DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

May 3, 2004

FILE COPY

Frederick H. Branding
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Chicago, Illinois 60602-4207

Dear Mr. Branding:

Your petition requesting the Food and Drug Administration to make a determination that no abbreviated new drug application for Fluticasone Propionate Nasal Spray will be approved unless it contains bioavailability and bioequivalence studies, was received by this office on 05/03/2004. It was assigned docket number 2004P-0206/CP1 and it was filed on 05/03/2004. Please refer to this docket number in future correspondence on this subject with the Agency.

Please note that the acceptance of the petition for filing is a procedural matter in that it in no way reflects an agency decision on the substantive merits of the petition.

Sincerely,

Jennie C. Butler, Director
Division of Dockets Management
Office of Management Programs
Office of Management

2004P-0206

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May 1, 2004

VIA FACSIMILE (301-827-6870)
and UPS OVERNIGHT

Dockets Management Branch
U.S. Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

CITIZEN PETITION

The undersigned petitioner submits this Citizen Petition in quadruplicate, pursuant to Section 505(j)(8) of the Federal Food, Drug, and Cosmetic Act ("the FD&C Act"), 21 U.S.C. § 355(j)(8), as amended, and regulations 21 C.F.R. §§ 10.20, 10.30, 314.94(a)(7), and 320.21.

A. Action Requested

Petitioner requests that the Food and Drug Administration ("FDA") make the determination that no Abbreviated New Drug Application ("ANDA") seeking FDA premarket approval of a generic formulation of Fluticasone Propionate Nasal Spray, 50 mcg shall be received for substantive review, or granted final approval, unless such an ANDA contains successful results of bioavailability and bioequivalence studies conducted under the methodologies set forth in FDA's draft guidance document entitled *Draft Guidance for Industry, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, dated April 2003.

B. Statement of Grounds

The reference listed drug for ANDAs for Fluticasone Propionate Nasal Spray, 50 mcg is Flonase®, manufactured by GlaxoSmithKline. Flonase® is a drug product with a suspension formulation and a metered-dose nasal spray delivery system, indicated for local action in the treatment of chronic obstructive pulmonary disease.

In April 2003, FDA issued a draft guidance document entitled *Draft Guidance for Industry, Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (hereafter, "Nasal Spray Bioequivalence Guidance"). This guidance prescribes, *inter alia*, criteria for bioequivalence studies that are required in ANDAs seeking regulatory

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approval to market locally acting drugs in metered-dose inhalers, and in metered-dose spray pumps (such as Fluticasone Propionate Nasal Spray, 50 mcg).

Petitioner maintains that the scientific principles and testing criteria set forth in the Nasal Spray Bioequivalence Guidance are reasonable and appropriate standards for establishing the bioequivalence of generic formulations of Fluticasone Propionate Nasal Spray, 50 mcg, to Flonase®. In this regard, petitioner notes that: (1) FDA guidance documents have been upheld by the courts (see Berlex Laboratories v. Food and Drug Administration, 942 F. Supp. 19 (D.D.C. 1996); (2) FDA often requires adherence to the criteria of draft guidances, even before they are issued in final form; and (3) the recently-enacted Medicare Prescription Drug, Improvement, and Modernization Act of 2003 amends the FD&C Act to give FDA explicit authority to establish bioavailability standards for non-systemically absorbed drugs, such as Fluticasone Propionate Nasal Spray, 50 mcg. 21 U.S.C. § 355(j)(8)(A)(ii).

Accordingly, petitioner requests that FDA:

- require the following bioequivalence tests and studies prescribed by the Nasal Spray Bioequivalence Guidance be conducted and submitted to the agency in any ANDA for Fluticasone Propionate Nasal Spray, 50 mcg, to permit the ANDA to be received by the agency for substantive review (pursuant to 21 C.F.R. §§ 314.94(a)(7) and 314.101); and

- require the results of such tests to establish the bioequivalence of any generic formulation of Fluticasone Propionate Nasal Spray, 50 mcg to Flonase®, to permit final approval of any such ANDA (pursuant to 21 U.S.C. § 355(j)(8)(A)(ii) and 21 C.F.R. § 320.21).

1. ***In Vitro* Bioequivalence (BE) Tests**

Seven *in vitro* tests are recommended by the Nasal Spray Bioequivalence Guidance (pp. 10-21) to characterize locally acting drugs delivered by nasal sprays:

- 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
- Drug particle size distribution by microscopy
- Spray pattern
- Plume geometry
- Priming and repriming

These tests are relevant to nasal sprays, whether formulated as solution or suspension products. The Nasal Spray Bioequivalence Guidance recommends a population bioequivalence (PBE) approach for demonstrating BE for different tests, such as (1) single actuation content, (2) droplet size distribution by laser diffraction, (3) particle/droplet size distribution by cascade

impactor, and (4) spray pattern. The Guidance unfortunately does not describe the method of statistical analysis to be used under the PBE approach, and FDA has not published the statistical methods for this recommended approach. Once the appropriate statistical method becomes available from the agency, PBE may be applied to the recommended in vitro tests. In the absence of public availability of any validated methodology, it is essential that these *in vitro* tests are evaluated on the basis of point estimates (90% - 110%), the comparative variability (range) of the test and reference product. These standards should not be relaxed.

2. *In vivo* BE Study with Clinical Endpoint for Local Delivery

The clinical BE study for any Fluticasone Propionate Nasal Spray, 50 mcg generic drug product should be conducted by strictly following the procedures recommended in the Nasal Spray Bioequivalence Guidance (pp. 21-25). In particular, the equivalence analysis should be conducted as an evaluable analysis rather than intent-to-treat analysis. In addition, an efficacy analysis should be conducted to demonstrate study sensitivity to the test and reference products. The efficacy analysis should be conducted as an intent-to-treat analysis, and the intent-to-treat population should be clearly defined. The endpoints for the equivalence and efficacy analyses should be expressed as mean change from baseline (pretreatment) of the Total Nasal Symptom Score (TNSS), expressed in absolute units, rather than percentage change from baseline. For the equivalence and efficacy analyses, the primary endpoint should be reflective of scores for the 12-hour pooled TNSS over the two-week randomization period of the study. The instantaneous scores should be submitted as a secondary endpoint.

For equivalence comparison of test and reference products, statistical equivalence criteria (90% confidence interval) for the specified endpoints must be within the acceptable BE limits. The BE limits for the 90% confidence interval for the test/reference ratio of the change from baseline in the untransformed TNSS should be within 80% to 125%. In addition, 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. These standards should not be relaxed.

3. *In vivo* BE Study with Pharmacokinetic Endpoint (Systemic Exposure Study)

This type of study, also prescribed by the Nasal Spray Bioequivalence Guidance (pp. 25-27) assesses the systemic exposure of the absorbed drug, and applies to this product because of the known systemic effects of Fluticasone Propionate. Flonase® is a suspension formulation, and the active drug can be assayed reliably in the appropriate biological fluid when dosed at the maximum labeled adult dose in a single dose study. The bioequivalence studies should be conducted at a dose not exceeding the daily recommended dose. Reliable pivotal BE measures, such as $AUC_{0\text{-}tlast}$ (total exposure) should be estimated and C_{max} (peak exposure) should be measured 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).

Bioequivalence should be assessed by applying statistical bioequivalence criteria. The 90% confidence intervals for $AUC_{0\text{-tlast}}$ and C_{max} should remain within the acceptable range (80% - 125%). This standard for documentation of BE should not be relaxed.

C. Environmental Impact

Under 21 CFR § 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

D. Economic Impact Statement

According to 21 CFR § 10.30 (b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

E. 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 that are unfavorable to the petition.

Respectfully submitted,

Frederick H. Branding

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FXB:kxm
cc: Gary J. Buehler, R.Ph. (HFD-600)
Dale P. Conner, Pharm.D. (HFD-650)