) at 3 (stating that it is “unclear which test(s) [outlined in the 2003 Draft Guidance] is the primary measure of equivalence” and requesting FDA to “clarify its position regarding the pass/fail criteria for approval of ANDAs performing the proposed tests”).

24/ See Comments of W. Adams, Ph.D., before the OINDP Subcommittee of the ACPS (July 17, 2001), Transcript at 36, at <http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3764t1.txt>. (“I wanted to emphasize that the issue of establishing bioequivalence for nasal sprays goes back for many years. In fact, Beconase AQ, a GlaxoSmithKline product, went off exclusivity back in July of 1990, and at the present time, 11 years later, there is still no generic product for this innovator product. So, we are still struggling with issues with regard to establishing bioequivalence for such products.”).

whether reasonable, scientifically supported, or "scientifically valid" criteria had been applied. 21 USC 355(j)(8)(C); *see A.L. Pharma, Inc. v. Shalala*, 52 F.3d 1484, 1490 (D.C. Cir. 1995) (remanding case to FDA to obtain explanation of Agency bioequivalency determination).

GSK has no objection to FDA approval of an ANDA for a fluticasone propionate nasal spray product that meets the statutory criteria and can otherwise be assured of being therapeutically equivalent to Flonase®. Here, however, the question of what is required scientifically to make the requisite showing is by no means straightforward. GSK believes that the guidance development process for nasal spray products is, in this instance, the only suitable means of establishing valid BA and BE methods, as required by the statute. The nasal spray guidance process has been supported by the work of numerous Agency committees, public meetings, and public comments. *See* Section II.B, *supra*. GSK and others have submitted extensive comments on the 1999 and 2003 versions of the Draft BA/BE Guidance and are prepared to comment promptly on the promised statistical appendices to the 2003 Draft BA/BE Guidance. *See* Tab 2, at 3 (noting that a series of attachments are still being drafted by the Agency and are not yet available for comment). Completing the guidance development process is the means for FDA to meet the statutory requirement set forth in section 505(j)(8) for developing valid criteria, *a priori*, to assess the BA and BE of non-systemic drug products.

IV. CONCLUSION

It is premature for the Agency to take action on any pending ANDA's for generic fluticasone propionate nasal spray products. Rather, GSK urges the Agency to expeditiously complete the guidance process, taking into account the many thoughtful comments that have been presented to date. Until the Agency has finally determined and issued a scientifically valid set of measures and methods for assessing the BE of nasal spray products, it would be inappropriate to take any action on any ANDAs that reference Flonase®.

Thus, based on the foregoing grounds, GSK requests that the Commissioner take, and/or refrain from taking, the actions specifically described at the outset of this petition, under "ACTIONS REQUESTED."

V. ENVIRONMENTAL IMPACT

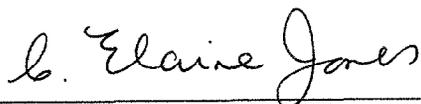
The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

VI. ECONOMIC IMPACT

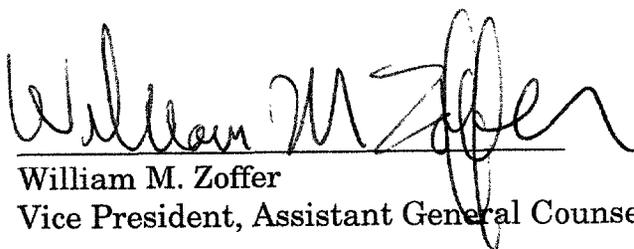
Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

VII. CERTIFICATION

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.



C. Elaine Jones, Ph.D.
Vice President, US Regulatory Affairs



William M. Zoffer
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cc: David M. Fox
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