Review of A Bioequivalence Study with a Clinical Endpoint

ANDA # 77-538

Apotex Inc.

Fluticasone Propionate Nasal Spray, 50 mcg

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Submission dates reviewed: 2/25/05, , 5/26/05, 8/12/05, 8/30/06

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Executive Summary

This double-blind, randomized, multi-center, placebo controlled, parallel-group study in the treatment of the symptoms of seasonal allergic rhinitis (SAR) demonstrates that Apotex Inc.'s Fluticasone Propionate Nasal Spray, 50 mcg, is bioequivalent to Flonase® Nasal Spray, 50 mcg.. The sponsor's statistical analyses shows that the 90% CI of the test/reference ratio of the mean change from baseline reflective Total Nasal Symptom Score (TNSS) to the average reflective TNSS over the 14-day treatment period is (85%, 114%)[1]. The sponsor's analysis also concluded that both Flonase® Nasal Spray, 50 mcg, and Apotex Inc.'s Fluticasone Propionate Nasal Spray, 50 mcg, are superior to placebo ($p<0.05$) product.

The FDA statistical review, following adjustment in the FDA per protocol population[2], concludes that the 90% CI of the test/reference ratio of the mean change from baseline at the sample median (8.57) of the reflective Total Nasal Symptom Score (TNSS) to the average reflective TNSS for the sample over the 14-day treatment period is (80.2%, 107.2%), within the bioequivalence limits of (80%, 125%). The FDA statistical consultant confirmed that both the test and reference products were shown to be statistically superior to placebo (test vs. placebo: $p=0.012$; reference vs. placebo: $p=0.005$) demonstrating that the study is sensitive enough to detect a difference between products.

Of 1117 screened patients, 875 patients were enrolled into a 7-day placebo lead-in period receiving only placebo nasal spray. According to the sponsor's statistical analyses, 618 patients were randomized into the active treatment period and included in the Safety population, 573 in the Intent-to-Treat (ITT) population and 525 in the Per Protocol population (PPP)[3]. After further adjustment in the FDA statistical analysis, a total of 576 patients were included in the FDA modified ITT population (MITT) and 529 in the FDA per protocol population.

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[1] Excluded patients #0026 and 0016; the sponsor did not report the 90% CI including these two patients that were later included in their per protocol population.

[2] FDA per protocol population included patients #0026, 0016, 0014 and excluded patients 0067, 0004, 0037, 0012, from the sponsor's per protocol population. See statistical review for details.

[3] ITT: all safety patients who had completed placebo run-in period (at least 6 doses recorded in period 1), had mean reflective TNSS at least 6 during the last 3 days of placebo run-in period and Day 1 AM of treatment period (period 2), had a valid baseline measure, and had at least 1 post randomization measurement.
PPP: all ITT patients who had 7 assessments during the last 3 days of placebo run-in period and the AM of Day 1, had a period 2 first dose date less than 2 days after the period 1 last dose date, had compliance of at least 80% (at least 11 doses completed) in study drug administration, had a compliance of at least 80% (at least 22 valid assessments completed) and had no medical conditions/protocol deviations. Included patients #110026 and #060016.

I. Recommendation for Approval

The data submitted to ANDA 77-538, using the primary endpoint of the mean change from baseline[4] at the sample median (8.57) of the reflective Total Nasal Symptom Score (TNSS) to the average reflective TNSS over the 14-day treatment period, are adequate to demonstrate bioequivalence of Apotex Inc.'s Fluticasone Propionate Nasal Spray, 50 mcg, with the reference listed drug, GlaxoSmithKline's Flonase® Nasal Spray, 50 mcg. Both active products demonstrated superiority over the Placebo arm. Therefore, the test product is recommended for approval.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The study #FLUT-NASO-01NB06-PA was a randomized, double blind, comparative study of Apotex Inc.'s Fluticasone Propionate Nasal Spray, 50 mcg, versus the reference listed drug, Flonase® Nasal Spray, 50 mcg, in the treatment of seasonal allergic rhinitis (SAR). Eight hundred seventy five (875) patients with a TNSS of at least 6 based on combined signs and symptoms of sneezing, nasal itching, nasal congestion, and rhinorrhea were enrolled into a 7-day placebo lead-in period to identify and exclude placebo responders. Placebo responders were defined by the sponsor as patients with the mean baseline TNSS less than 6. Six hundred eighteen (618) patients with a mean reflective score of 6 or greater during the last 3 days of placebo run-in period and Day 1 AM were randomized to receive the test, reference or placebo product once a day for 14 days.

B. Comparative Efficacy

The accepted primary endpoint of this study is the mean change from baseline reflective Total Nasal Symptom Score (TNSS) to the average reflective TNSS over the 14-day treatment period. The baseline reflective TNSS was assessed by the mean (based on total of all four individual symptoms) score from twice daily reflective TNSS assessments on Day -3, Day -2 and Day -1 reflective TNSS and reflective TNSS on the morning of Day 1 (total of 7 evaluations). Instead of averaging the TNSS over the entire 14-day treatment period as recommended, the sponsor reported the 90% CI of the least squares (LS) mean reduction of reflective TNSS from baseline to Day 14 for the test and reference products as (85% and 114%).

Reviewer's Comments: *The sponsor calculated the 90% CI of the T/R ratio using the following method: [(LsMean Flonase change + UCL 90% CI)/LsMean Flonase Change, (LsMean Flonase Change + LCL 90% CI)/LsMean Flonase Change]; where, the UCL and LCL are defined as the upper and lower confidence interval of the difference=(Ls Mean Fluticasone - Ls Mean*

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[4] The draft guidance recommends defining the average TNSS at baseline as the average (arithmetic mean) of the AM and PM TNSS's from days 5, 6, and 7 of the baseline period, plus the AM TNSS from day 8 (first day of the treated period). Thus, seven individual TNSS's-four AM and three PM- are to be averaged.

Flonase). The 90% CI for the difference in mean change from baseline between the test and reference products was reported as a secondary endpoint.

The FDA statistical consultant stated that the sponsor's 90% CI approach is an outmoded approximate method and unacceptable. See FDA statistical summary for details.

The OGD recommends that the baseline be calculated by averaging the 7 reflective TNSS scores of day -3 through day 1 (AM TNSS from the first day of the treatment period), for each treatment group. The treatment period reflective TNSS is to be averaged over the entire 14-day treatment period for each treatment group. To meet the bioequivalence criteria, 90% CI of the test/reference ratio of the mean change from baseline reflective Total Nasal Symptom Score (TNSS) to the average reflective TNSS over the 14-day treatment period must be within the limits of 80% and 125%, using ANCOVA with baseline as a covariate for calculating the 90% CI at the sample median (not mean) of the baseline reflective TNSS scores in the evaluable population for all 3 study arms.

C. Comparative Safety

The safety data submitted in this ANDA confirm that the test product did not cause any worse adverse events compared to the reference product in the treatment of SAR. Headache (Test: 2.8%, Reference: 3.5%, Placebo: 3.4%) was the most frequent adverse event reported during the treatment period.

No serious adverse events occurred during the treatment period. One patient (site #02/0046) experienced a serious adverse event during the placebo lead-in period unrelated to the study medication. This patient was hospitalized and treated for gastroenteritis.

Clinical Review

I. Introduction and Background

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity. Flonase® (fluticasone propionate) nasal spray is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. It is indicated for the management of the nasal symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and nonallergic rhinitis in adults and pediatric patients four years of age and older. Adult patients are to be started on a 200-mcg once daily regimen (two 50-mcg sprays in each nostril once daily). An alternative 200-mcg/day dosage regimen can be given as 100 mcg twice daily (one 50-mcg spray in each nostril twice daily). Maximum total daily doses should not exceed two sprays in each nostril (total dose, 200 mcg/day). There is no evidence that exceeding the recommended dose is more effective.

Fluticasone propionate delivered by the intranasal route has an absolute systemic bioavailability averaging less than 2%. Intranasal treatment of patients with allergic rhinitis results in low plasma concentrations of fluticasone propionate that are not always measurable by conventional techniques.

However, there are now more sensitive analytical techniques that are adequate for evaluating pharmacokinetics of this product in the blood stream.

A. Drug Established Name, Drug Class,

Drug Established Name: Fluticasone Nasal Spray, 50 mcg
Drug Class: Corticosteroid

B. Trade Name of Reference Drug, NDA number, Date of approval, Approved Indication(s), Dose, Regimens

Reference Drug (NDA number): Flonase® Nasal Spray, 50 mcg (NDA 20-121), GlaxoSmithKline
Date of approval: 10/19/94
Approved indication(s): It is indicated for the management of the nasal symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and nonallergic rhinitis in adults and pediatric patients four years of age and older.

Recommended dosing regimens: two 50-mcg sprays in each nostril once daily or one 50-mcg spray in each nostril twice daily as directed

C. Regulatory Background

The following submissions have been reviewed by the OGD for fluticasone propionate nasal spray:

1. INDs, Protocols (P), and/or Control Documents (CD) submitted by Apotex

Submission date	OGD document no.	Sponsor
10/2/01	01-505	Apotex

2. INDs, Protocols (P), and/or Control Documents (CD) submitted by other generic sponsors

Submission date	OGD document no.	Sponsor
1/21/00	00-038	(b) (4)
8/16/00	00-341	Hi-Tech
6/21/01	01-338	Hi-Tech
7/20/01	01-383	(b) (4)
6/12/02	IND (b) (4)	(b) (4)
6/14/02	02-343	Hitech Pharmacal
7/26/02	02-439	(b) (4)
9/12/02	02-603	(b) (4)
10/28/02	IND (b) (4)	(b) (4)
2/14/03	IND	
4/22/03, 5/12/03	P03-020/03-303, 03-379	(b) (4)
6/13/03	P03-035	(b) (4)
7/2/03	03-524	(b) (4)
12/5/03	P03-070	(b) (4)

3. Previous ANDA submissions for same or related product submitted by Apotex: none

4. Previous ANDA submissions for same or related product submitted by other generic sponsors

Submission	Submission date (approval date)	Name of the Product/Sponsor
ANDA 76-504	10/4/02 (2/22/06)	Fluticasone Nasal Spray, 50 mcg; Roxane
ANDA (b) (4)	3/3/03 (pending review)	Fluticasone Nasal Spray, 50 mcg, (b) (4)
ANDA (b) (4)	8/6/03 (deficiency issued 10/31/05)	Fluticasone Nasal Spray, 50 mcg, (b) (4)
ANDA (b) (4)	5/24/04 (pending review)	Fluticasone Nasal Spray, 50 mcg, (b) (4)
ANDA (b) (4)	12/30/04 (pending review)	Fluticasone Nasal Spray, 50 mcg, (b) (4)
ANDA 77-570	4/14/05 (pending review)	Fluticasone Nasal Spray, 50 mcg, Hi-Tech

D. Other Relevant Information: None

II. Description of Clinical Data and Sources

Study Centers/Investigators: The study was performed by 25 principal investigators at 25 sites.

Site	Investigator	Address	*Number of patients	Site	Investigator	Address	*Number of patients
1	Adelglass, Jeffrey, MD	Research Across America, Dallas TX	25	14	Lampi, Kathy L., MD	Asthma & Allergy Associates, Rockville, MD	15
2	Andrews, Charles P., MD	Allergy Diasnostics, San Diego, CA	39	15	Maccia, Ciement A., MD	Asthma, Sinus & Allergy Centers LLC, Warren, NJ	25
3	Brandon, Milan, MD	California Research Foundation, San Diego, CA	5	16	Manning, Michael E, MD	Allergy & Immunology Associates, Scottsdale, AZ	38
4	Coats, Teresa, MD	Benchmark Research, Austin, TX	14	17	Matz, Jonathan, MD	Atlantic Asthma & Allergy Center, Inc. MD	22
5	De Angelo, James, MD	Allergy & clinical Immunology Associates Pittsburgh, PA	34	18	Pollard, Stephen J, MD	Family Allergy & Asthma Research Institute, Louisville, KY	20
6	DeCotiis, Bruce, MD	Ocean Allergy & Respiratory Research Center, Brick NJ	15	19	Ratner, Paul H, MD	Sylvana Research Associates, San Antonio, TX	40
7	Emanuel, Ivor A, MD	Benchmark Research, San Francisco, CA	25	20	Rowe, Michael S, MD	Michigan Respiratory Health & Research Institute, Novi, MI	16
8	Ford, Linda B., MD	The Asthma and Allergy Center, P.C.	35	21	Seger, William, MD	Benchmark Research, Fort Worth, TX 76135	25
9	Goldstein, Stanley, MD	Island Medical Research, P.C., Commack, NY	8	22	Sullivan, Michael J, MD	Allergy, Asthma, and Immunology Associates, PC, Lincoln, NE	32
10	Gould, Andrew, MD	Commonwealth Ear, Nose & Throat, Louisville, KY	14	23	Tripathy, Ita, MD	Clinical Research of the Ozarks, Inc., Rolla, MO	47
11	Hampel, Frank C, MD	Central Texas Health Research, New Braunfels, TX	40	24	Wald, Jefferey A, MD	Kansas City Allergy & Asthma, Overland Park, KS	24
12	Herrington, Darrell T., D.O	West Texas Medical Associates, San Angelo, TX	10	25	Winder, John A, MD	Toledo Center for Clinical Research, Sylvania, OH	11
13	LaForce, Craig F, MD.	North Carolina Clinical Research, Raleigh, NC	39	-	-	-	-

*randomized

Study Period: August 13, 2004 to November 4, 2004

Enrollment: A total of 618 patients who met the inclusion/exclusion criteria were randomized into the 7-day placebo lead-in period.

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission: ANDA 77-538, Electronic Submission in FDA review (e-CTD) format, submitted on 2/25/05

Study Amendments: Amendment #1 submitted on 5/26/05 included correction of patient diary data. In response to the OGD's request of a list of investigators and patients randomized into each site, the sponsor submitted the amendment #002 on 8/12/05. On August 30, 2006, the sponsor submitted additional data requested by the OGD.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations (DSI) Report (7/31/06):

Based on inspection results from three clinical sites (#2, 13, and 23), the DSI concluded that the authenticity of the drugs used in this study can not be assured because these sites failed to maintain the reserve samples at the inspected clinical sites.

Reviewer's Comments: *Other than issues related to maintenance of retention sample and sealed code for FDA inspection, the investigator found no other major objectionable evidence that indicate that the study data are not acceptable. The sponsor is advised of the need to comply with the regulations regarding retention of study drug samples. If this is not done correctly in future studies, the study may be found unacceptable to support approval of the application.*

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor stated that the study was conducted according to Good Clinical Practice (GCP) regulations, U.S. Food and Drug Administration regulations (CFR 21 Parts 50, 56, and 312) and applicable International Conference on Harmonization Guidelines (ICH) guidelines.

The sponsor's original protocol and consent forms were reviewed and approved by the Institutional Review Board (IRB) prior to initiation of the study. Patients were required to sign and date an informed consent form approved by an IRB/Ethics Board prior to screening.

Reviewer's Comment: *The sponsor's study appears to be in compliance with accepted ethical standards.*

D. Evaluation of Financial Disclosure: The sponsor provided signed financial disclosure documents certifying that they have not entered into any financial arrangement with study investigators that could be affected by the outcome of the study.

IV. Review of Bioequivalence Study with Clinical Endpoints

A. Brief Statement of Conclusions

The FDA statistical analysis confirms that the study meets established bioequivalence criteria for the test product vs. the reference product.

B. General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's study (protocol #FLUT-NASO-01NB06-PA) was reviewed to determine bioequivalence of the test product and the reference product. The accepted primary endpoint for bioequivalence studies of this product is the mean change from baseline reflective Total Nasal Symptom Score (TNSS) to the average reflective TNSS over the 14-day treatment period. The sponsor's proposed primary efficacy parameter was different than that recommended by OGD. Therefore, the FDA statistician evaluated the accepted endpoint for bioequivalence, using the recommended statistical analysis. Secondary parameters were considered as supportive information.

C. Detailed Review of Bioequivalence Studies with Clinical Endpoints

In support of the approval of their product, the sponsor submitted a bioequivalence study with clinical endpoints (protocol #FLUT-NASO-01NB06-PA).

Protocol Review (FLUT-NASO-01NB06-PA):

1. Apotex submitted an original protocol (OGD control document #01-505) on 10/2/01.
2. Based on the decision (see meeting minutes of 11/6/01) of the working group refining the guidance for bioequivalence studies of nasal steroid drug products, the sponsor was advised (11/20/01) to use 2 sprays per nostril once a day, evaluate both instantaneous and reflective scores twice daily at 12-hour intervals, calculate baseline period from both AM and PM reflective TNSS for the 3 days immediately prior to randomization, including Day 1 AM measurement, and treat baseline as a covariate in the analysis.
3. On 2/19/02, the OGD clarified (OGD control document #01-598) that the sponsor's proposed primary efficacy parameter, "the mean change from baseline of the TNSS reflective scores over the entire treatment period", is acceptable.
4. The original protocol dated 7/13/04 was approved by the IRB and amended (7/28/04) once prior to initiation of the study. The protocol was revised primarily to clarify inclusion/exclusion criteria and the study procedures.
5. On 8/13/04, the first patient was enrolled into this study.

Sponsor's protocol#: FLUT-NASO-01NB06-PA

Title: Bioequivalence study of 200 mcg of fluticasone propionate nasal spray (Apotex Inc., Canada) vs. 200 mcg of Flonase® Nasal Spray (GlaxoSmithKline, USA) in patients with seasonal allergic rhinitis

Objective: The primary purpose of this study was to evaluate the bioequivalence of fluticasone propionate nasal spray vs. the US brand reference product, Flonase® Nasal Spray, in the treatment of symptoms of seasonal allergic rhinitis

Study Design: This was a randomized, double-blind, parallel-group study design comparing the following three products during the 14 day treatment period:

1. Test: Apotex Inc.'s Fluticasone propionate nasal spray 200 mcg (50 mcg per actuation), 2 sprays in each nostril once daily, lot # GN-4297 (b) (4) batch #R04 0420, R04 0437)
2. Reference: Flonase® Nasal Spray, 200 mcg (GlaxoSmithKline), lot # C099476 (R04 0419, R04 0436), 2 sprays in each nostril once daily
3. Vehicle (Placebo): Apotex Inc., Canada, lot# 04020604 (R04 0421, R04-0438), 2 sprays in each nostril once daily

All treatments were administered intranasally in the morning at approximately 8 am, except the first dose, which was administered in the study area during Visits 1 and 2. Patients were randomly assigned in a 2:2:1 ratio to one of the three treatment groups.

The study included two periods: an initial single-blind, placebo run-in period (Period 1), followed by a double-blind, randomized, placebo-controlled, parallel group treatment period (Period 2). Patients who met the screening criteria were to participate in the single-blind placebo run-in period of 7-8 days (Period 1) to determine baseline nasal symptom scores. During this time, all patients received placebo. Patients were instructed to record daily diary cards, nasal symptom scores and adverse events. Patients who were considered placebo responders were not enrolled into Period 2 of the study.

Patients had to have mean reflective AM and PM total nasal symptom scores (TNSS) of at least 6 measured during the last three days of the placebo run-in and the morning (pre-dose) of Day 1 of the treatment period to receive the study drug. The treatment period (Period 2) began the day of Visit 2 and the duration of treatment was 14 days. Patients returned for the final visit (Visit 3) on Day 14-16.

Blinding:

(b) (4) . packaged all study drug and placebo medications. The study medications used for the placebo run-in and treatment period were placed in a masking device, a black opaque container, to ensure blinding. The smell and taste of the study medications were indistinguishable. Medication labels did not identify the treatment.

Individual patient randomization codes were available to the investigator in case of emergency. The code could have been accessed by scratching off the laminate on one part of the 2-part label applied to the masking device. Access was to be documented and the research contracting organization (CRO) was to have been notified. According to the sponsor's study report, no patients were unblinded in this study.

AAI Development Services, Inc. (AAI), CRO for this study, was involved in protocol development, monitoring project management, quality assurance, data management, and statistical analysis. The randomization code was not to be accessible to any staff involved in the conduct, monitoring, or management of the study until the database was locked. The randomization code was stored at (b) (4) and was also provided to a statistician at AAI not involved in the study. The code was sealed in a tamper-evident envelope and kept in a secure locked place until after all data had been collected.

Study Population:

Inclusion Criteria

Patients who met the following criteria were enrolled by the sponsor:

1. Patients who gave their written informed consent.
2. Males and females at least 18 years of age or older.
3. Females of childbearing potential had to use effective contraceptive measures, defined as abstinence or use of an effective method of birth control (double barrier [partner using condom, and female using diaphragm, contraceptive sponge, spermicide, or intrauterine device (IUD)] or use a hormonal contraceptive [oral, patch, inserted under the skin, or injected into the muscle]). Female patients using oral contraceptives or levonorgestrel implants must have started the method at least 90 days prior to the screening visit. Female patients who were postmenopausal or surgically sterile for at least 1 year did not have to use any birth control measures.
4. Clinically acceptable medical history consistent with seasonal allergic rhinitis, defined as symptoms present during the previous two grass and/or pollen seasons or past two years.
5. Positive skin test to at least one seasonal allergen present in the geographical area that had a predictable allergen season (e.g., birch pollen, ragweed, grasses) with a minimum skin test response of 3 mm greater than a negative control within 12 months of screening.
6. Patient had not started immunotherapy or had a change in dose in the one month prior to Visit 1, and did not plan on starting immunotherapy during the study.
7. Patients were not to receive pre-seasonal shots while in the study.
8. In order to enter the placebo run-in period, a reflective TNSS of at least 6 in the 24 hours prior to Visit 1.
9. In order to enter the treatment period, a baseline reflective TNSS should be at least 6, based on the mean TNSS for the last 3 days of the placebo run-in period plus the morning (pre-dose) of Day 1 of the treatment period.
10. Clinically acceptable results from the screening physical and nasal examinations, and medical history.

11. In order to enter the treatment period, clinically acceptable results for laboratory tests were required. Patients with clinically significant findings may have been excluded from the treatment period, at the Investigator's discretion.
12. Patient must have been available for the full duration of the study and must not have planned to travel outside the study area for a substantial portion (> 48 hours) of the study period.

Exclusion Criteria

Patients were excluded if any of the following criteria were present:

1. Presence of complete or almost complete nasal obstruction, acute or chronic sinusitis, abnormal sinus radiograph, an upper or lower respiratory tract infection or rhinitis medicamentosa.
2. Systemic or intranasal decongestants of any kind, hydroxyzine, or anticholinergics in the 3 days prior to Visit 1.
3. Anti-allergy therapy (e.g., antihistamines): those with QD or BID dosing in the 7 days prior to Visit 1, and those with TID or QID dosing in the 3 days prior to Visit.
4. Nedocromil or cromolyn sodium, or leukotriene antagonists in the 14 days prior to Visit 1.
5. Corticosteroid therapy (parenteral, intranasal, oral, inhaled, or potent topical) in the one month prior to Visit 1.
6. Tricyclic antidepressants in the 60 days prior to Visit 1.
7. Respiratory tract infection requiring antibiotic treatment within four weeks of Visit 1.
8. Presence of a marked septal deviation.
9. Presence of large nasal polyps.
10. Nasal septal ulcers, nasal surgery, or trauma within three months of Visit 1.
11. Known or suspected hypersensitivity to corticosteroids.
12. Presence or history of tuberculosis, or cardiovascular, renal, neurologic, liver, or endocrine dysfunction.
13. Identified as placebo responder.
14. Must not have received an investigational drug in the 30 days preceding Visit 1.
15. History of alcohol, drug, or substance abuse in the 12 months prior to screening.
16. Known non-responder to corticosteroids.
17. Use of any other rhinitis treatments during the study other than the study drugs provided.
18. Uncooperative or noncompliant.
19. Female patient who was pregnant or breastfeeding.
20. Current asthma, with the exception of mild intermittent asthma.
21. Current ocular herpes simplex.
22. Current cataracts.
23. History of glaucoma.
24. History of hypersensitivity to fluticasone propionate.

Restricted concomitant medication use

- Start or a change in dose of immunotherapy in the one month prior to Visit 1
- Systemic or intranasal decongestants of any kind, hydroxyzine, or anticholinergics in the three days prior to Visit 1
- Anti-allergy therapy (e.g., antihistamines): those with QD or BID dosing in the seven days prior to Visit 1, and those with TID or QID dosing in the three days prior to Visit 1

- Nedocromil or cromolyn sodium, or leukotriene antagonists in the 14 days prior to Visit 1
- Corticosteroid therapy (parenteral, intranasal, oral, inhaled, or potent topical) in the one month prior to Visit 1
- Tricyclic antidepressants in the 60 days prior to Visit 1.

Patients were instructed not to receive preseasonal shots during the study. All concomitant medications were documented and reviewed by an investigator.

Removal or early termination of study patients

Reasons for early termination include the following:

- A placebo responder
- Required therapy with any excluded medication
- Interrupted study drug administration for more than 3 days
- Diary cards showed less than 80% compliant in Period 1
- An adverse event such that the patient's health would be in jeopardy from continued participation in the study or unable to complete the study successfully
- Unable to comply with study requirements
- Patients with reported upper respiratory tract infection may be withdrawn at the discretion of the investigator.

Study participants who were discontinued from the study treatment period for any reason were to have the same study exit procedures as per Visit 3. An investigator conducted nasal examinations as soon as possible (within seven days) after discontinuation, and the results were recorded.

Procedures/Observations, and safety measures:

Patients who met inclusion/exclusion criteria and did not meet the definition of placebo responder during the placebo run-in period were randomized to one of the three treatment groups. Study medication was provided to the sites in groups of 5 patients. Each nasal spray container was labeled with randomization/medication number which was designated as the "patient number". The batch number packaged by (b) (4) was designated as "lot number". Sites were instructed to assign the study medication sequentially from the lowest number.

The study included two periods: an initial single-blind, placebo run-in period (Period 1), followed by a double-blind, randomized, placebo-controlled, parallel group design treatment period (Period 2).

The sponsor's study schedule is listed below.

Study Schedule

		Period 1	Period 2		
Screening		**Visit 1**	**Visit 2**	**Telephone Contact**	**Visit 3**
Study Day	**Up to Day -38**	**Day -7 to -8**	**Day 1**	**Day 7**	**Day 14 - 16**
Assignment of Screening Number	X				
Study Procedures Reviewed with Patient	X	X	X	X	X
Study Informed Consent	X				
Medical History	X				
Physical Examination	X				
Nasal Examination	X		X		X
Skin Testing	X				
Urine pregnancy test (all females)	X		X		X
Laboratory Testing	X				X
Inclusion/Exclusion Criteria		Xβ	Xφ		
Adverse Event Reporting		X	X	X	X
Vital Signs (Blood Pressure, Heart Rate)	X	X	X		X
Assignment of Medication Number			X		
Drug administration		X	X	X	
Daily Diary Cards		Xα	Xα	Xα	
Study Medication Dispensed		X	X		
Study Medication Returned			X		X
Study Medication Primed		X	X		

α - Two diary card entries per day (AM and PM)
β - All inclusion / exclusion except inclusion #8
φ - Inclusion criterion #8 and review all other inclusion/exclusion criteria

Screening Visit (performed from -38 days prior to Visit 1)

- Patients were instructed to read and sign an informed consent form. Screening evaluations included collection of demographic information, vital signs, relevant medical and allergy history. Physical exam included nasal examination.
- Patients were given a skin prick test to identify positive allergy to prevalent allergens if no skin test results were available within the past 12 months.
- Blood and urine samples were collected for hematology, biochemistry, urine pregnancy test for females if applicable, and urinalysis.

Period 1: Placebo Run-In

Visit 1(Day -7 to -8)

- Any concomitant medication use within the previous 30 days was recorded.
- Investigator reviewed patients' medical history and medication use.
- Patients were provided with the nasal dispenser and study medication (placebo) supply.
- All nasal dispensers were to be primed prior to distribution. All patients were scheduled to receive placebo but were blinded to this fact.
- The first dose of placebo was administered in the study area. Patients were instructed to administer the study medication once daily in the morning (approximately 8 a.m., except for the first dose during Visit 1) for 7-8 days.
- Instructions on the proper use of daily diary cards were provided to each patient and Daily diary cards were provided. Patients were required to complete daily diary cards (AM and PM), including time of study drug administration, symptom scores, and adverse events.
- Patients recorded both 12-hour "reflective (assessment over the last 12 hour period)" score

and "instantaneous (how patient feels at the time completing assessment)" score twice a day approximately 12 hours apart.

- Four signs and symptoms of SAR were evaluated using the following 4-points scale for sneezing, nasal itching, congestion, and rhinorrhea. Each symptom was rated by the patient using the following numerical rating scale:

  0=none
  1=mild, sign or symptom clearly present but minimal awareness; easily tolerated
  2=moderate, definite awareness of sign or symptom that is bothersome but tolerable
  3=severe, sign or symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping

- Patients were asked to record a reflective TNSS for the previous 24 hours. Reflective scores of four symptoms (sneezing, nasal itching, congestion, and rhinorrhea) on a four points scale ranging from 0 (no symptom) to 3 (severe symptom) were recorded. If total TNSS is less than 6, the patient did not continue in the study. The sponsor calculated TNSS using the sum of each individual symptom scores at each assessment.
- Patients were asked to return the diary cards and the nasal dispensers at the next visit.
- Patients were instructed to return to the clinic for scheduled visit 2 in the morning.

Period 2: Treatment (Day 1 to Day 14)

Treatment was 14 days in duration. Patients were randomized into one of three treatment groups (test, US reference, placebo) in a ratio of 2:2:1, respectively, and were assigned a study-specific medication number. Daily diary cards (AM and PM) were to be completed throughout this time.

Visit 2 (Day 1, 7-8 days after Visit1): Active treatment visit

- Patients were instructed to return to the clinic in the morning and provide used medication canisters and daily diary cards.
- Patient's diary cards were reviewed to check patient compliance. If the patient was not compliant, counseling was provided.
- Investigator conducted nasal examinations and the results were recorded.
- Females had a urine sample for pregnancy testing and a negative test result was required prior to continuation of the study.
- Patients had to have mean AM and PM total nasal symptom scores (TNSS) of at least 6 measured during the last three days of the placebo run-in and the morning (pre-dose) of Day 1 of the treatment period to be eligible to receive the study drug. Potential placebo responders were excluded from the study if the mean baseline total nasal symptom score (TNSS) was less than 6.
- A new canister of medication and new diary cards were provided. All nasal dispensers were primed prior to distribution.
- Patient was instructed to administer the study medication once daily at 8:00 AM for 14 days (on Day 1, dosing may occur later than 8:00 AM) and record diary cards daily.
- A telephone contact was performed on Day 7 to monitor the patient compliance or adverse event.

- Patients were instructed to stop the study medication after taking the last medication on Day 14 and to stop diary card completion after Day 14, and return to the clinic on Day 14, 15 or 16.

Visit 3 (Final Visit, Day 14-16)

Fourteen days after starting the active treatment, the patient returned for the final visit (Visit 3) on Day 14-16.

- Used medication canisters and diary cards were returned.
- All adverse events were recorded.
- Investigator conducted nasal examinations and the results were recorded.
- Eligible females repeated pregnancy test.
- Blood and urine samples were obtained for hematology, chemistry, and urinalysis.

Endpoints:
The total nasal symptom score (TNSS) from the patient diary cards was the efficacy measurement in this study. It combined scores from rhinorrhea, nasal congestion, nasal itchiness, and sneezing, each on a scale of 0-3, with a maximum possible combined score of 12. Morning and evening (AM and PM) scores were obtained immediately prior to dosing and approximately 12 hours later, respectively. Reflective scores were recorded by the patient for the period since the last scoring (previous 12 hours) and instantaneous scores were recorded by the patient for their current condition.

The establishment of baseline score was based on the reflective AM and PM scoring on the last 3 days of the placebo run-in period, and AM scoring (prior to the study drug dosing) on Day 1 of the 14 day randomized treatment period, resulting in 7 total AM and PM ratings. Potential placebo responders were excluded from the study if the mean baseline total nasal symptom score (TNSS) was less than 6.

Baseline was calculated with the average of the AM and PM reflective scores during the last three days of the placebo run-in period and AM reflective score on Day 1 of the treatment period (average of 7 TNSS). The primary efficacy variable was the absolute change from baseline in reflective TNSS, calculated by subtracting the baseline from the average of the PM reflective score on Day 1 of the treatment period and the AM and PM reflective scores on Days 2 to 14 (a total of 27 TNSS).

Reviewer's Comments: *The accepted primary endpoint of this study is the mean change from baseline reflective TNSS to the average reflective TNSS over the 14-day treatment period. A statistical review was requested to verify the sponsor's analysis.*

Pollen Counts:

All sites were required to keep daily logs of the pollen counts in their local area throughout the study. The daily pollen count logs were retained as part of source documentation at each study site.

Reviewer's Comments: *The primary allergens were identified for each patient and pollen counts were documented for each site. Most patients had a positive allergen test to ragweed in all treatment groups. At least one seasonal allergen pollen count was above the moderate pollen count range at each site during the study period.*

Statistical analysis plan

It was anticipated that the majority of the patient's self-assessed symptom scores would be accurate and non-missing. Therefore, for purposes of statistical analysis, missing score self-assessments were recorded as missing. No imputation of the symptom scores was performed to "adjust" for the missing scores.

Primary Endpoint: The primary endpoint was the mean change from baseline for the reflective TNSS averaged over a period of two weeks (PM score on Day 1 and 26 AM and PM scores on Days 2 to 14). The per protocol population was used for the bioequivalence analysis and the intent-to-treat population for superiority testing.

Sample Size: Based on the sponsor's data, the change from baseline was expected to have a standard deviation of 2.5 units. Assuming that there was a difference of 1.5 units (effect size) in mean change from baseline for the reflective TNSS between the reference product and placebo, the sponsor calculated that a sample size of 180 evaluable patients would provide over 80% power to show that the 90% confidence interval of the difference between the test and reference products would be less than 0.5 (delta) of the TNSS effect size.

Therefore, a sufficient number of patients were enrolled in the placebo run-in period to allow 560 patients to be randomized to study treatment (224 to each active treatment and 112 to placebo) in order to obtain at least 450 evaluable patients (180 in each active treatment arm and 90 on placebo) for the equivalence assessment. The sponsor's calculations included a dropout/non-compliance rate of 20%.

Analysis:
According to the sponsor, bioequivalence to the reference product was to be declared if the 90% confidence interval for the difference in change from baseline in reflective TNSS between the test and reference product was within 0.5 (plus or minus) of the drug effect size. The drug effect size was based on the difference in change from baseline in TNSS between the reference product and placebo. The mean change from baseline for the reflective TNSS (averaged over the two-week treatment period) was compared among the treatment groups using an analysis of covariance (ANCOVA) with terms for treatment, pooled site, and baseline TNSS. The baseline TNSS measurement was used as the covariate. The mean change from baseline was calculated by subtracting the baseline from the average of the PM score on Day 1 and the AM and PM scores during Days 2 to 14 of the treatment phase of the study. Efficacy was declared for the test and/or reference product if the Type 1 probability associated with the comparison with the placebo group was less than 0.05. The 90% confidence interval for the difference in mean change from baseline between the test and reference products was calculated.

Laboratory values and vital sign measurements were summarized by descriptive statistics.

Reviewer's Comments: *To meet the bioequivalence criteria, the 90% CI of the test/reference ratio of mean change from baseline reflective TNSS [averaging reflective AM and PM scores on Days -3, -2 and -1 of the placebo run-in period and the AM score (prior dosing) on Day 1 of the active treatment period] to the average reflective TNSS over the 14-day treatment period must be within 80% and 125%.*

The OGD recommends the use of ANCOVA for the statistical analysis of this study. The baseline TNSS should be used as a covariate for calculating the 90% CI at the sample median of the baseline reflective TNSS in the FDA evaluable population for all 3 study arms.

Study Conduct

Discussion of Safety, ITT and PP populations:

Safety population was defined as all patients who received at least one dose of study medication after randomization. ITT and PP populations for efficacy analysis were defined by the sponsor as follows:

Intent-to-treat (ITT) population
- Received one dose of study drug post-randomization
- Completed placebo run-in period (at least 6 doses recorded in Period 1)
- Had a mean reflective TNSS of at least 6 during the last three days of placebo run-in period and the AM assessment of Day 1 of treatment period (Period 2)
- Had a valid baseline measurement
- Had at least one post-randomization measurement.

Per-protocol population (PPP)
- Were included in the ITT population
- Had seven assessments during the last three days of placebo run-in period and the AM of Day 1
- Had a Period 2 first dose date less than two days after the Period 1 last dose date
- Had compliance of at least 80% in study drug administration, e.g., the number of study drug doses was at least 11 in Period 2
- Had a compliance of at least 80% in recording reflective TNSS scores on diary, e.g., number of valid assessments was at least 22 or the number of missing or invalid assessments was less than 6 in Period 2. The following was used for the determination of valid assessments:
    - Any PM assessments done less than 8 hours after the AM dose were considered invalid, and
    - Any AM assessments done after dose administration were considered invalid.

Discussion of compliance:

A patient was considered dosing compliant if he/she completed at least 80% (number of study drug doses was at least 11 in period 2) of study drug dosing.

A patient was considered compliant with recording of TNSS diary if he/she had seven assessments during the last three days of placebo run-in period and the AM of Day 1 and had recorded at least 80% of the expected TNSS scores on the diary, e.g., number of valid assessments was at least 22 or the number of missing or invalid assessments was less than 6 in Period 2.

Reviewer's Comments: *Most patients were at least 80% compliant in terms of study medication intake. The minimum number of doses a patient could have taken to be eligible for inclusion in the FDA evaluable population is 11 (75% dosing compliant). The minimum number of reflective TNSS scores required for the FDA evaluable population analysis is 21 (>75% compliant).*

Retention of Reserve Samples:

(b) (4) . packaged all study drug and placebo medications. At the end of the study, (b) (4) retained at least 50 units each of test product, reference product, and placebo. The test articles for retain requirements were randomly selected by each of the clinical sites and sent back to (b) (4) for storage.

Baseline Characteristics

Of 1117 patients screened, 875 patients entered the placebo run-in period. Of these patients, 618 patients who met the randomization criteria were randomized to the active treatment period and were included in the sponsor's safety population. Of these patients, 12 patients did not complete the study due to the following reasons: required therapy with excluded medication (1), non-compliant (2), had upper respiratory tract infection (1), adverse event other than upper respiratory infection (1), protocol violation (3), and other (4).

The sponsor tabulated demographic and baseline characteristics of all treatment groups in Table I.

Table I: Baseline Characteristics (ITT population per sponsor)

	Reference Flonase® Nasal Spray (n=238)	Test Fluticasone Nasal Spray (n=225)	Placebo (n=110)	P-value
Age in years (mean ± SD)	38.27± 11.80	39.37 ± 11.83	35.58 ±12.25	0.0240
Age min, max	18-71	18-73	18-80	
Gender (number, %)				0.3033
Male	78 (32.8%)	59 (26.2%)	33 (30%)	
Female	160 (67.2%)	166 (73.8%)	77 (70.0%)	

Race (number, %)				0.3529
Caucasian	184 (77.3%)	175 (77.8%)	81 (73.6%)	
Black	19 (8%)	20 (8.9%)	10 (9.1%)	
Hispanic	21 (8.8%)	25 (11.1%)	17 (15.5%)	
Asian	8 (3.4%)	8 (1.3%)	1 (0.9%)	
Other	6 (2.5%)	2 (0.9%)	1 (0.9%)	
^Baseline ITT population :mean ± SD (range)				
rTNSS score	8.50 ± 1.68 (6-12.00)	8.73 ± 1.70 (6-12.00)	8.95 ± 1.69 (6-12.00)	0.0557
iTNSS score	7.97 ± 1.98 (3.29-12.00)	8.23 ± 2.03 (3.29-12.00)	8.22 ± 1.95 (3.71- 12.0)	0.3056

All percentages are based on non-missing data.
^Baseline score is derived from the average of the AM and PM scores from last 3 placebo run-in days and the Day 1 AM score.

*Number of years with known allergy (mean ± SD)				
Years	22.8 (13.05)	19.7 (11.61)	20.9 (12.56)	
^^Primary Allergen (number, %)				
Grass	69 (7.96%)	64 (7.38%)	34 (3.92%)	
Tree	53 (6.11%)	56 (6.46%)	29 (3.34%)	
Ragweed	237 (27.34%)	218 (25.14%)	107 (12.34%)	

*Based on patients randomized into active treatment period (Test: 246, Reference: 254, Vehicle 118)
^^based on patients randomized into placebo run-in period (Test: 338, Reference: 359, Vehicle: 170)

Reviewer's Comment: *The baseline characteristics appear to be comparable in all treatment groups. The FDA statistician confirmed that all baseline characteristics are not statistically different among treatment groups (p≥ 0.14), except for age. The mean age in the vehicle group is slightly lower than the active treatment groups (T: 39, R: 38, V:36).*

Results

Of 618 patients randomized into the active treatment period, 254 were randomized to the reference group, 246 were randomized to the test group, and 118 were randomized to the placebo group. Of these patients, 12 patients (4 reference, 7 test, 1 vehicle) were discontinued and 606 patients completed the study. 573 patients were included in the ITT population, and 523 patients were included in the PP population by the sponsor.

At site 22, the baseline TNSS could not be validated in any of the 32 patients randomized because the patients were inadvertently provided with the information about baseline TNSS requirements for eligibility during the screening visit. Therefore, these patients were not included in the sponsor's equivalence or efficacy analyses. This decision was made by the sponsor prior to completion of the study.

On February 25, 2005, the sponsor noted error in data entry and submitted revised data. Patient #060016 (site 6) was initially designated as a non-evaluable patient because this patient had missing TNSS PM assessment on Day 6 of the placebo run-in period. AAI data management verified the hard copy of the case report form and found that the patient's assessment score had not been properly scanned, leaving blanks on the scanned copy of the CRF. If the period 1 Day 6 PM assessment was captured in the database, this patient would have been deemed evaluable and included in the sponsor's per protocol population analysis.

On May 20, 2005, data management verified that several other patient's diary data were questionable. Patients #230062 and #210057 had scores recorded as "4" on the hard copy of the diary. Since patients were instructed to record their TNSS by using the scale of 1 to 3, a score of "4" noted on the diary was transcribed as blank in the dataset. Patient #110026 was originally designated as a non-evaluable based on missing value for Day 5 PM reflective rhinorrhea score in the dataset. However, based on the information confirmed by the hard copy of the case report form, the missing value was changed to "3".

Therefore, patients #110026 and #060016 who had been incorrectly excluded from the sponsor' s PP population analysis were included in the sponsor's modified dataset. [see updated submissions dated #0001 (5/26/05) and #0002(8/12/05) for details]

The sponsor's summary of results is shown in Table II (per sponsor).

PPP	**Reference (n=219)**	**Test (n=204)**	**Placebo (n=102)**
LSMean reduction in reflective TNSS (rTNSS) at day 14 compared to baseline	-2.36	-2.34	-1.45
^90% CI for the ratio of the mean reduction (rTNSS)	(0.85, 1.14)		
LSMean reduction in instantaneous TNSS (iTNSS) at day 14 compared to baseline	-1.99	-2.09	-1.29
^90% CI for the ratio of the mean reduction (iTNSS)	(0.89, 1.21)		
ITT population	**Reference (n=238)**	**Test (n=225)**	**Placebo (n=110)**
Change in mean instantaneous TNSS LSMean from baseline to on-treatment period	-1.99	-2.06	-1.34
Test vs. placebo	P=0.0024		
Reference vs. placebo	P=0.0057		
Change in mean reflective TNSS LSMean from baseline to on-treatment period	-2.33	-2.33	-1.52
Test vs. placebo	P=0.0011		
Reference vs. placebo	P=0.0009		

^90% CI of ratio is defined by the sponsor as: [(LSMean Flonase Chg + UCL 90% CI)/LSMean Flonase Chg,(LSMean Flonase Chg + LCL 90% CI)/LSMean Flonase Chg]; Where, the UCL and LCL are defined as the Upper and Lower Confidence Interval of the Difference=(LS Mean Fluticasone - LS Mean Flonase). This is based on previous population analysis (T: 203, R: 218, P: 102) without two patient's data (#110026, 050016). The sponsor did not provide revision to 90% CI calculation for the ratio of the mean reduction.

Reviewer's Comments:

1. The sponsor included patients that received ongoing immunotherapy (allergen) for treatment of SAR during the study in the per protocol population. Receiving immunotherapy for treatment of SAR may alter the outcome of the study. However, if they have received these medications at least a month prior to the study and no dosing adjustment occurred during the study, this reviewer agrees with the sponsor to include those patients in the evaluable population. These patients were spread among all 3 study arms.

2. The sponsor stated that sites with less than 15 patients were pooled by geographic region prior to unblinding of the data for analysis of efficacy. Site 25 had 16 patients but was pooled with site #20 due to geographic proximity. Sites pooled together for these analyses were : (#4, 12, 10) and (#18, 3), and (#7, 6, 9) and (#20, 25). All other sites remained separate. A statistical review is requested to evaluate the sponsor's analysis.

3. Patients #110026 and #060016 should be included in the PP population. The FDA statistical reviewer was requested to verify and include these patients in the analysis.

4. Patient #14 (site 13) was excluded by the sponsor because this patient discontinued the study early. The case report form documented that this patient requested to receive other treatment for increasing signs and symptoms of SAR. Due to lack of efficacy, this patient should be included in the per protocol population analysis using LOCF.

5. The sponsor excluded 32 patients who were enrolled at site 22 from their analysis because the baseline TNSS could not be validated. According to the sponsor, these patients were inadvertently provided with the information about baseline TNSS requirements for eligibility during the screening visit. This is appropriate since these patients may have reported higher scores in order to be eligible for participation.

D. Bioequivalence Conclusion

The FDA statistical analysis confirms that the study meets the 90% CI requirements for bioequivalence. The test/reference ratio of the mean change from baseline TNSS to the average reflective TNSS over the 14-day treatment period at the sample median was (80.2%, 107.2%), which is within the bioequivalence limits of (80% , 125%).

V. Comparative Review of Safety

A. Brief Statement of Conclusions

This study showed no clinically significant difference between the generic and reference products with regard to the adverse events reported.

B. Description of Adverse Events

No death occurred in the study. Most patients reported adverse events mild or moderate in severity.

Of 618 patients randomized into the active treatment period, 110 patients (42 in the test, 47 in the reference, and 21 in placebo group) experienced at least one treatment-emergent adverse event. Adverse events reported as possibly or probably related to the study drug occurred in 17 patients (6.7%) in the reference group vs. 12 patients (4.9%) in the test group. The most frequently reported adverse event was headache (Test: 2.8%, Reference: 3.5%, Placebo: 3.4%).

The most common treatment-emergent adverse events by organ class reported in the study patients were respiratory, thoracic, and mediastinal disorders (Test: 5.3%, Reference: 8.7%, Placebo: 5.9%). Of these, pharyngolaryngeal pain (Test: 2.0%, Reference: 2.0%, Placebo: 0.8%) was the most reported symptom. None of these events was reported by a higher proportion of test or placebo patients compared to the reference group.

One serious adverse event (Patient #02/0046) unrelated to the study medication was reported during the placebo lead-in period. This patient was hospitalized for treatment of gastroenteritis and did not enter the treatment period.

Two patients (07/0039, 11/0023) discontinued participation in the treatment period due to adverse events unrelated to the study drugs. Patient #07/0039 developed severe flu symptoms 2 days after initiation of placebo treatment (period 2). Patient #11/0023 developed a cold the day after initiation of test product. Both patients recovered completely.

Several patients had hematology, chemistry, and urinalysis values outside the normal range at the end of treatment period (Visit 3) as follows.

Site	Patient	Treatment	Comment
7	28	Test	Decreased WBC count to 2.4 (10^9/L) from baseline of 4.5 (10^9/L), low neutrophils of 1.1 (10^9/L), and low platelets of 108 (10^9/L)
7	32	Reference	Elevated AST, LDH
8	13	Test	Elevated platelet counts from 335 (10^9/L) at baseline to 436 (10^9/L) at visit 3 but returned to normal value after a repeated test in 1 week
8	34	Placebo	Elevated eosinophils
10	27	Reference	Elevated uric acid
16	34	Test	Elevated AST, ALT, and LDH; each of these elevations was less than 3 times the upper limit of the reference ranges.
17	12	Test	3+ hemoglobin in urine
23	24	Reference	Elevated AST and ALT

Investigators reported these abnormalities to be clinically significant, but deemed not to be related to the study drug.

Reviewer's comment: *Given that these laboratory abnormalities affected a very small proportion of patients, distributed among all treatment arms, and involved a variety of different findings, they do not suggest a drug-related effect.*

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Review of the Division of Scientific Investigation (DSI) Report (7/31/06)

Based on inspection results from three clinical sites (#2, 13, and 23), the DSI concluded that the authenticity of the drugs used in this study can not be assured because these sites failed to maintain the reserve samples at clinical sites. The investigator stated that each site failed to retain a sealed code for FDA to break the blind so whether all patients at these sites were dosed according to the randomization code is questionable. The DSI also recommended exclusion of patient #0067/2043 from site #2 from the bioequivalence evaluation due to prohibited medication use during the study.

Based on the DSI final report, a Form FDA-483 was issued to sites #23 and #2. At site #23, two objectionable items were noted. The investigator noted that this site failed to maintain and provide a sealed code for use by the FDA. There was no blinding code for treatment randomization available at the site to verify subject dosing because "scratch off" coding was sent to the sponsor and the sponsor maintained control of all randomization documents. Since the chain of custody was broken, randomization of the blinded study could not be confirmed. The investigator also stated that the study samples were not retained at the site and available for the FDA inspection. All clinical sites were instructed by the sponsor to return reserve samples to (b) (4)., which was involved in packaging and randomization of the study samples. Although study samples were sent back to this clinical site upon the FDA field investigator's request during the inspection, this procedure could not eliminate the possibility of the sample substitution/or alteration of the reserve samples by the sponsor.

Both of these above objectionable findings were also documented for sites #2 and 13 as well but the field investigator did not issue an FDA 483 for site #13.

At site #2, the investigator stated that patient #0067/2043 took benadryl during the treatment period and it was not reported in the case report form. The investigator recommended excluding this patient's data from the PP population analysis.

Reviewer's Comment: *As recommended by the DSI inspector, this reviewer agrees to exclude patient #0067/2043 from the PP population analysis but include in the ITT population analysis.*

Other than improper maintenance of retention sample and sealed code, the investigator found no other major objectionable evidence that indicate that the study data are not acceptable.

It is the sponsor's responsibility to ensure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63. If the sponsor fails to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.

For a blinded study, the study sponsor and/or drug manufacturer should provide a sealed randomization code for use by FDA. The sealed code should be maintained at each testing facility. In addition, the retention samples must not be returned to a the third party involved in packaging and randomization of the study samples. Please refer to "Handling and Retention of BA and BE Testing Samples", posted 5/25/04 for details.

B. Review of the FDA Statistical Report (5/21/06)

The FDA statistical analysis supports a finding of bioequivalence of the test and the reference products. The 90% CI of the test/reference ratio of the mean change from baseline reflective Total Nasal Symptom Score (TNSS) to the average reflective TNSS over the 14-day treatment period at the sample median for the FDA per protocol population is (80.2%, 107.2%), which is within the bioequivalence limits of 80% and 125%. Bioequivalence of the test product was demonstrated using baseline as a covariate for calculating the 90% CI at the sample median (8.57) of the baseline reflective TNSS scores in the evaluable population for all 3 study arms. The test and reference products also demonstrate superiority over Placebo group. See the FDA statistical review for details.

Based on this reviewer's comments above, the FDA statistician adjusted the sponsor's per protocol population by including patients #0026, 0016, 0014 and excluding patients #0067, 0004, 0037, 0012 in the FDA PP population. The summary of the equivalence test for the FDA PP population was shown below:

Equivalence analysis (FDA PP population)

Total mean Change from Baseline of the Reflective TNSS	Test LS Mean[1]	Reference LS Mean	The 90% CI for the Ratio of Means	Pass/Fail
Baseline of TNSS (Median = 8.57)	2.438	2.625	(0.802 , 1.072)	P
Baseline of TNSS (Mean = 8.78)	2.580	2.768	(0.812 , 1.068)	P
Baseline of TNSS (Cut off point = 8.521)	2.405	2.592	(0.800 , 1.073)	P
Change in Mean Instantaneous TNSS from Baseline				
Baseline of TNSS (Median = 8.14)	2.246	2.276	(0.839 , 1.159)	P
Baseline of TNSS (Mean = 8.16)	2.261	2.291	(0.840 , 1.158)	P
Baseline of TNSS (Cut off point = 7.34)	1.782	1.812	(0.800 , 1.204)	P

[1] The LS Means, in this case, are estimated means for each treatment at the indicated value of baseline, putting equal weight on each site.

Efficacy analysis (MITT population)

Change in Mean TNSS from Baseline	LS Means			p-value	
	Test	Reference	Vehicle	Test vs. Vehicle	Reference vs. Vehicle
Change in Mean Reflective TNSS from Baseline	2.25	2.36	1.54	0.012	0.005
Change in Mean Instantaneous TNSS from Baseline	2.26	2.40	1.52	0.008	0.001

Reviewer's Comments: *Based on the FDA statistical analysis, the test product is shown to be bioequivalent to the reference product. The 90% CI of the test/reference ratio of the mean change from baseline of the reflective Total Nasal Symptom Score (TNSS) to the average reflective TNSS for the sample over the 14-day treatment period at the sample median (8.57) is (80.2%, 107.2%), within the bioequivalence limits of (80%, 125%). Both the test and reference products were shown to be statistically superior to vehicle (test vs. placebo: p=0.012; reference vs. placebo: p=0.005).*

The FDA statistician also performed the 90% CI of the test/reference ratio of the mean change from baseline of the reflective Total Nasal Symptom Score at the sample mean (8.78) and instantaneous TNSS at the sample mean (8.16) and median (8.16). These secondary endpoint results were supportive of the primary endpoint results.

VII. Formulation

Ingredients	**Test Product** (%w/w)	***Flonase®** (%w/w)
Fluticasone Propionate	0.05	0.05
Benzalkonium Chloride, NF	(b) (4)	
Microcrystalline cellulose and carboxymethyl-cellulose sodium NF	(b) (4)	
Dextrose USP,	(b) (4)	
Phenylethyl alcohol USP	0.25	0.25
Polysorbate 80, NF	(b) (4)	
Water, Purified, USP		

*per Bioequivalence Checklist for First Generic ANDA 76-504 (Roxane)

** (b) (4) .

Reviewer's Comment: *According to the OGD Chemistry review #1, Apotex formulation was previously evaluated by the OGD Chemist and found acceptable by the Division of Bioequivalence in the review of IND* (b) (4) *(submission dated May 14, 2003,* (b) (4) *. Based on this review,* (b) (4) *labeled as* (b) (4) *in the reference formulation and* (b) (4) *, in Apotex' formulation is the same.*

The test formulation is qualitatively and quantitatively the same (within ± 5%) as the RLD.

VIII. Conclusion and Recommendation

A. Conclusion

The FDA statistical review of the data presented in this ANDA 77-538 supports a conclusion that Apotex Inc.'s Fluticasone Propionate Nasal Spray, 50 mcg, is bioequivalent to the reference listed drug, Flonase® Nasal Spray, 50 mcg. The 90% CI of the test/reference ratio of the mean change from baseline at the sample median (8.57) of the reflective TNSS to the average reflective TNSS over the 14-day treatment period is (80.2% , 107.2%), which is within the bioequivalence limits of (80% and 125%). Both the test and the reference products showed superiority over the placebo group.

B. Recommendations to be conveyed to Sponsor

The data submitted to ANDA 77-538, using the primary endpoint of the mean change from baseline reflective Total Nasal Symptom Score (TNSS) to the average reflective TNSS over the 14-day treatment period for the per protocol population, are adequate to demonstrate bioequivalence of Apotex Inc.'s Fluticasone Propionate Nasal Spray, 50 mcg, with the reference listed drug, GlaxoSmithKline's Flonase® Nasal Spray, 50 mcg. Both active treatments demonstrated superiority over the Placebo arm.

1. The current criterion for establishing bioequivalence of a generic fluticasone nasal spray based on the clinical endpoint study is a 90% confidence interval of the Test: Reference ratio of the mean change from baseline in the reflective TNSS score within the limits of (80%, 125%). The agency used ANCOVA method with baseline TNSS score as a covariate for calculating the 90% CI at the sample median (not mean) of the baseline reflective TNSS scores in the evaluable population for all 3 study arms.

2. Bioequivalence of your product was demonstrated using baseline as a covariate for calculating the 90% CI at the sample median (8.57) of the baseline reflective TNSS scores in the per protocol population for all 3 study arms.

3. According to the FDA statistical review, your proposed 90% CI approach is an outmoded approximate method. The method, based on the test and reference means difference confidence interval, does not take into account the uncertainty in the LSMean estimator and is no longer acceptable [(see Berger, R.L. and Hsu, J.C. (1996)].

4. The DSI issued a FDA Form 483 to two of three inspected sites because these sites failed to follow protocol procedures, maintain proper records and reserve samples at clinical sites. The reserve samples should not be transferred back to any organization that deals with packaging the test articles and reference standard for storage. This is to eliminate the possibility of commingling reserve samples from packaging activities (21 CFR 211.84 and 211.170) and bioequivalence studies (21 CFR 320.38 and 320.63). For your study, reserve

samples were sent to (b) (4)., which was involved in packaging and randomization of the study samples.

It is your responsibility to ensure that the clinical sites for all future BE studies comply with the current requirements as recommended in the final guidance, the *CDER Guidance for Industry: Handling and Retention of BA and BE Testing Samples, posted May 2004*. If you fail to comply with the Agency's regulations in 21 CFR 320.38 and 320.63 in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.

Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

Date

Dena Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

Date

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drug

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Carol Y. Kim
8/10/2007 08:04:29 AM
BIOEQUIVALENCE CLINICAL END POIN

Dena Hixon
8/10/2007 11:06:04 AM
MEDICAL OFFICER

Dale Conner
8/10/2007 04:47:13 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-538
Drug Product Name	Fluticasone Propionate Nasal Spray (Aqueous Suspension)
Strength	50 ug per Spray
Applicant Name	Apotex Inc.
Address	Richmond Hill, Ontario, Canada
Submission Date(s)	August 14, 2007
Amendment Date(S)	
Reviewer	Hoainhon Nguyen
First Generic	No
File Location	DFS

I. Executive Summary

The firm has submitted the current amendment in response to the DBE's deficiency comments sent in the letter dated July 27, 2007. The firm has adequately addressed the deficiencies concerning the validation procedure and data for the HPLC assay method used in the Cascade Impaction test. Although the validation procedure for the HPLC assay method of the Cascade Impaction test was found less than ideal, the validity of the data can be fully supported based on the additional information and data submitted in the current amendment. The firm is advised to use more relevant QC concentrations and more relevant lower calibration standards in future testing of similar samples. This *in vitro* test is now considered acceptable. The DSI inspection is considered not necessary at this time and the inspection request is withdrawn.

The *in vivo* BE study and the *in vitro* equivalence studies for the test product are **acceptable** with no further deficiencies.

The application is complete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray
Reference Listed Drug (RLD) Product	Flonase® (Fluticasone Propionate) Nasal Spray (Aqueous Suspension), 50 ug per spray
RLD Product's Manufacturer	GlaxoSmithKline
NDA No.	20-121
RLD Product's Approval Date	October 19, 1994
Indication	Flonase® Nasal Spray 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.

B. PK Information

See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc.

C. Contents of Submission

Study Types	Yes/No?	How many?
Amendment	Yes.	1

D. In-Vivo Study

See file v:\firmsam\apotex\ltrs&rev\77538n0205.doc for a detailed review.

Single-Dose Bioequivalence Study (PK Study)

Study Summary	
Study No.	AA23357
Study design	Randomized, Single-Dose, Two-Way Crossover
No. of subjects enrolled	100
No. of subjects completed	100
No. of subjects analyzed	99*
Subjects (Healthy/Patients?)	Healthy
Sex(es) included for subjects that completed the study(how many?)	Male: 45 Female: 54
Test product	Fluticasone Propionate Nasal Spray Aqueous Suspension
Reference (RLD) product	Flonase® (Fluticasone Propionate) Nasal Spray Aqueous Suspension
Strength tested	50 ug per spray
Dose	200 µg (50 µg spray X2 in each nostril)

*NOTE: Subject #29 had a nosebleed 32 minutes after dosing in Period I. Since this event occurred before the expected Tmax (approximately 2 hours), the adverse event was expected to affect the absorption of fluticasone for this subject. For this reason, the samples of Subject #29 were not analyzed and not included in the study analysis.

Summary of Statistical Data (N=99)		
Parameter	**Point Estimate**	**90% Confidence Interval (CI)**
LAUC0-t	0.99	91.3-107.9
LAUC∞	1.08	97.2-120.7
LCmax	1.01	94.0-109.4
Summary of Statistical Data (N=99) – Supportive Analysis*		
Parameter	**Point Estimate**	**90% Confidence Interval (CI)**
LAUC0-t	0.96	86.4-106.5
LCmax	1.01	94.0-109.4

***NOTE:** In the supportive analysis, AUCt and Cmax were calculated as specified in the DBE recommendation stated in Control Document No. 03-361 (See the DBE History section of this review):
"The AUCt should be based on at least four consecutive nonzero plasma concentration values. The AUC computation should be terminated at the last quantifiable plasma concentration before the first zero (BLQ) value following these four or more values. The PK analysis should include only those subjects that meet this rule for both periods, i.e., for both Test product and RLD.
"The Cmax should be computed as the maximum plasma concentration that occurs among the values used to compute the AUCt. A second maximum concentration that may occur after the data points used in the computation of AUCt [i.e., following the above mentioned zero (BLQ) value] is not the Cmax of interest."
In the main analysis, AUCt, AUCinfinity and Cmax were calculated with all data points included, whereas in the supportive analysis, any non-zero data point following the first zero (BLQ) value was excluded.

Comment on the Bioequivalence Study (PK Study):

The 90% confidence intervals for lnCmax, lnAUCt and lnAUCinfinity (main analysis only) were within the acceptable limits of [80.0;125.0] in the main and supportive analysis. The bioequivalence study conducted under fasting conditions is **acceptable**.

E. Formulation

See the review v:\firmsam\apotex\ltrs&rev\77538n0205.doc.

G. In-Vitro Equivalence Studies

See file v:\firmsam\apotex\ltrs&rev\77538n0205.doc for a detailed review.

H. Firm's Responses to DBE's Deficiency Comments:

The following deficiency comments were communicated to the firm in the letter dated July 27, 2007:

"In the current amendment, you informed the DBE that the previous HPLC assay validation data for the Cascade Impaction test were reported based on ***the total spiked amount not on the concentration****. We found the manner in which the validation data obtained and presented to the Agency rather unusual and unconventional. For the purpose of further verification of the HPLC assay validation data used in the Cascade Impaction test, we are requesting the following additional information:*

Please submit all relevant SOP's, all raw assay validation data, all actual Cascade Impaction sample data obtained by HPLC, chromatograms and copies of notebooks used in the validation of the HPLC assay for the Cascade Impaction test. Please be sure the address of the laboratory, the name of the analyst(s), their training records, the approval(s) by the laboratory supervisor(s), the dates of the validation as well as the dates of the Cascade Impaction sample analyses, and any deviations from the validation SOPs are clearly documented."

NOTE: The above information, which is usually examined in a study audit, was requested because the DSI could not schedule promptly a DBE-requested For-Cause inspection due to resource constrains.

In the current amendment, the firm has submitted the requested information and data which are summarized by the firm in the cover letter of the amendment (See the Appendix of the current review). The firm has also provided further detailed explanation concerning the unusual and unconventional manner in which the HPLC assay validation data were originally provided for the Cascade Impaction test.

- **Firm's Current, Additional Detailed Explanation Concerning the HPLC Assay Validation Data Submitted Previously for the Cascade Impaction Test:**

Response: Your comments are noted. Upon reflection of the statement in the current amendment that the previous assay validation data for the Cascade Impaction test is *based on the total spiked amount not on the concentration,* we would like to provide the following clarification for your consideration. We acknowledge that the statement was somewhat ambiguous and may have been an inaccurate depiction of what we meant to indicate.

In addition, as requested, all relevant SOPs, all raw assay validation data, all actual cascade impaction sample data obtained by HPLC, chromatograms and copies of notebooks used in the validation of the HPLC assay for the cascade impaction test have been provided. For ease of review, a hyperlinked guide to the information provided is available at the end of this response.

Clarification:

In the June 13, 2006 amendment, we presented QC samples at the levels 50% (250 µg/mL), 100% (500 µg/mL) and 150 % (750 µg/mL) in Table 1. It should be noted that the units were incorrectly presented in that table, in that they should have read "µg/g" rather than "µg/mL". As such, the use of the term total spiked amount was meant to explain that the values of 250, 500 and 750 µg/mL that was presented in Table 1, Question 2 of the June 13, 2006 amendment referred to the amount of the fluticasone proprionate spiked in samples to represent the QC concentrations.

Explained in more detail, the values of 250 µg/g, 500 µg/g and 750 µg/g reflect the amount of fluticasone propionate in samples as they would be collected from the cascade impaction apparatus. As per the cascade impaction method (PD-084), ten sprays are collected into the cascade impaction apparatus. If 100% of the sprays are collected from the apparatus for subsequent processing and HPLC injection, you would have 1 g of sample (i.e. 10 sprays x ~ 100 mg/spray = 1000 mg = 1 g) containing 500 µg of fluticasone propionate (i.e. each spray contains 50 µg of fluticasone propionate, and 10 x 50 µg = 500 µg). Hence, the sample

collected contains 500 µg fluticasone propionate/g of sample (i.e. 100% QC = 500 µg/g). Likewise, a QC standard at the 50% level would contain 250 µg/g and a QC sample at the 150% level would contain 750 µg/g.

To correlate these QC samples with the actual concentration of the analytical sample, the following explanation is provided. For HPLC analyses, the samples collected from the cascade impaction apparatus (glass adaptor, inlet cone and stage 0) are diluted in 200 mL of solvent and further diluted (4 mL in 10 mL). In the July 20, 2006 amendment, we converted the above, undiluted concentrations (i.e. 250 µg/g, 500 µg/g and 750 µg/g) to the diluted concentrations that would be injected into the HPLC in order to reflect the approach taken for presentation of concentrations in our standard curve (presented in Table 2 of the April 20, 2006 amendment). This was accomplished by taking into account the dilution factors, and the potency of fluticasone propionate. For example, at the 50% level, the concentration (µg/mL) of fluticasone propionate in the diluted sample was calculated as follows:

$$\frac{248.05\ \mu g/g}{200\ mL} \times \frac{4\ mL}{10\ mL} * 1g = 0.4961\ \mu g/mL$$

Note, the value of 248.05 µg/g is based upon addition of 2.843 mg of fluticasone propionate to a 11.3697 g sample of placebo (i.e. 2.843 mg/11.3697 g x 1000 µg/mg = 250.05 µg/g) and a potency value of 99.2% for fluticasone propionate (i.e. 250.05 µg/g x .992 = 248.050 µg/g).

Likewise, the values for the 500 µg/g (100% level) and 750 µg/g (150% level) samples were converted to values of 0.9922 µg/mL, and 1.4386 µg/mL, respectively.

Table 1 has been provided below to clearly illustrate the correlations between values presented in our June 13th and July 20th amendments for each QC level (50%, 100% and 150%).

Table 1 – Correlation between QC values presented in the June 13th and July 20th Amendments

	A	B	C	D	E
QC Std	Amount of Fluticasone Propionate Raw Material Added to QC Sample (mg)	Amount of Placebo added to QC Sample (g)	Concentration of Fluticasone Propionate in Undiluted QC Sample – uncorrected for potency [(A/B)*1000] (µg/g)	Concentration of Fluticasone Propionate in Undiluted QC Sample – corrected for potency [C*P] (µg/g)	Concentration of Fluticasone Propionate in diluted sample [(D/200mL)*4mL/ 10mL*1g)] (µg/mL)
~50%	2.843	11.3697	250.05	248.050	0.4961
~100%	5.848	11.6934	500.11	496.110	0.9922
~150%	7.506	10.3514	725.12	719.318	1.4386

Potency of Fluticasone Propionate (P) = 99.2%;
Lab Book Reference: 10040005, p.g. 187-199
1 gram of sample was extracted as per method

In summary, the validation was in fact performed at appropriate concentration levels within the range of the standard curve, however, the way in which we initially presented the values for the QC samples was not in line with the format in which we presented the values for the standard curve.

We trust that this explanation will provide clarification to the Agency that demonstrates that the manner in which the validation data was obtained is not unusual or unconventional and that essentially, the presentation is representative of the data obtained except for the initial misrepresentation of the units of the QC samples of µg/mL instead of µg/g. As such, it is considered that the validation data is adequately supportive of the method used for the Cascade Impaction test for Fluticasone Propionate Nasal Spray.

- **Training Records for Analysts:** The names of the analysts and their training records were provided. The firm also had the following comments concerning the training records:

As per company policy, employees must be trained on a procedure before they can perform a task. Since mid 2003, training records for all employees are maintained using a computer-based, validated SAP system. Reports printed from this electronic system are provided in this response. The chemists involved in the validation of the assay method and testing of the samples by cascade impaction were trained, however their training records relevant to laboratory testing from prior to implementation of the computer-based system (which are in hard copy) cannot be located. Ongoing efforts are in place to locate these records.

- **Relevant SOP's:** The firm has submitted the following SOPs:

SOP 12-0008: Elements Required for Validation of Analytical Method
Rev. 8 (Effective between 09/20/1999 – 04/16/2001)
Rev. 9 (Effective between 04/17/2001 – 10/07/2002)

SOP 12-0012: Elements Required for Validation of Analytical Assay Method
Rev. 0 (Effective between 10/08/2002 – 07/17/2003)
Rev. 1 (Effective between 07/18/2003 – current)

Please note that SOP 12-0008 was a general SOP for Validation of Analytical methods that was revised and divided into separate SOPs. SOP 12-0012 is applicable to the validation of analytical assay methods.

- **Initial (Pre-Study) Raw Assay Validation Data:** The data were obtained between 08/15/2000 and 09/20/2000 and included the validation protocol, lab book entries and chromatograms for: system precision data, method precision data (repeatability, interday collection, inter-lot collection), linearity, linearity range, limit of quantitation, limit of detection, robustness, specificity (interference and filter studies) and stability of standard and sample solution. The calibration standard used in the pre-study validation data included the following concentrations: 0.014 mcg/mL (also called "LOQ"), 0.155 mcg/mL, 0.306 mcg/mL, 0.608 mcg/mL, 1.21 mcg/mL and 1.95 mcg/mL.

- **Additional (Pre-Study) Raw Assay Validation Data: Method Precision – Repeatability and Intermediate Method Precision:** The data were obtained between 05/25/2004 and 06/08/2004 and included lab book entries and chromatograms for method precision (within-analyst) and intermediate method precision (between-analyst) studies. NOTE: The repeatability and intermediate precision studies used samples collected from the Cascade Impactor. Calibration standards used in these studies included 0.010 (also called "LOQ"), 0.36, 0.60, 1.2, and 1.7 mcg/mL, and QC (or "check standard") concentration of 1.2 mcg/mL.

- **Additional (Post-Study) Raw Validation Data: Accuracy and Precision @ 50%, 100% and 150%:** The data were obtained between 06/23/2006 and 06/06/2006 in response to the DBE's deficiency comments in the letter dated May 23, 2006. The data included the updated protocol "Validation Protocol for Aerodynamic Particle Size Determination in Fluticasone Propionate Nasal Spray, 50 µg/spray" dated 06/03/2006, lab book entries and chromatograms for the additional accuracy and precision studies. Calibration standards used in these studies included 0.009 (also called "LOQ"), 0.37, 0.62, 1.2, and 1.7 mcg/mL, and QC concentrations of 0.496, 0.992 and 1.44 mcg/mL.

- **Cascade Impaction Testing for Fluticasone Propionate Nasal Spray: Protocol and Sample Collection:** The Cascade Impaction testing and sample collection were conducted between 08/05/2004 and 08/17/2004. The lab book entries included the collection procedure, the ID's of the samples tested, the

weights of the samples before and after sample collection by the Cascade Impactor, the (b) (4) printouts of automated parameters of the Cascade Impactor, with warning signals, if any, for each run.

- **Cascade Impaction Testing for Fluticasone Propionate Nasal Spray: Sample Preparation and Acquisition of Data by HPLC:** The lab book entries between 08/05/2004 and 08/17/2004 for standard and sample preparations, including standard concentrations and sample dilutions prior to HPLC injection, were provided in this section of the amendment. The assay method No. PD-084 was cited. HPLC parameters and (b) (4) automated data acquisition parameters for each run were entered in this section of the lab book.

- **Cascade Impaction Testing for Fluticasone Propionate Nasal Spray: HPLC Chromatograms (Runs between 08/06/2004 – 08/17/2004):** Chromatograms for HPLC assays of the Cascade Impaction testing were provided serially.

I. DBE's Deficiency Comments for Firm's Current Responses:

1. In the current amendment, the firm's additional clarification and explanation for the previous erroneous and questionable presentation of the QC concentrations were corroborated by the lab book entries dated 06/03/2006, as well as corresponding chromatograms. It should be noted that the actual HPLC assay runs of the Cascade Impaction test samples included only the so-called "100% QC" (approximately 1.2 µg/mL) in duplicate at the beginning of each run (also called "checking standards"). The data for the so-called 50%, 100% and 150% QCs, as submitted in the amendment dated June 13, 2006, were obtained post-study, in response to the DBE's request for the validation data in the letter dated May 23, 2006.

2. Based on all lab book entries and chromatograms submitted in the current amendment, the following could be established concerning the during-study assay method validation procedure:

- For each bottle tested, there were three samples collected: Group 1 sample (of particle size >9 µm), Group 2 sample (of particle size of <9 µm) and Group 3 sample (of particle size of (b) (4)). These samples were diluted (with dilution factors of 200, 10 and 25, respectively) and run in duplicates.
- For each assay run, the sequence of the run was as follows: At beginning of each run, "checking standards" (same as "100% QC") in duplicate were placed, followed by 5 calibrations standards (with concentrations of 0.072 (also called "LOQ"), 0.36, 0.60, 1.21 and 1.69 µg/mL) and 2 blank samples. After that, duplicates of Group 1 sample of one tested bottle, duplicates of Group 2 sample and duplicates of Group 3 samples of the same bottle followed. The next group of samples of the next tested bottle followed the first group of samples, and so on. A new set of 5 calibration standards was placed after every 4 to 7 groups of samples and at the end of each run. The maximum number of bottles analyzed per run was 10, and the minimum was 4. NOTE: There was no other QCs beside the "100% QC" placed in duplicate at the beginning of each run.

- The areas measured for the calibration standards ranged 0.7 – 170 mAU*s (NOTE: The peak area for the "LOQ" standard, 0.07 µg/mL, was approximately 0.7 mAU*s, the peak area for the lowest standard, 0.36 µg/mL, was approximately 36 mAU*s, and the peak area for the highest standard, 1.69 µg/mL, was approximately 170 mAU*s. mAU*s is the unit used in measurement of the peak area.). The peak areas measured for Group 1 samples (after dilution) were approximately 80-90 mAU*s, Group 2 (after dilution), 15-21 mAU*s and Group 3 (after dilution), 7.2-7.8 mAU*s. ***It can be seen that the concentrations of all of Group 2(after dilution) and Group 3(after dilution) samples were between the "LOQ" (0.07 µg/mL) and the lowest calibration standard (0.36 µg/mL).*** (NOTE: The pooled mass of drug deposited on all lower stages (Stage 1 and Stages 2-7 of the Cascade Impactor) with size of particles less than 9 microns was the sum of Groups 2 and 3)
- The so-called 50%, 100% and 150% QCs (with actual after-dilution concentrations of 0.496, 0.992 and 1.439 µg/mL) included in the post-study validation (submitted on 06/13/2006) could be considered relevant only for analysis of Group 1 samples.
- Although inadequate QCs and lower standards were used in the during-study and post-study validation, the following can be used to argue in support of the validity of the assay: The LOQ (0.07 µg/mL) was always included in the calibration calculation. Correlation coefficients for all standard curves ranged 0.9999 to 1.0000. If interpreting the "LOQ" as the lowest standard instead, and the calibration standards at the middle and end of each run as QCs, the difference of the lowest "QCs" (~0.0725 µg/mL) from the nominal value was within 15%, the difference of the second lowest "QCs" (0.362 µg/mL) from the nominal value was within 1%, and the difference of the "QCs" of 1.208 µg/mL was within 1%, as calculated by the reviewer and summarized in Table 1 in the Appendix. Based on the recalculation results of these "QCs", the concentrations of the samples from Groups 2 and 3, which were bracketed within the lowest "QCs" and second lowest "QCs", as well as the samples from Group 1, which were closest to the "QCs" of 1.208 µg/mL, can be considered accurate and precise.
- The HPLC assay validation data for the current Cascade Impaction testing, therefore, is considered adequate. However, the firm is recommended that in future testing, more QCs with concentrations relevant to the actual lower sample concentrations (of Groups 2 and 3) should be used throughout each assay run. In addition, more calibration standards of concentrations between 0.1 µg/mL and 0.25 µg/mL should be added to assay runs of similar Cascade Impaction test samples of Groups 2 and 3.
- The training records for the analysts as submitted showed that the analysts underwent many trainings for general but relevant laboratory procedures including HPLC operation and validation. The records of the trainings in the specific procedures were not submitted, as indicated by the firm, as the laboratory underwent automation of training records only in 2003 and the older records could not be located at this time. However, for the purpose of verifying the general conduct of the laboratory, the training records as submitted are considered adequate.

3. Since the firm's responses in the current amendment are considered adequate in addressing the DBE's questions concerning the HPLC assay validation for Cascade Impaction test samples, the DSI inspection is not considered necessary at this time and the inspection request is withdrawn.

4. Currently, the firm has addressed adequately all deficiencies concerning *in vivo* and *in vitro* bioequivalence testing for the test product. The *in vivo* BE study and *in vitro* equivalence studies are acceptable.

J. Recommendations

The i*n-vitro* equivalence studies conducted by Apotex Inc. for its Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 ug per spray, comparing it to Flonase® Nasal Spray (Aqueous Suspension), 50 ug per spray, manufactured by GlaxoSmithKline, are **acceptable.** In addition, the *in vivo* bioequivalence study conducted to compare the test product with the RLD product has previously been found acceptable) See file v:\firmsam\apotex\ltrs&rev\77538n0205.doc for a detailed review).

The application is complete with respect to *in vivo* and *in vitro* bioequivalence testing.

VI. Appendix

A. Firm's Current Responses as Summarized in the Cover Letter:

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

August 14, 2007

Dr. Aaron Sigler
Project Manager, Division of Bioequivalence
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Dr. Sigler:

Re: BIOEQUIVALENCY AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg; ANDA No. 077538

Apotex Inc. is hereby submitting a Bioequivalency Amendment to ANDA number 077538 for Fluticasone Propionate Nasal Spray, 50 mcg in response to the FDA deficiency letter dated July 27, 2007.

This amendment is in eCTD format and is included on the enclosed CD. A signed Form FDA 356h is also provided.

Please note that the enclosed electronic CD has been confirmed to be virus free using McAfee VirusScan Enterprise 7.1.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone: (954) 384-3986 or fax: (954) 349-4233. Alternatively, please do not hesitate to contact myself at telephone: (416) 401-7889.

Sincerely,
Apotex Inc.

for: Bernice Tao
Director, Regulatory Affairs US

BT:rw

Encl.

150 Signet Drive, Toronto, Ontario, Canada M9L 1T9
Tel: (416) 749-9300 • Fax: (416) 401-3649 • www.apotex.com

MEMBER CGPA

Following this page, 9 pages withheld in full - Sponsor letter dated 8/14/2007 - (b)(4)

B. Table 1: Reviewer's Recalculation of During-Study QCs*

Run No.	Slope	Y-intercept	QC's Area mAU*s	QC's Calculated Conc. mcg/mL	QC's Nominal Conc. mcg/mL	%Difference
1	100.73	0.0541	0.6862	0.006275	0.0072	-13.41
1	100.73	0.0541	36.4464	0.361290	0.3623	-0.29
1	100.73	0.0541	122.1528	1.212156	1.2080	0.34
2	100.06	0.0285	0.7322	0.007033	0.0072	-2.95
2	100.06	0.0285	36.1273	0.360777	0.3623	-0.43
2	100.06	0.0285	120.9234	1.208244	1.2080	0.02
3	100.04	0.0053	0.7246	0.007189	0.0072	-0.80
3	100.04	0.0053	36.1984	0.361771	0.3623	-0.16
3	100.04	0.0053	121.5423	1.214834	1.2080	0.57
3	100.04	0.0053	0.6899	0.006843	0.0072	-5.57
3	100.04	0.0053	36.2098	0.361885	0.3623	-0.13
3	100.04	0.0053	121.3385	1.212796	1.2080	0.40
4	99.92	0.1276	0.7798	0.006528	0.0072	-9.92
4	99.92	0.1276	36.1786	0.360797	0.3623	-0.43
4	99.92	0.1276	121.3493	1.213182	1.2080	0.43
4	99.92	0.1276	0.7958	0.006687	0.0072	-7.72
4	99.92	0.1276	36.1559	0.360570	0.3623	-0.49
4	99.92	0.1276	120.9536	1.209222	1.2080	0.10
5	99.77	0.1456	0.9741	0.008303	0.0072	14.58
5	99.77	0.1456	36.0747	0.360103	0.3623	-0.62
5	99.77	0.1456	121.5674	1.216961	1.2080	0.74
5	99.77	0.1456	0.9269	0.007831	0.0072	8.06
5	99.77	0.1456	36.1913	0.361272	0.3623	-0.29
5	99.77	0.1456	121.0425	1.211701	1.2080	0.31
6	100.56	0.0189	0.7361	0.007132	0.0072	-1.58
6	100.56	0.0189	36.5036	0.362826	0.3623	0.13
6	100.56	0.0189	121.5017	1.208099	1.2080	0.01
6	100.56	0.0189	0.7493	0.007263	0.0072	0.23
6	100.56	0.0189	36.3401	0.361200	0.3623	-0.31
6	100.56	0.0189	122.5277	1.218302	1.2080	0.85
7	100.39	0.0742	0.8022	0.007252	0.0072	0.07
7	100.39	0.0742	36.6016	0.363857	0.3623	0.42
7	100.39	0.0742	122.6304	1.220806	1.2080	1.06
7	100.39	0.0742	0.7750	0.006981	0.0072	-3.66
7	100.39	0.0742	36.6737	0.364574	0.3623	0.62
7	100.39	0.0742	122.6329	1.220830	1.2080	1.06

Run No.	Slope	Y-intercept	QC's Area	QC's Calculated	QC's Nominal	%Difference
8	100.39	0.1142	0.8127	0.006958	0.0072	-3.98
8	100.39	0.1142	36.6202	0.363659	0.3623	0.36
8	100.39	0.1142	123.2752	1.226883	1.2080	1.56
9	100.53	0.0479	0.7244	0.006729	0.0072	-7.15
9	100.53	0.0479	36.4108	0.361694	0.3623	-0.18
9	100.53	0.0479	121.8343	1.211385	1.2080	0.28

***NOTE:** As discussed under the Comments section of the current review, these "QCs" were actually some of the reinjected calibration standards which were placed after samples of every 4-7 bottles in each run. The reviewer recalculated these QC concentrations based on the first calibration curve of each corresponding run and the areas measured for these "QCs".

BIOEQUIVALENCE COMMENTS

ANDA: 77-538 APPLICANT: Apotex Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 µg/Spray

The Division of Bioequivalence has completed its review and has no further questions at this time.

In future testing, for validation of the HPLC assay of samples from the Cascade Impaction test, please use Quality Controls (QCs) with concentrations more relevant to the actual lower sample concentrations of Groups 2 and 3 (i.e., with the concentration range of approximately 0.10 to 0.25 µg/mL). These QCs should be placed throughout each assay run. In addition, more calibration standards of concentrations between 0.10 to 0.25 µg/mL should be added to assay runs of Cascade Impaction test samples of Groups 2 and 3.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-538

BIOEQUIVALENCE – ACCEPTABLE

Submission Date: 08-14-07

1. OTH (Amendment)

Strength: 50 ug
Outcome: **AC**

OUTCOME DECISION: **AC** – Acceptable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hoainhon T. Nguyen
9/6/2007 10:17:29 AM
BIOPHARMACEUTICS

Moheb H. Makary
9/6/2007 10:22:36 AM
BIOPHARMACEUTICS

Dale Conner
9/6/2007 11:28:11 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-538

STATISTICAL REVIEWS

ANDA 77-538
Drug Product: Fluticasone Propionate Nasal Spray, 50 mcg
Sponsor: Apotex Inc.
Reference Listed Drug: Flonase® Nasal Spray, 50 mcg GlaxoSmithKline, NDA 20-121
Recommended dosing regimens: two 50-mcg sprays in each nostril once daily or one 50-mcg spray in each nostril twice daily as directed
Submission dates: Electronically submitted to FDA on 2/25/05

Reviewer: Mohamed Moustapha, DB6/OB/CDER
Requestor: Carol Kim, Pharm.D., OGD/CDER, 05/02/2006

Sponsor's protocol#: FLUT-NASO-01NB06-PA

Title: Bioequivalence study of 200 mcg of fluticasone propionate nasal spray (Apotex Inc., Canada) vs. 200 mcg of Flonase® Nasal Spray (GlaxoSmithKline, USA) in patients with seasonal allergic rhinitis

The primary objective of the study was to establish the bioequivalence of the Test product, Apotex, Inc., Fluticasone Propionate Nasal Spray, 50 mcg (FANS) and the Reference product, Glaxosmithkline, Flonase@ Nasal Spray, 50 mcg, and to show superiority of the two active treatments to the placebo (without active ingredient), in the treatment of seasonal allergic rhinitis (SAR).

Protocol Review (FLUT-NASO-01NB06-PA):

1. Apotex submitted an original protocol (OGD control document #01-505) on 10/2/01.
2. Based on the decision (see meeting minutes of 11/6/01) of the working group refining the guidance for bioequivalence studies of nasal steroid drug products, the sponsor was advised (11/20/01) to use 2 sprays per nostril once a day, evaluate both instantaneous and reflective scores twice daily at 12-hour intervals, calculate baseline scores from both AM and PM reflective TNSS for the 3 days immediately prior to randomization, plus the Day 1 AM measurement, and treat baseline as a covariate in the analysis.
3. On 2/19/02, the OGD clarified (OGD control document #01-598) that the sponsor's proposed primary efficacy parameter, "the mean change from baseline of the TNSS reflective scores over the entire treatment period", is acceptable.
4. The original protocol dated 7/13/04 was approved by the IRB and amended (7/28/04) once prior to initiation of the study. The protocol was revised primarily to clarify inclusion/exclusion criteria and the study procedures.
5. On 8/13/04, the first patient was enrolled into this study.

Study Design

Study Design: This was a randomized, double-blind, parallel-group study design comparing the following three products during the 14 day treatment period:

1. Test: Apotex Inc.'s Fluticasone propionate nasal spray 200 mcg (50 mcg per actuation), 2 sprays in each nostril once daily, lot # GN-4297 ((b) (4) batch #R04 0420, R04 0437)
2. Reference: Flonase® Nasal Spray, 200 mcg (GlaxoSmithKline), lot # C099476 (R04 0419, R04 0436), 2 sprays in each nostril once daily
3. Vehicle (Placebo): Apotex Inc., Canada, lot# 04020604 (R04 0421, R04-0438), 2 sprays in each nostril once daily

All treatments were administered intranasally in the morning at approximately 8 am, except the first dose, which was administered in the study area during Visits 1 and 2. Patients were randomly assigned in a 2:2:1 ratio to one of the three treatment groups.

The study included two periods: an initial single-blind, placebo run-in period (Period 1), followed by a double-blind, randomized, placebo-controlled, parallel group treatment period (Period 2).

Period 1 (Placebo Run-In, Day -7 or -8 to -1): Patients who met the screening criteria were to participate in the single-blind placebo run-in period of 7-8 days (Period 1) to determine baseline nasal symptom scores. During this time, all patients received placebo. Patients were instructed to record daily diary cards, nasal symptom scores and adverse events. Patients who were considered placebo responders were not enrolled into Period 2 of the study.

Four signs and symptoms of SAR were evaluated using the following 4- point scale for sneezing, nasal itching, congestion, and rhinorrhea. Each symptom was rated by the patient using the following numerical rating scale:

0=none
1=mild, sign or symptom clearly present but minimal awareness; easily tolerated
2=moderate, definite awareness of sign or symptom that is bothersome but tolerable
3=severe, sign or symptom is hard to tolerate; causes interference with activities of daily living and/or sleeping.

- Patients were asked to record a reflective Total Nasal Symptom Score (TNSS) for the previous 24 hours. Reflective scores of four symptoms (sneezing, nasal itching, congestion, and rhinorrhea) on a four points scale ranging from 0 (no symptom) to 3 (severe symptom) were recorded. If total TNSS was less than 6, the patient did not continue in the study. The sponsor calculated TNSS using the sum of each individual symptom scores at each assessment.
- Patients were asked to return the diary cards and the nasal dispensers at the next visit.

- Patients were instructed to return to the clinic for scheduled visit 2 in the morning.

Period 2 (Treatment period, Day 1 to Day 14): On Day 1 of the treatment period (after the Day 1 AM assessment but before the Day 1 PM assessment) eligible patients were randomized to receive one of the three study treatments. The assigned treatment was administered once a day for the fourteen days (Day 1 – Day 14) of the treatment period, as described previously.

The CDER guidance recommended the Total mean of TNSS at baseline to be the average over the last 7 reflective scores (3 AM and 3 PM scores on Days -3, -2, and -1 in the placebo run-in period/pre-treatment period and one AM score on Day 1 in the treatment period) and the Total mean of TNSS in the treatment period to be the average over the 27 reflective scores (14 PM scores on Day 1 – 14 and 13 AM scores on Day 2-14 in the treatment period). This statistical review used the Total mean of TNSS recommended by the CDER guidance[1].

Exclusion/inclusion from the FDA's per protocol (FPP) population

Per the OGD Medical reviewer's comments the following adjustments were made to the sponsor's dataset:

1) The sponsor revised their PP population dataset including patient 0026 (Site 11) and 0016 (Site 06). These patients were included in the PP population analysis.

2) Patient #14 (site 13) was excluded by the sponsor because this patient discontinued the study early. The case report form documented that this patient requested to receive other treatment for increasing signs and symptoms of SAR. Due to lack of efficacy, this patient was included in the per protocol population analysis using LOCF.

3) Patient 0067 (Site 2043) was excluded from the PP population analysis as recommended by the DSI inspector and was included in the ITT population analysis.

4) In addition to the patients included and/or excluded, as recommended by the OGD Clinical reviewer, the following patients did not meet the baseline requirement and therefore were excluded for both the ITT and PP population analyses, since they have a baseline average TNSS less than 6: Patient # 0004 (Site 08) in the Test group, and Patients # 0037 (Site 08), # 0012 (Site 24) in the Reference group.

Outcome Variables

Endpoints:

Per the OGD medical reviewer, the primary efficacy variable was the total mean change from baseline of reflective TNSS (i.e., the pretreatment period mean – treatment period mean).

The efficacy measurement in this study was total nasal symptom score (TNSS) from the patient diary cards. It combined scores from rhinorrhea, nasal congestion, nasal itchiness, and sneezing, each on a scale of 0-3, with a maximum possible combined score of 12. Morning and evening (AM and PM) scores were obtained immediately prior to dosing and approximately 12 hours later, respectively. Reflective scores were recorded by the patient for the period since the last scoring (previous 12 hours) and instantaneous scores were recorded by the patient for their current condition.

The establishment of baseline score was based on the AM and PM scoring on the last 3 days of the placebo run-in period, and AM scoring (prior to the study drug dosing) on Day 1 of the 14 day randomized treatment period, resulting in 7 total AM and PM ratings. Potential placebo responders were excluded from the study if the mean baseline total nasal symptoms score (TNSS) was less than 6.

Total mean change from baseline of Instantaneous TNSS was analyzed as a secondary endpoint.

Statistical Analysis Methods

Analysis of Covariance (ANCOVA) model:

The efficacy and equivalence analyses for the mean change from baseline of TNSS were conducted using a general linear model containing the factors treatment, investigator, and the corresponding TNSS mean at baseline as a covariate (Total TNSS Reflective mean variable used the Total TNSS Reflective at baseline as a covariate). There were no statistically significant treatment by investigator interactions from the GLM model for each variable.

Efficacy Analysis

The comparisons for the primary and secondary efficacy variables were made between treatment arms at the 5% level of significance (two-sided). The efficacy analysis for each active treatment was tested separately by comparing with the placebo. The arms should be similar at baseline (pretreatment period), and the active treatment should be more distinguishable from placebo as the study progresses.

The means (least square means) and p-values were obtained from the general linear model. Two pairwise comparisons, Test vs. Vehicle and Reference vs. Vehicle, were done by including two treatments (Test and Vehicle or Reference and Vehicle) in each analysis.

Equivalence Analysis

The compound hypothesis to be tested is:

H_0: $\mu_T/\mu_R < \theta_1$ or $\mu_T/\mu_R > \theta_2$ versus H_A: $\theta_1 \leq \mu_T/\mu_R \leq \theta_2$

In accordance with the standard in OGD for equivalence analyses for continuous endpoints, α=0.05, θ_1=0.80, and θ_2=1.25. Consequently, for the endpoints the 90% confidence interval (corresponding to two one-sided tests at level α=0.05, as described by Sasabuchi) based on Fieller's method is calculated for the equivalence test. The null hypothesis H_0 is rejected if the 90% confidence interval for μ_T/μ_R is contained in the (0.80, 1.25) interval.

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products. Calculation of the 90% confidence intervals (Test versus Reference), using Fieller's method, was facilitated by using the GLM procedure in SAS®. This resulted in putting equal weight on each investigator (center).

The 90% confidence interval depends on the value of the baseline at which it is evaluated. Thus we need to find a cut off point, namely a baseline value for which equivalence must be demonstrated for any value of baseline greater than or equal to the cut off point. One possible strategy is that equivalence must be demonstrated for values of baseline greater than or equal to the average value of baseline seen in the study.

Statistical Analysis Results

Demographic characteristics:

A total of 619 patients was enrolled in the study. Of the patients enrolled, 576 patients were qualified to be in the MITT population (230 in the Test product group 236 in the Reference product group and 110 in the Vehicle product group). For the PP population there were 529 patients in the final per protocol population analysis (210 in the Test product group, 218 in the Reference product group and 101 in the Vehicle product group).

Table 1 - Population distributions

Population	Test (N = 230)	Reference (N = 236)	Vehicle (N = 110)	Total (N = 576)
Subjects Enrolled	251 (100%)	251 (100%)	117 (100%)	619 (100%)
Patients Excluded from MITT	21 (8%)	15 (6%)	7 (6%)	43 (7%)
Total Patients in the MITT	230 (92%)	236 (94%)	110 (94%)	576 (93%)
Patients Excluded from PP	41 (16%)	33 (13%)	16 (14%)	90 (15%)
Total Patients in the PP	210 (84%)	218 (87%)	101 (86%)	529 (85%)

For the TNSS mean at baseline there was no statistically significantly different across treatment groups, the p-value was = 0.14.

Table 2 - Total TNSS mean at Baseline

Baseline Parameter	Test (N = 230)	Reference (N = 236)	Vehicle (N = 110)	P-Value
MAX	12	12	12	0.14
MEAN	8.80	8.66	9.02	
MIN	6	6	6	
N	230	236	110	
STD	1.58	1.54	1.58	

The population at baseline consisted of 441 subjects who are white, 51 who are black, 63 who are Hispanic, 12 who are Asian, and 9 who are of other Ethnicity. Overall there was no statistically significantly different across treatment groups, the p-value was = 0.33. The population consisted of 172 Males, and 404 Females, however there was no statistically significantly different across treatment groups, the p-value was = 0.31. Table 3 describes the Demographic characteristics in the MITT population.

Table 3 - Demographic characteristics (MITT)

Age	Test (N = 230)	Reference (N = 236)	Vehicle (N = 110)	p-value
MAX	73	71	80	0.02
MEAN	39	38	36	
MIN	18	18	18	
N	230	236	110	
STD	12	12	12	
Race				0.33
Caucasian	178 (30.9%)	182 (31.6%)	81 (14.1%)	
Black	22 (3.8%)	19 (3.3%)	10 (1.7%)	
Asian	3 (0.5%)	8 (1.4%)	1 (0.2%)	
Hispanic	25 (4.3%)	21 (3.6%)	17 (3.0%)	
Others	2 (0.3%)	6 (1.0%)	1 (0.2%)	
Male	61 (10.6%)	78 (13.5%)	33 (5.7%)	0.31
Female	169 (29.3%)	158 (27.4%)	77 (13.4%)	

Efficacy:

The Test and Reference treatments were statistically significantly better than Vehicle for the Total mean change from baseline of the Reflective TNSS. The p-values for the Test vs. Vehicle and the Reference vs. Vehicle were 0.012 and 0.005 respectively.

In addition, the Test and Reference treatments were statistically significantly better than Vehicle for the Total mean change from baseline of the Instantaneous TNSS. The p-

values for the Test vs. Vehicle and the Reference vs. Vehicle were 0.008 and 0.001 respectively.

Table 4 – Efficacy analysis (MITT population)

Change in Mean TNSS from Baseline	LS Means			p-value	
	Test	Reference	Vehicle	Test vs. Vehicle	Reference vs. Vehicle
Change in Mean Reflective TNSS from Baseline	2.25	2.36	1.54	0.012	0.005
Change in Mean Instantaneous TNSS from Baseline	2.26	2.40	1.52	0.008	0.001

Equivalence:

The equivalence test passed for the Total mean change from baseline of the reflective TNSS for the sample mean and median (calculated for all three treatments) baseline for the FDA's PP population. Table 5 below also provides the minimum value of baseline for which the products passed the usual equivalence test for the Total mean change from baseline of TNSS. The cut off point of 8.521 is the minimum baseline for which the 90% confidence interval falls within [80%, 125%] – the 90% confidence interval falls within these limits for all baseline values ≥ 8.521. Similar results for the Total mean change from baseline of the Instantaneous TNSS are included in Table 5.

Table 5 – Equivalence analysis (FDA PP population)

Total mean Change from Baseline of the Reflective TNSS	Test LS Mean[1]	Reference LS Mean	The 90% CI for the Ratio of Means	Pass/Fail
Baseline of TNSS (Median = 8.57)	2.438	2.625	(0.802 , 1.072)	P
Baseline of TNSS (Mean = 8.78)	2.580	2.768	(0.812 , 1.068)	P
Baseline of TNSS (Cut off point = 8.521)	2.405	2.592	(0.800 , 1.073)	P
Change in Mean Instantaneous TNSS from Baseline				
Baseline of TNSS (Median = 8.14)	2.246	2.276	(0.839 , 1.159)	P
Baseline of TNSS (Mean = 8.16)	2.261	2.291	(0.840 , 1.158)	P
Baseline of TNSS (Cut off point = 7.34)	1.782	1.812	(0.800 , 1.204)	P

[1] The LS Means, in this case, are estimated means for each treatment at the indicated value of baseline, putting equal weight on each site.

Comments on the Sponsor's Analysis

OGD Reviewer's Comments: To meet the bioequivalence criteria, the 90% CI of the Test/Reference ratio of mean change from baseline reflective TNSS [averaging reflective AM and PM scores on Days -3, -2 and -1 of the placebo run-in period and the AM score (prior dosing) on Day 1 of the active treatment period] to the average reflective TNSS over the 14-day treatment period must be within 0.80 and 1.25.

The sponsor's summary of results is shown in Table II (per sponsor).

PP population	**Reference (n=219)**	**Test (n=204)**	**Placebo (n=102)**
LSMean reduction in reflective TNSS (rTNSS) at day 14 compared to baseline	-2.36	-2.34	-1.45
^90% CI for the ratio of the mean reduction (rTNSS)	(0.85, 1.14)		
LSMean reduction in instantaneous TNSS (iTNSS) at day 14 compared to baseline	-1.99	-2.09	-1.29
^90% CI for the ratio of the mean reduction (iTNSS)	(0.89, 1.21)		
ITT population	**Reference (n=238)**	**Test (n=225)**	**Placebo (n=110)**
Change in mean instantaneous TNSS LSMean from baseline to on-treatment period	-1.99	-2.06	-1.34
Test vs. placebo	P=0.0024		
Reference vs. placebo	P=0.0057		
Change in mean reflective TNSS LSMean from baseline to on-treatment period	-2.33	-2.33	-1.52
Test vs. placebo	P=0.0011		
Reference vs. placebo	P=0.0009		

^90% CI of ratio is defined by the sponsor as: [(LSMean Flonase Chg + UCL 90% CI)/LSMean Flonase Chg,(LSMean Flonase Chg + LCL 90% CI)/LSMean Flonase Chg]; Where, the UCL and LCL are defined as the Upper and Lower Confidence Interval of the Difference=(LS Mean Fluticasone - LS Mean Flonase). This is based on previous population analysis (T: 203, R: 218, P: 102) without two patient's data (#110026, 050016). The sponsor did not provide revision to 90% CI calculation for the ratio of the mean reduction.

The sponsor's 90% confidence interval approach (described above) is an outmoded approximate method. The method, based on the Test and Reference means difference confidence interval, does not take into account the uncertainty in the LSMean estimator, and is no longer acceptable (see Berger, R. L. and Hsu, J. C. (1996) Bioequivalence trials, intersection-union tests and equivalence confidence sets. Statistical Science, 11(4): 283-319.)

In addition, the sponsor's PP population is different from that of FDA's PP population.

Conclusion

Efficacy

The Test and Reference treatments were statistically significantly better than Vehicle for both the primary and the secondary endpoint (Total mean change from baseline of the Reflective and Instantaneous TNSS) for the MITT population.

Equivalence

The equivalence Test passed for the Total mean change from baseline of TNSS at both the sample mean and median baseline for FDA's PP population, as well as for all baseline values greater than or equal to 8.521 (in the case of reflective TNSS) or 7.34 (in the case of instantaneous TNSS.)

The inclusion of the baseline as a covariate in the statistical model, while it may reduce the variance, makes the ratio of the Test product mean over the Reference product mean depend on baseline, which means that the equivalence test is a function of the baseline value at which the confidence interval is evaluated. Generally, if the slope relating change from baseline to baseline is positive (i.e. persons with a higher value of baseline tend to achieve a higher change from baseline), if the 90% confidence interval evaluated at a given value of baseline falls within the bioequivalence limits of [0.80, 1.25], confidence intervals evaluated at any higher value of baseline will also fall within the bioequivalence limits. One possible baseline value for which equivalence should be demonstrated is the average value of baseline in the study. "Average value" could be interpreted as the *mean* baseline observed in the study. However in some studies where the distribution of baseline values is skewed, the median is a more appropriate measure of "average value" than the mean. In this study, equivalence was demonstrated at both the mean and the median baseline for both endpoints.

Mohamed Moustapha
Mathematical Statistician, DB6

Donald J. Schuirmann
Expert Mathematical Statistician, DB6

Stella G. Machado, Ph.D.
Director, DB6

cc: Original ANDA 76-538 HFD-600
Dena Hixon, Carol Kim, Debra M. Catterson HFD-705

Stella Machado, Donald J. Schuirmann, Mohamed Moustapha, DB6 Chron

This Review Includes 9 pages.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mohamed Moustapha
5/22/2007 04:35:38 PM
BIOEQUIVALENCE STATISTICIAN

Donald Schuirmann
5/22/2007 04:42:47 PM
BIOMETRICS

Stella Machado
5/22/2007 05:22:42 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-538

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

505(j)(2)(A)
OK 5-3-05 for

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

February 28, 2005

Document Control Room
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Original Abbreviated New Drug Application (Pre-Assigned ANDA No. 077538)
Fluticasone Propionate Nasal Spray, 50 mcg

To Whom It May Concern:

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1994, Apotex Inc. is submitting an original Abbreviated New Drug Application in eCTD (Electronic Common Technical Document) format for Fluticasone Propionate Nasal Spray, 50 mcg. The drug product described herein is equivalent to Flonase®, marketed by GlaxoSmithKline.

Enclosed is a CD that contains the Fluticasone Propionate Nasal Spray, 50 mcg submission and hard copy of the following documents with the original signature. Please note that these documents have been provided electronically in the appropriate sections in the submission.

- FDA Form 356h
- FDA Form 3454
- Patent and Exclusivity Certification
- Generic Drug Enforcement Act Certification
- Request for Categorical Exclusion of Environmental Assessment

Please direct any communications regarding this application to Ms. Marcy Macdonald at Apotex Corp., the authorized US agent for Apotex Inc., at telephone: (847) 279-7740 or fax: (847) 353-2982, or for any concerns related to the submission of the eCTD format, please do not hesitate to contact me directly at telephone: (905) 508-2396 or fax: (905) 884-0357.

Sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:mt

cc: Apotex Corp.

RECEIVED
MAR 0 1 2005
OGD / CDER

380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2
Tel. 905.884.2050 Fax. 905.884.9876 www.apotex.com

Proudly Canadian

ANDA 77-538

Apotex Corp.
U.S. Agent for: Apotex Inc.
Attention: Marcy MacDonald
616 Heathrow Drive
Lincolnshire, IL 60069

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Fluticasone Propionate Nasal Spray, 0.05 mg/spray

DATE OF APPLICATION: February 28, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 1, 2005

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ann Vu
Project Manager
(301)827-5848

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-538
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92
Endorsement:
HFD-615/MShimer, Chief, RSB For: date 03 APRIL 05
HFD-615/IMargand, CSO date 5/3/05
Word File V:\Firmsam\Apotex\Ltrs&rev\77538.ack
F/T 5/3/05
ANDA Acknowledgment Letter!

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

May 26, 2005

ORIG AMENDMENT
N /AA

Document Control Room
Office of Generic Drugs, HFD-600
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Sir/Madam:

Re: GRATUITOUS AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg, ANDA No. 077538

In accordance with 21 CFR 314.96(a)(1), we are submitting a Gratuitous Amendment to our unapproved application for Fluticasone Propionate Nasal Spray, 50 mcg. Enclosed is a CD that contains the Gratuitous Amendment for Fluticasone Propionate Nasal Spray, 50 mcg. An application Form FDA 356h has been prepared and a hard copy with original signature is included. Please note that this form has also been provided electronically in the appropriate section of the submission.

We would like to inform the Agency that there was an error in the data entry of a diary card that resulted in an eligible patient being deemed ineligible in the clinical study. This information is in addition to the original clinical study report and the appendix to the clinical study report dated 02/25/2005. The data provided in this appendix demonstrates that the inclusion of the two patients (combined missing entries from both appendices) in the per-protocol population does not significantly change the final analysis of the report. The appendix, dated 05/20/2005 has been included in Module 5 (5.3.1.2, FLUT-NASO-01NB06-PA (efficacy), 16.1).

We trust that the information submitted at this time is sufficient for review of this gratuitous amendment for Fluticasone Propionate Nasal Spray, 50 mcg. Should you require any further information, or have any questions or comments please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 884-0357.

Yours sincerely,

for Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

RECEIVED
MAY 31 2005
OGD / CDER

380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2
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Proudly Canadian

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

August 12, 2005

ORIG AMENDMENT

N/A B

Ms. Krista Scardina
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Scardina:

Re: TELEPHONE AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg; ANDA No. 77-538

Further to your telephone call to Kalpesh Shroff of Apotex Corp. on August 03, 2005 we are pleased to provide you with our response electronically in a question-and-answer format. Enclosed is the CD that also contains the response and a hard copy of the FDA Form 356h with the original signature.

1. *Please provide a list of the number of enrolled subjects by site and the number of evaluable subjects by site.*

   Response: As requested, a table that summarizes the number of subjects randomized per site and the number of evaluable subjects by site (in ITT and in PP) has been provided on the following page.

.../cont'd

380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2
Tel. 905.884.2050 Fax. 905.884.9876 www.apotex.com

Study Identifier: FLUT-NASO-01NB06-PA

Site #	Randomized	Evaluable in ITT	Evaluable in PP
1	25	24	21
2	39	39	37
3	5	4	4
4	14	13	11
5	34	32	27
6	15	15	13
7	25	23	17
8	35	35	34
9	8	8	8
10	14	14	12
11	40	39	36
12	10	9	7
13	39	39	37
14	15	15	14
15	25	25	23
16	38	38	36
17	22	21	19
18	20	20	20
19	40	38	35
20	16	16	16
21	25	24	21
22	32	0	0
23	47	47	44
24	24	24	20
25	11	11	11
Total	618	573	523

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396, or fax your requests to (905) 884-0357.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

August 30, 2005

Mr. Gary Buehler, Director
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Dear Mr. Buehler:

Re: US Agent Change - ANDA No. 77-538
Fluticasone Propionate Nasal Solution, 50 mcg/metered spray

This letter serves to inform you that the US Agent for Apotex Inc.-Richmond Hill Site will be moving from their current office in Lincolnshire, Illinois to a new office in Weston, Florida, effective September 1, 2005.

The new contact information for our US Agent is as follows:

Name: Kalpesh Shroff
Address: Apotex Corp.
2400 North Commerce Parkway, Suite 400,
Weston, Florida 33326
Tel: (954) 349-4217
Fax: (954) 349-4233

We are submitting a copy of this letter to each Apotex Inc.-Richmond Hill Site ANDA currently under review with the Agency or approved by the Agency, however, a comprehensive list of all Apotex Inc.-Richmond Hill Site ANDAs is appended to this letter for your convenience. Please be reminded that on August 15, 2005 the Agency was notified of a transfer of ownership of Apotex Corp. products to Apotex Inc.-Richmond Hill Site. Accordingly, products formerly belonging to Apotex Corp. are also impacted by this change.

If you have any questions, please do not hesitate to contact me by phone at (905) 508-2396, by Fax at (905) 884-0357 or email at pbonnici@apotex.com.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs (Liquids)

PB:cd

Encl.

380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2
Tel. 905.884.2050 Fax. 905.884.9876 www.apotex.com

18.1

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 16, 2005

TO: Directors, Investigations Branch

Dallas District Office
4040 N. Central Expy
Suite 300
Dallas, TX 75204

Atlanta District Office
60 8th Street, NE
Atlanta, GA 30309

Kansas District Office
11630 West 80th Street
Lenexa, KS 66214-3338

FROM: C.T. Viswanathan, Ph.D. CTV 9/19/05
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2005, Pre-Approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: ANDA 77-538
DRUG: Fluticasone Propionate Nasal Spray, 50 µg
SPONSOR: Apotex Inc.
Richmond Hill, Ontario
CANADA

This memo requests that you arrange for inspection of the relevant clinical portions of the following multi-site clinical endpoint bioequivalence study.

Study: Protocol FLUT-NASO-01NB06-PA - Bioequivalence Study of 200 mcg of Fluticasone Propionate Nasal Spray (Apotex Inc., Canada) vs. 200 mcg of Flonase® Nasal Spray (GlaxoSmithKline, USA) in Patients with Seasonal Allergic Rhinitis.

Clinical Site #1:	Allergy Diagnostics 4410 Medical Drive, Suite 360 San Antonio, TX 78229
Clinical Investigator:	Charles P. Andrews, M.D.
# of Subjects:	39
Clinical Site #2:	North Carolina Clinical Research 4301 Lake Boone Trail, Suite 309-A Raleigh, NC 27607
Clinical Investigator:	Craig F. LaForce, M.D.
# of Subjects:	39
Clinical Site #3:	Clinical Research of the Ozarks, Inc. 509 East 10th Street Rolla, MO 65401
Clinical Investigator:	Ita Tripathy, M.D.
# of Subjects:	47

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study comparing the bioequivalence of Apotex Inc.'s fluticasone propionate nasal spray with that of the reference formulation, Flonase® (GlaxoSmithKline, USA) in subjects with seasonal allergic rhinitis.

Please check the batch numbers of the placebo, test, and reference drug formulations used in the study with descriptions in the documents submitted to the Agency. **Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and 320.63.** The site conducting the study (i.e., the testing facility) is responsible for randomly selecting reserve samples from the batches of test and reference products available for dosing. Please refer to the Final Rule[1] and CDER's guidance document[2] for more guidance concerning the reserve

[1] "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, 1993)
[2] "Handling & Retention of BA and BE Testing Samples" (May 2004) http://www.fda.gov/cder/guidance/index.htm

sample requirements for bioavailability and bioequivalence studies. Reserve samples of the placebo, test and reference drug formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Please have the records of all study subjects audited. Please determine if the patients met the protocol inclusion/exclusion criteria. The subject records in the ANDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. **Since this is a blinded study, the inspected facility should have a sealed code available for FDA to break the blind. Please use the sealed code to verify that subjects were dosed according to the randomization code.** The Final Rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, April 28, 1993) specifically discusses the necessity of a sealed code for blinded studies. Please document your findings regarding the sealed code.

Following the identification of the investigator, background materials will be forwarded directly.

Headquarters Contact Person: John A. Kadavil, Ph.D.
(301) 594-1048

cc:
HFD-45/RF
HFD-48/Kadavil(2)/Himaya/CF
HFD-600/Scardina/ANDA 77-538
HFR-SW1540/Martinez (BIMO, please fax)
HFR-SE150/Hubbard (BIMO, please fax)
HFR-SW350/Montgomery (BIMO, please fax)
Draft: JAK 9/15/05
Edit: MKY 9/16/05
DSI: 5644 O:\BE\assigns\bio77538.doc
FACTS 668864

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

November 08, 2005

ORIG AMENDMENT
N/AF

Beverly Weitzman, PharmD
Division of Labeling and Program Support
Office of Generic Drugs, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Weitzman:

Re: LABELING AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg; ANDA No. 077538

Further to your Labeling Amendment letter dated August 25, 2005, we are pleased to provide you with our response in an electronic (CD) format. For ease of review, we have enclosed a copy of your letter in section 1.2 and prepared our responses in a question-and-answer format. An updated Application Form FDA 356h has been prepared and is enclosed in section 1.1.2 along with a hard copy with the original signature. A paper (hard) copy of each labeling piece in final print is also provided.

Labeling Deficiencies:

1. ***CONTAINER** (50 mcg) – Satisfactory in DRAFT.*

2. ***CARTON** (50 mcg) – Satisfactory in DRAFT.*

   Response: Apotex Inc. acknowledges that the container label and carton submitted are considered satisfactory in draft. However, we have made some minor amendments to the information on the labeling. Please refer to section 1.14.3.1 for an annotated comparison of the changes.

3. ***PATIENT INSTRUCTION***
   a. *Revise "Please read this patient* (b) (4) *carefully before you start to take your medicine" to read "Please read patient leaflet carefully before you start to take your medicine".*

   b. ***USING YOUR NASAL SPRAY** – Revise the first sentence in the first bullet point to read "Follow the instructions shown in the rest of this patient leaflet".*

   Response: As requested, the information above has been revised.

.../cont'd

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c. ***FURTHER INFORMATION**: Revise the first sentence to read "This leaflet does not contain the complete information about your medicine.*

Response: The sentence has been revised to read, "This patient leaflet does not contain the complete information about your medicine."

4. ***INSERT** – Above the "DESCRIPTION" section add the statement "SHAKE GENTLY BEFORE USE".*

Response: As requested, the statement has been added.

Please revise your labeling, as instructed above, and submit each labeling piece in final print.

Response: The final printed container label and carton are included in section 1.14.2.1. The final printed package insert (prescribing information and patient leaflet) is provided in section 1.14.2.2 and the corresponding word file is provided in section 1.14.2.3. An annotated comparison for all labeling changes is included in section 1.14.3.1.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:mt

Encl.

NOV 14 2005

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-538 APPLICANT: Apotex Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg/spray

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

1.

2.

Following this page, 4 pages are withheld in full (b)(4).

6. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

M Smela for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ORIGINAL

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

January 11, 2006

N/AM

Mr. Peter Chen
Project Manager
Office of Generic Drugs, CDER, FDA
Document Controlled Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Chen:

Re: MINOR AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg; ANDA No. 077538

Further to your Minor Amendment letter dated November 14, 2005, we are pleased to provide you with our response in an electronic (CD) format. For ease of review, we have enclosed a copy of your letter in section 1.2 and prepared our responses in a question-and-answer format. An updated Application Form FDA 356h has been prepared and is enclosed in section 1.1.2 along with a hard copy with the original signature.

A. Deficiencies:

(b) (4)

1.

2.

.../cont'd

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JAN 13 2006

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Following this page, 20 pages are withhed in full. (b)(4)

(b) (4)

[redacted]

6. *An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.*

   Response: Apotex Inc. hereby acknowledges that an acceptable compliance evaluation is needed for approval.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

for: Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:mt

Encl.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-538 APPLICANT: Apotex Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg/spray

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5.

6. (b) (4) [redacted]

7. DMF (b) (4) is deficient. The holder has been notified. Please ensure a response.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

2. A Methods Validation study is needed to support the ANDA and it will be scheduled concurrent with your response to this communication.

3. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

4. We note and acknowledge your commitments regarding the establishment of DSD and Spray Pattern specifications post-approval. However, with regard to sample requirements, we request that you provide data from 5 units from each of the first 20 batches, as we would like to standardize the data collection and evaluation for all generic applicants of this drug product. As a result, we request that you comply with our request as previously stated and provide data from 5 units per batch.

Sincerely yours,

M. Smela for 2/16/06

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
W/AM.

March 22, 2006

Mr. Peter Chen
Project Manager, Division of Chemistry I
Office of Generic Drugs (HFD-620)
CDER, FDA
Document Controlled Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
MAR 24 2006
OGD / CDER

Dear Mr. Chen:

Re: MINOR AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg; ANDA No. 077538

Further to your Minor Amendment letter dated February 21, 2006, we are pleased to provide you with our response in an electronic (CD) format. For ease of review, we have enclosed a copy of your letter in section 1.2 and prepared our responses in a question-and-answer format. An updated Application Form FDA 356h has been prepared and is enclosed in section 1.1.2 along with a hard copy with the original signature.

A. Deficiencies:

1. (b) (4)

2.

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.../cont'd

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Following this page, (4) pages are withheld in full. (b) (4)

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:ks

Encl.

.../cont'd

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
N/AA

April 05, 2006

Mr. Peter Chen
Project Manager, Division of Chemistry I
Office of Generic Drugs (HFD-620)
CDER, FDA
Document Controlled Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Chen,

Re: GRATUITOUS AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg, ANDA No. 077538

In accordance with 21 CFR 314.96(a)(1), we are submitting a Gratuitous Amendment to our unapproved application for Fluticasone Propionate Nasal Spray, 50 mcg. Enclosed is a CD that contains the Gratuitous Amendment for Fluticasone Propionate Nasal Spray, 50 mcg. An application Form FDA 356h has been prepared and a hard copy with original signature is included. Please note that this form has also been provided electronically in the appropriate section of the submission.

This Gratuitous Amendment is submitted for the following:

1. In-Process Checks and (b) (4) :

Apotex Inc. would like to inform the Agency of a change to the in-process checks of the filling process for Fluticasone Propionate Nasal Spray, 50 mcg. The change is a (b) (4) filling operation according to our Standard Operating Procedure.

RECEIVED
APR 06 2006
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.../cont'd

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Following this page, (1) page is withheld in full. (b) (4)

We trust that the information submitted at this time is sufficient for review of this gratuitous amendment for Fluticasone Propionate Nasal Spray, 50 mcg. Should you require any further information, or have any questions or comments please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

for Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
N/A B.

April 20, 2006

Mr. Aaron Sigler
Project Manager, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Sigler:

Re: BIOEQUIVALENCY AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg; ANDA No. 077538

Further to your Bioequivalency Amendment letter dated April 12, 2006, we are pleased to provide you with our response in an electronic (CD) format. For ease of review, we have enclosed a copy of your letter in section 1.2 and prepared our responses in a question-and-answer format. An updated Application Form FDA 356h has been prepared and is enclosed in section 1.1.2 along with a hard copy with the original signature.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies concerning in vitro studies have been identified:

1. ***Automated Spray Pump Actuation Systems:***

SOP No. GM-143 refers to three pump actuation systems: Automated Spray Pump Actuation Station (b) (4).), (b) (4) Nasal Spray Pump Actuation Station ((b) (4) and (b) (4) (b) (4)). It is not clear which system was used for the following tests: Single Actuation Content, Spray Pattern, Priming and Repriming tests. Please identify the pump actuation systems used for these tests and the pump parameters for each of these tests. In addition, please confirm that the operation parameters used for the test and reference products are the same. Although the test and reference products may have the same type of metering nasal pump (i.e, (b) (4) the resistance of different pumps within the same type may be different. However, it is essential that the operation parameters for the test and reference pumps are the same for the purpose of accurate comparison.

Response: The tests for Single Actuation Content, Priming/Re-priming and Spray Pattern all used the Innova automated actuation station (b) (4). The (b) (4) pump actuation parameters used for the (b) (4) are as follows:

.../cont'd

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TABLE 1d (cont.) - Intermediate Precision

	(%) Assay	(%) Assay
	Instrument: HPLC (Unit #28) Column: (b) (4) Serial No.:	Instrument: HPLC (Unit #26) Column: (b) (4) Serial No.:
Mean:	107.4	106.4

3. ***Particle Size Distribution by Cascade Impactor Test:***

You did not submit any validation data for standard curves of the concentration range of 0.36 – 1.68 µg/mL and for the QCs based on this concentration range.

Response: Validation data of the Cascade Impaction test method (PD-084) is provided in Table 2 for the standard curves of the concentration range 0.36-1.68 µg/mL and for the QCs based on this concentration range.

TABLE 2 – Linearity of Detector Response for Cascade Impaction

Level (%)	Concentration of Fluticasone Propionate (µg/mL)	Observed Area (Mean)	Concentration Response
LOQ (1%)	0.01219	1.21669	99.84326
12.5	0.15232	14.12837	92.75453
25	0.30465	28.36941	93.12132
50	0.60930	56.50677	92.74047
100	1.21859	112.61317	92.41268
160	1.94974	181.98936	93.34032
For Concentration Response: Mean: CV (%)			 94.03543 3.0
Coefficient of Determination (R^2) Y-intercept: Slope:			0.99996 -0.129112 93.15243

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
N/F

April 25, 2006

Beverly Weitzman, PharmD
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Weitzman,

Re: GRATUITOUS LABELING AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg, ANDA No. 077538

In accordance with 21 CFR 314.96(a)(1), we are submitting a Gratuitous Labeling Amendment to our unapproved application for Fluticasone Propionate Nasal Spray, 50 mcg. Enclosed is a CD that contains the Gratuitous Labeling Amendment. An updated Application Form FDA 356h has been prepared and is enclosed in section 1.1.2 along with a hard copy with the original signature.

This Gratuitous Labeling Amendment is submitted to revise the Apotex Inc. labeling so it does not infringe upon GlaxoSmithKline's marketing exclusivity rights for information on results of a long term longitudinal growth study and pediatric safety information (M-24). The text changes made to the Apotex Inc. labeling are consistent with the labeling approved for Roxane's Fluticasone Propionate Nasal Spray, ANDA 076504.

The Exclusivity Statement has also been revised to indicate that the Apotex Inc. product will not infringe upon GlaxoSmithKline's marketing exclusivity rights. In addition, the reference to a new dosing schedule (D-76) has been removed from the Exclusivity Statement as this period of marketing exclusivity has expired. The revised statement is included in section 1.3.5.2.

In accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of Apotex Inc.'s final printed package insert (prescribing information and patient leaflet) provided in this Gratuitous Labeling Amendment with those provided in the Labeling Amendment submitted on November 08, 2005, with differences annotated and explained, has been provided in section 1.14.3.1.

We hereby confirm that the printer's proofs provided are a true representation of the final printed labeling. In the event that there are any additional changes to the proofs prior to approval, we will notify the agency as necessary.

.../Cont'd

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We trust that the information submitted at this time is sufficient for review of this Gratuitous Labeling Amendment for Fluticasone Propionate Nasal Spray, 50 mcg. Should you require any further information, or have any questions or comments please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

April 28, 2006

ORIG AMENDMENT
N/A/M.

Mr. Ken Furnkranz
Division of Chemistry
Office of Generic Drugs (HFD-620)
CDER, FDA
Document Controlled Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Furnkranz:

Re: TELEPHONE AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg; ANDA No. 077538

Further to the telephone conversation between Mike Smela and Ken Furnkranz of FDA and Gina Sirianni and myself on April 19, 2006, we are pleased to provide you with our response electronically in a question-and-answer format. An updated Application Form FDA 356h has been prepared and is enclosed in section 1.1.2 along with a hard copy with the original signature.

1. *The drug substance, fluticasone propionate is a USP substance; please update documentation (including specifications, test methods, manufacturing documents, and the composition statement in the ANDA) to state fluticasone propionate USP.*

   Response: As requested, (b) (4)

2. *On the drug substance specification, the acceptance criteria for* (b) (4)

   Response: As requested, (b) (4)

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MAY 02 2006
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.../cont'd

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Following this page, (2) pages are withheld in full. (b) (4)

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

fax: Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
NDF

May 26, 2006

Beverly Weitzman, PharmD
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Weitzman,

Re: GRATUITOUS LABELING AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg, ANDA No. 077538

In accordance with 21 CFR 314.96(a)(1), we are submitting a Gratuitous Labeling Amendment to our unapproved application for Fluticasone Propionate Nasal Spray, 50 mcg. Enclosed is a CD that contains the Gratuitous Labeling Amendment. An updated Application Form FDA 356h has been prepared and is enclosed in section 1.1.2 along with a hard copy with the original signature.

Further to the Gratuitous Labeling Amendment that we submitted on April 25, 2006 we have noticed an error in the PDF version of the package insert. Figure 1 is missing from the patient leaflet information. The figure is present in the MS Word file, however it was inadvertently missed in the PDF file.

In accordance with 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of Apotex Inc.'s final printed package insert (prescribing information and patient leaflet) provided in this Gratuitous Labeling Amendment with those provided in the Gratuitous Labeling Amendment submitted on April 25, 2006, has been provided in section 1.14.3.1.

We hereby confirm that the printer's proofs provided are a true representation of the final printed labeling. In the event that there are any additional changes to the proofs prior to approval, we will notify the agency as necessary.

Please note that the enclosed electronic CD has been confirmed to be virus free using McAfee VirusScan Enterprise 7.1.

RECEIVED
MAY 30 2006
OGD / CDER

.../Cont'd

380 Elgin Mills Road East, Richmond Hill, Ontario, Canada L4C 5H2
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We trust that the information submitted at this time is sufficient for review of this Gratuitous Labeling Amendment for Fluticasone Propionate Nasal Spray, 50 mcg. Should you require any further information, or have any questions or comments please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
N/A/R

June 13, 2006

Mr. Aaron Sigler
Project Manager, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Sigler:

Re: BIOEQUIVALENCY AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg; ANDA No. 077538

Further to your Bioequivalency Amendment letter dated May 23, 2006, we are pleased to provide you with our response in an electronic (CD) format. For ease of review, we have enclosed a copy of your letter in section 1.2 and prepared our responses in a question-and-answer format. An updated Application Form FDA 356h has been prepared and is enclosed in section 1.1.2 along with a hard copy with the original signature.

1. *For the validation for the HPLC assay used in the Single Actuation Content test, please submit representative data for a daily calibration check of the analytical balance. In addition, please submit the amended test method (TM-1174) with the section 3.2.P.5.3 included for validation of the spray weighing.*

   Response: As requested, representative data for the daily calibration check of the analytical balance used during the time of the single actuation content testing (July 2004-Aug 2004) is provided below. In addition, the amended test method TM-1174 has been included in section 3.2.P.5.2 for your review.

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JUN 14 2006
OGD / CDER

.../cont'd

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Following this page, two pages withheld in full - (b)(4)

2. *For the validation of the HPLC assay used in the Cascade Impaction test, the data of the standard curve are acceptable. However, to demonstrate that the assay performs with acceptable precision and accuracy, please submit the data of QCs, separate from the standard data, for at least 3 concentrations within the concentration range of the standard curve. The QC data may be submitted in a similar format as that of Table 1c, presented in your current response #2 (ii) for the validation of the HPLC assay used in the Single Actuation Content test:*

Response: In order to determine that the HPLC assay used in the cascade impaction test (test method PD-084) performs with acceptable precision, the data of QCs at 3 concentration levels (50%, 100% and 150%) within the linear concentration range of the standard curve are provided in Table 1.

TABLE 1 – Precision of the Method at the Extremes of the Range

Injection No.	Observed Area		
Level (%)	50 (250 µg/mL)	100 (500 µg/mL)	150 (750 µg/mL)
1 2 3 4 5 6		(b) (4)	
Mean	45750	91479	137547
CV (%)	0.3	0.3	0.1

In order to determine that the HPLC assay used in the cascade impaction test performs with acceptable accuracy, a mixture of Fluticasone Propionate Raw Material (Batch No. 05ST75MHQ00022, manufactured by (b) (4) and Placebo (Lot No. 04020604) containing analyte concentrations at the 50%, 100% and 150% level were prepared and analysed as per test method PD-084. The mean recovery is shown in Table 2.

Table 2: Accuracy (Recovery)

%Theory	Theoretical Concentration (µg/mL)	Recovered Concentration (µg/mL)	Recovery (%)	Mean Recovery (%)
50	252.192	250.427	99.3	99.7
	259.832	259.053	99.7	
	248.968	248.968	100.0	
100	514.069	497.619	96.8	97.1
	502.163	486.596	96.9	
	503.353	491.776	97.7	
150	753.629	746.092	99.0	97.9
	726.367	706.029	97.2	
	746.508	727.099	97.4	

.../cont'd

Please note that the enclosed electronic CD has been confirmed to be virus free using McAfee VirusScan Enterprise 7.1.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIG AMENDMENT
N/A

July 18, 2006

Mr. Peter Chen
Project Manager, Division of Chemistry I
Office of Generic Drugs (HFD-620)
CDER, FDA
Document Controlled Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Chen,

Re: GRATUITOUS AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg, ANDA No. 077538

Further to your conversation with Robin Windover on July 12, 2006 and in accordance with 21 CFR 314.96(a)(1), we are submitting a Gratuitous Amendment to our unapproved application for Fluticasone Propionate Nasal Spray, 50 mcg. Enclosed is a CD that contains the Gratuitous Amendment for Fluticasone Propionate Nasal Spray, 50 mcg. An application Form FDA 356h has been prepared and a hard copy with original signature is included. Please note that this form has also been provided electronically in the appropriate section of the submission.

This Gratuitous Amendment is submitted to notify the agency that Apotex Inc. intends to withdraw (b) (4) as a contract testing facility. Please notify the Office of Compliance of this gratuitous amendment so they can re-assess the compliance evaluation associated with our ANDA.

We trust that the information submitted at this time is sufficient for review of this gratuitous amendment for Fluticasone Propionate Nasal Spray, 50 mcg. Should you require any further information, or have any questions or comments please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

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PB:rw

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APOTEX INC.
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SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

July 20, 2006

ORIG AMENDMENT
N-000-AB

Mr. Aaron Sigler
Project Manager, Division of Bioequivalence
Office of Generic Drugs
CDER, FDA
Document Controlled Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Sigler:

Re: BIOEQUIVALENCY AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg; ANDA No. 077538

Further to your Bioequivalency Amendment letter dated July 14, 2006, we are pleased to provide you with our response in an electronic (CD) format. For ease of review, we have enclosed a copy of your letter in section 1.2 and prepared our responses in a question-and-answer format. An updated Application Form FDA 356h has been prepared and is enclosed in section 1.1.2 along with a hard copy with the original signature.

The following deficiencies concerning in-vitro studies have been identified:

1. *Your response to Deficiency #1 is adequate concerning the representative daily calibration check data and the added procedure for validation of spray weighing. However, from the SOP entitled "Amendment of Validation for Assay of Fluticasone per Spray in Fluticasone Propionate Nasal Spray, 50 µg/spray" (generated 04/17/2006) and the SOP entitled "Assay of Fluticasone Propionate Per Spray and Total Number of Sprays per Bottle Delivered from Actuator in Fluticasone Propionate Nasal Spray" (generated 05/29/2006), it is not clear to which part of which SOP the "section 3.2.P.5.2" was referred. No such "section" was found in either of the two documents submitted. Please clarify the reference of "section 3.2.P.5.2.".*

   Response: Please note that the reference to section 3.2.P.5.2 was to identify the location of the information in module 3 of the eCTD, not a specific step in the procedure.

   Within section 3.2.P.5.2 of the eCTD is test method TM-1174 that was revised in our last response dated June 13, 2006 to include the procedure for spray weighing. The test method contains the procedure for spray weighing and is entitled "Assay of Fluticasone Propionate Per Spray and Total Number of Sprays per Bottle Delivered from Actuator in Fluticasone Propionate Nasal Spray".

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Following this page, (2) pages are withheld in full. (b) (4)

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

Robin Wrobleski

for Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:rw

Encl.

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

August 30, 2006

ORIG AMENDMENT

Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs
CDER, FDA
Document Controlled Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Dr. Kim,

Re: RESPONSE TO REQUEST FOR INFORMATION
Fluticasone Propionate Nasal Spray, 50 mcg, ANDA No. 077538

Further to your memorandum dated July 26, 2006 we are pleased to provide you with our response in an electronic (CD) format. For ease of review, we have enclosed a copy of your letter in section 1.2 and prepared our responses in a question-and-answer format. An updated Application Form FDA 356h has been prepared and is enclosed in section 1.1.2 along with a hard copy with the original signature.

1. *A single summary dataset in the SAS transport file should be submitted. A list of file names included in the CD or diskette(s), with a simple description of the content of each file, should be included. Please provide "define.pdf" with detailed description of code that you use for each variable in the dataset (for example, 0=yes, 1=no for analysis population). (See http://www.fda.gov/cder/guidance/2353fnl.pdf regarding define.pdf) All SAS transport files should use .xpt as the file extension and should not be compressed. A simple SAS program to open the transport files and an explanation of the format for each SAS variable should be included.*

   Primary data set should consist of two data sets: No Last Observation Carried Forward (No LOCF – pure data set) and Last Observation Carried Forward (LOCF – modified data set). Per each patient, the following variables should be contained in the data set:

   - *Center/site*
   - *patient number, sex, race, age, drug/treatment*
   - *safety population (yes/no), reason for exclusion from safety population*
   - *ITT population (yes/no), reason for exclusion from ITT population*
   - *PP population (yes/no), reason for exclusion from PP population*
   - *Reflective and instantaneous TNSS scores at beginning of the placebo run-in period*

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Response: The number of patients for each primary allergen per treatment group at baseline, the number of years with current known allergy per treatment group at baseline and graphs of each relevant pollen count over the time period of the study by each site are provided at the end of this cover letter.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2396 or fax your requests to (905) 508-2359.

Yours sincerely,

Paul Bonnici, B.Sc., MBA
Director, Regulatory Affairs

PB:mt

Encl.

APOTEX CORP.

September 11, 2006

N/NC

Mr. Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

RE: ANDA # 77-538
Fluticasone Propionate Nasal Spray, 50 mcg
- Change in Point Of Contact Information

This letter is to notify FDA (Office of Generic Drugs) that we have hired a US Director of Regulatory affairs and thus, Mr. John Lay will be the primary point of contact, effective September 11, 2006 in relation to the above-mentioned ANDA application.

The new contact information is as follows:

John G. Lay, B.Sc., RAC
Director, Regulatory Affairs
Apotex Corp.
2400 N. Commerce Parkway Suite 400
Weston, FL 33326

Telephone: (954) 384-3987
Fax: (954) 349-4233

Should you have any questions, please do not hesitate to me at the information above.

Sincerely,

Tammy McIntire

Tammy McIntire, M.S., R.Ph.
President

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SEP 14 2006
OGD / CDER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

Apotex Corp. U.S. Agent for: Apotex Inc.
Attention: John G. Lay
2400 North Commerce Parkway
Suite 400
Weston, FL 33326

Dear ANDA Holder/Applicant:

We are writing to you as the sponsor of pending abbreviated new drug application(s) (ANDAs) supported by bioequivalence studies in which the bioanalytical analysis was conducted by MDS Pharma Services (MDS) at the St. Laurent (Montreal) and Blainville sites in Quebec, Canada.

FDA has conducted several comprehensive inspections of bioequivalence studies conducted by MDS since 2000. The findings of these inspections raise significant concerns about the validity of the reported results of these analytical studies conducted in support of drug applications for marketing. Our findings from these inspections include, but are not limited to, the following:

- Failure to conduct a systematic and thorough evaluation to identify and correct sources of contamination.
- Failure to investigate anomalous results.
- Lack of assay reproducibility between original and repeat results.
- Assay accuracy not assured under the conditions of sample processing.
- Biased manipulation of study data resulting in the acceptance of failed runs.
- Failure to demonstrate the accuracy of analytical methods with appropriate validation experiments and documentation.

As a result of these findings, MDS agreed to conduct an audit of data from all its bioequivalence studies generated from January 2000 to December 2004. However, FDA identified significant deficiencies with the MDS audit during its most recent inspection. Thus, serious questions remain about the validity of bioequivalence data generated by MDS in studies during this time period that have not been inspected by FDA, including the studies you have submitted in support of your applications. In view of these findings, FDA is informing holders of pending ANDA(s) of these issues and would like to know what steps are being taken by you to assure the accuracy of data submitted in these applications and confirm the validity of MDS's analytical studies that

were conducted from January 2000 through December 2004 and subsequently submitted to the FDA. Accordingly, with respect to these studies submitted in your application(s), we request that you do one of the following, in order of FDA preference:

1. Repeat the bioequivalence studies.

2. Re-assay the samples at a different bioanalytical facility. For this option, the integrity of the original samples must be demonstrated for the frozen storage period.

3. Commission a scientific audit by a qualified independent expert, who is knowledgeable in the area of bioequivalence studies and bioanalytical data, and selected by your company rather than by MDS, to verify the results obtained by MDS.

In addition, because one of the agency's significant findings for the inspected MDS studies was the presence of anomalous results, we are requesting for all of the above options that the blood/plasma level results obtained in the studies be compared to any published literature or other relevant information that is publicly available. If you are unable to complete one of these options within the recommended six month time frame, please inform us of the reason(s) and your estimated time of completion.

If you choose to conduct an audit, we request that the completed audit reports be maintained at your site. If the audit finds the study acceptable, we request that you submit a certification to your application that formally attests in writing to the validity of the results obtained by MDS upon which your application relies. If the audit finds the study to be unacceptable, you should either repeat the bioequivalence study and submit the information within 6 months of the completed audit or withdraw the application. Please note that these audits would also be subject to validity assessment by the agency upon submission.

The audit criteria provided below includes, but is not limited to, examples of areas that should be evaluated.

- The audit criteria for reviewing pre-study validation data should address whether accuracy and stability were demonstrated with appropriate validation experiments and documentation, and under the conditions of sample processing used for the analysis of samples from study subjects.

- The audit criteria for reviewing the results of the bioequivalence studies should address whether anomalous results were investigated and issues related to contamination were identified and corrected. It should also determine if a comparison of all available original and repeat results demonstrated assay reproducibility, and whether analytical runs were accepted in accordance with established procedures and without bias.

The new bioequivalence data or the re-analysis of the existing data should be submitted to your application as an amendment. If the new information does not support a finding of bioavailability/bioequivalence, the FDA may refuse to approve your application(s). Please find

attached the list of your pending applications with studies conducted at MDS during the specified time period.

If you have any questions regarding this letter, please contact Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 240-276-9310.

Sincerely,

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Apotex Corp. U.S. Agent for: Apotex Inc. ANDAs with studies conducted at MDS:

65-317 Amoxicillin/Clavulanate
65-333 Amoxicillin/Clavulanate
77-120 Carbidopa/Levodopa
(b) (4)
77-538 Fluticasone

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gary Buehler
1/10/2007 08:08:46 AM

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

January 15, 2006

ORIG AMENDMENT
N/MC

Ms. Cecelia Parise
Regulatory Policy Advisor
Office of Generic Drugs (HFD-620)
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Parise:

Re: Apotex Pending ANDAs Supported by Comparative Bioavailability Studies Conducted by MDS Pharma Services (MDS)
ANDA No. 77-538

On January 10, 2007 Apotex Inc. received a letter from OGD listing several pending Apotex Inc. applications, for which bioanalytical analysis was conducted by MDS Pharma Services at the St. Laurent (Montreal) and Blainville sites in Quebec, Canada. One of the pending applications listed was for Fluticasone Propionate Nasal Spray, 50 mcg (ANDA No. 77-538) for which we would like to clarify that the bioanalytical analysis was conducted by MDS at the Lincoln, Nebraska site in the U.S.

Further to your recommendation during our discussion on January 11th, 2007 to contact Lizzie Sanchez, Special Assistant, Division of Bioequivalence regarding this matter, I would like to inform you that in a telephone discussion with Ms. Sanchez on January 12th, 2007, she has confirmed that ANDA No. 77-538 for Fluticasone Proprionate Nasal Spray can be removed from the Apotex pending ANDAs list where the bioanalysis is conducted by MDS at the Canadian sites.

As such, Apotex Inc. hereby requests that ANDA No.77-538 for Fluticasone Propionate Nasal Spray, 50 mcg be removed from OGD's list of pending applications for which bioanalysis was conducted at the MDS St. Laurent or Blainville sites.

If you have any questions, please do not hesitate to contact me at tel: (416) 401-7889 or fax: (416) 401-3809.

Yours sincerely,

for: Bernice Tao
Director, Regulatory Affairs US

BT:gs

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APOTEX CORP.

April 12, 2007

Mr. Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/mc

RE: ANDA # 77-538
Fluticasone Propionate Nasal Spray, 50mcg
US Agent Change in Contact Information

We would like to notify FDA (Office of Generic Drugs) of a change in the contact information of our US Agent, effective April 1, 2007 in relation to the above-mentioned ANDA application.

The new contact information is as follows:

Kiran Krishnan, MPharm, RAC
Project Leader, Regulatory Affairs
Apotex Corp.
2400 N. Commerce Parkway Suite 400
Weston FL
33326

Telephone: (954) 384-3986
Fax: (954) 349-4233

Should you have any questions, please do not hesitate to contact myself at tel: (416) 401-7889 or fax: (416) 401-3807.

Sincerely,

K. Krishnan

for Bernice Tao
Director, Regulatory Affairs (US)

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Enclosure- Change in US Agent and Point Of Contact Information Letter

BIOEQUIVALENCY AMENDMENT

ANDA 77-538

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Apotex Corporation TEL: 954-349-4200

ATTN: Tammy McIntire FAX: 954-349-4233

FROM: Aaron Sigler PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on February 28, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Nasal Spray, 50 mcg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 77-538 APPLICANT: Apotex Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 µg/Spray

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies concerning *in-vitro* studies have been identified:

In the current amendment, you informed the DBE that the previous HPLC assay validation data for the Cascade Impaction test were reported based on ***the total spiked amount not on the concentration***. We found the manner in which the validation data obtained and presented to the Agency rather unusual and unconventional. For the purpose of further verification of the HPLC assay validation data used in the Cascade Impaction test, we are requesting the following additional information:

Please submit all relevant SOP's, all raw assay validation data, all actual Cascade Impaction sample data obtained by HPLC, chromatograms and copies of *notebooks* used in the validation of the HPLC assay for the Cascade Impaction test. Please be sure the address of the laboratory, the name of the analyst(s), their training records, the approval(s) by the laboratory supervisor(s), the dates of the validation as well as the dates of the Cascade Impaction sample analyses, and any deviations from the validation SOPs are clearly documented.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Barbara Davit
7/27/2007 05:40:47 PM
Signing for Dale P Conner

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

ORIGINAL

August 14, 2007

Dr. Aaron Sigler
Project Manager, Division of Bioequivalence
Office of Generic Drugs
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

Dear Dr. Sigler:

Re: BIOEQUIVALENCY AMENDMENT
Fluticasone Propionate Nasal Spray, 50 mcg; ANDA No. 077538

Apotex Inc. is hereby submitting a Bioequivalency Amendment to ANDA number 077538 for Fluticasone Propionate Nasal Spray, 50 mcg in response to the FDA deficiency letter dated July 27, 2007.

This amendment is in eCTD format and is included on the enclosed CD. A signed Form FDA 356h is also provided.

Please note that the enclosed electronic CD has been confirmed to be virus free using McAfee VirusScan Enterprise 7.1.

Please direct any communications regarding this amendment to Kiran Krishnan at Apotex Corp., the authorized US agent for Apotex Inc., at telephone: (954) 384-3986 or fax: (954) 349-4233. Alternatively, please do not hesitate to contact myself at telephone: (416) 401-7889.

Sincerely,
Apotex Inc.

for: Bernice Tao
Director, Regulatory Affairs US

BT:rw

Encl.

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BIOEQUIVALENCY COMMENTS

ANDA 77-538

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Apotex, Inc.

TEL: 905-508-2445

ATTN: Gina Sirianni

FAX: 905-508-2359

FROM: Debra Catterson

PROJECT MANAGER: (240) 276-8963
(240) 276-8966 (fax)

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on February 28, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Nasal Spray, 50 mcg.

Reference is also made to your amendments dated May 26, 2005 and August 30, 2006.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has provided comments which are presented on the attached __2__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-538 APPLICANT: Apotex, Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 77-538, using the primary endpoint of the mean change from baseline reflective Total Nasal Symptom Score (TNSS) to the average reflective TNSS over the 14-day treatment period for the per protocol population, are adequate to demonstrate bioequivalence of Apotex Inc.'s Fluticasone Propionate Nasal Spray, 50 mcg, with the reference listed drug, GlaxoSmithKline's Flonase® Nasal Spray, 50 mcg. Both active treatments demonstrated superiority over the Placebo arm.

1. The current criterion for establishing bioequivalence of a generic fluticasone nasal spray based on the clinical endpoint study is a 90% confidence interval of the Test: Reference ratio of the mean change from baseline in the reflective TNSS score within the limits of (80%, 125%). The agency used the ANCOVA method with baseline TNSS score as a covariate for calculating the 90% CI at the sample median (not mean) of the baseline reflective TNSS scores in the evaluable population for all 3 study arms.

2. Bioequivalence of your product was demonstrated using baseline as a covariate for calculating the 90% CI at the sample median (8.57) of the baseline reflective TNSS scores in the per protocol population for all 3 study arms.

3. According to the FDA statistical review, the 90% CI approach that you used is an outmoded approximate method. The method, based on the test and reference means difference confidence interval, does not take into account the uncertainty in the LSMean estimator and is no longer acceptable [(see Berger, R.L. and Hsu, J.C. (1996)].

4. The DSI issued a FDA Form 483 to two of three inspected sites because these sites failed to follow protocol procedures, maintain proper records and reserve samples at clinical sites. The reserve samples should not be transferred back to any organization that deals with packaging the test articles and reference standard for storage. This is to eliminate the possibility of commingling reserve samples from packaging activities (21 CFR 211.84 and 211.170) and bioequivalence studies (21 CFR 320.38 and 320.63). For your study, reserve samples were sent to (b) (4) which was involved in packaging and randomization of the study samples.

   It is your responsibility to ensure that the clinical sites for all future BE studies comply with the current requirements as recommended in the final guidance, the *CDER Guidance for Industry: Handling and Retention of BA and BE Testing Samples, posted May 2004*. If you fail to comply with the Agency's regulations in 21 CFR 320.38 and 320.63 in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Dale Conner
8/20/2007 08:48:26 AM

BIOEQUIVALENCY AMENDMENT

ANDA 77-538

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Apotex Corporation

TEL: 954-349-4200

ATTN: Tammy McIntire

FAX: 954-349-4233

FROM: Aaron Sigler

PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on February 28, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Nasal Spray, 50 mcg.

Reference is also made to your amendment dated August 14, 2007.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified COMMENTS which are presented on the attached pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

SPECIAL INSTRUCTIONS:

No response is necessary.

BIOEQUIVALENCE COMMENTS

ANDA: 77-538 APPLICANT: Apotex Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray (Aqueous Suspension), 50 µg/Spray

The Division of Bioequivalence has completed its review and has no further questions at this time.

In future testing, for validation of the HPLC assay of samples from the Cascade Impaction test, please use Quality Controls (QCs) with concentrations more relevant to the actual lower sample concentrations of Groups 2 and 3 (i.e., with the concentration range of approximately 0.10 to 0.25 µg/mL). These QCs should be placed throughout each assay run. In addition, more calibration standards of concentrations between 0.10 to 0.25 µg/mL should be added to assay runs of Cascade Impaction test samples of Groups 2 and 3.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Dale Conner
9/10/2007 11:18:10 AM

OGD APPROVAL ROUTING SUMMARY

ANDA # 77 538 Applicant Apotex Inc.
Drug Fluticasone Propionate Nasal Spray Strength(s) 50 ug/Spray

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. Martin Shimer Chief, Reg. Support Branch	Date 19 July 2007 Initials MHS	Date 9/12/07 Initials rlw

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = _____ NDA# 20 121
Date Checked Previously granted
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification did applicant
Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval
Comments: No remaining patents or exclusivities protecting the RLD. ANDA is eligible for Full Approval.

2. Project Manager, Esther Chuh Team 2 Review Support Branch	Date 7/15/2007 Initials ec	Date _____ Initials _____

Original Rec'd date 3/1/2005
Date Acceptable for Filing 3/1/2005
Patent Certification (type) II
Date Patent/Exclus.expires 11/01/20006
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 7/26/2006
Date of Office Bio Review 9/6/2007
Date of Labeling Approv. Sum 10/25/2006
Date of Sterility Assur. App. n/a
Methods Val. Samples Pending Yes ☒ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement Reviewer:	Labeling Team Leader:
Date 7/6/2007	Date 7/6/2007
Name/Initials Charlie Hoppes	Name/Initials John Grace

Comments:

From: Grace, John F
Sent: Friday, July 06, 2007 3:01 PM
To: Hoppes, Charles V; Chuh, Esther
Subject: RE: ANDA 77 538 Apotex's Fluticasone

concur

From: Hoppes, Charles V
Sent: Friday, July 06, 2007 3:01 PM
To: Chuh, Esther; Grace, John F

Subject: RE: ANDA 77 538 Apotex's Fluticasone

Labeling summary in DFS still reflects the most recently approved labeling for RLD, Flonase NDA 20 121/S 030. No new labeling supplements for Flonase appear in EDR and Drugs @ FDA still lists S 030 as last approved labeling.

Labeling OK for approval.

4. David Read **(PP IVs Only)** Pre MMA Language included ☐ Date 9/12/07
OGD Regulatory Counsel, Post MMA Language Included ☐ Initials rlw/for
Comments:N/. No patents listed in the "Orange Book".

5. Div. Dir./Deputy Dir. Date9/11/07
Chemistry Div. I Initials RMP

Comments:The CMC section is satisfactory for AP except for minor pending issue on MV.

6. Frank Holcombe **First Generics Only** Date9/12/07
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. Roxane's ANDA 76-504 for this drug product was approved on February 22, 2006.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Flonase Nasal Spray (MDI) 0.05 mg/spray,
GlaxoSmithKline NDA 20 121

8. Peter Rickman Date9/12/07
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐;Petition: Yes☐ No☐
Comments:In support of bioequivalence to Flonase/GSK, Apotex submitted a pK study, a clinical endpoint study, and in vitro studies. The pK study was found acceptable by DBE 4/30/06. In vitro studies were found acceptable 9/6/07. The DSI inspection request to verify the validity of the cascade impaction request was cancelled. The clinical study was found acceptable 8/10/07 (in DFS). The statistical review supporting the clinical review was also found acceptable.

FPL found acceptable 10/25/06 (in DFS), as endorsed 7/6/07.

CMC found acceptable (Addendum #2 to Chemistry Review #3) 9/11/07. Methods validation was requested and is partially complete.

OR

8. Robert L. West Date 9/12/07
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments:Acceptable EES dated 7/26/06 (Verified 9/12/07). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

All of the review issues having been satisfactorily addressed, this ANDA is recommended for approval (Second generic approval).

9. Gary Buehler Date 9/12/07
Director, OGD Initials rlw/for
Comments:

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Esther Chuh Team 2 Date9/12/2007

Review Support Branch Initials ec
Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
9:30 AM Time notified of approval by phone
9:380AM Time approval letter faxed

FDA Notification:
9/12/2007 Date e mail message sent to "CDER OGDAPPROVALS" distribution list.
9/12/2007 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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/s/

Esther Chuh

9/12/2007 09:44:19 AM