CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-504

Name: Fluticasone Propionate

Sponsor: Roxane Labs

Approval Date: February 22, 2006

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APPLICATION NUMBER:

ANDA 76-504

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APPLICATION NUMBER:

ANDA 76-504

APPROVAL LETTER

ANDA 76-504

FEB 2 2 2006

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
Associate Director, DRA
1809 Wilson Road
Columbus, OH 43228

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated October 3, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluticasone Propionate Nasal Spray, 0.05 mg (50 mcg)/spray.

Reference is also made to your amendments dated June 5 and December 19, 2003; August 17, and December 21, 2004; and January 20, February 18, May 25, June 6, July 22, August 5, and September 22, 2005.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Fluticasone Propionate Nasal Spray, 0.05 mg/spray, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Flonase® Nasal Spray, 0.05 mg/spray, of GlaxoSmithKline).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with

applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications,
5901-B Ammendale Road
Beltsville, MD 20705-1266

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

You have been requested to provide information after the drug application has been approved. Any information submitted to meet the conditions requested in this letter is considered a "Post Approval Commitment Response". To alert the Office of Generic Drug staff to the fact that you are providing post approval commitment information, please designate your submission in your cover letter as "POST APPROVAL COMMITMENT RESPONSE".

Sincerely yours,

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

2/22/06

cc: ANDA 76-504
Division File
Field Copy
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HFD-205
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Endorsements:
HFD-625/M.Shaikh/ Mujeeb Shaikh 9/26/05

HFD-625/M.Smela/ M Smela 9/27/05

HFD-617/P.Chen/ 9/22/05

HFD-613/A.Payne/

HFD-613/J.Grace/ SEE ATTACHED EMAIL

Robert Lupfert 11/28/05 pending issuance of CR response.

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F/T by

APPROVAL - PACT

PS 9/21/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-504

LABELING

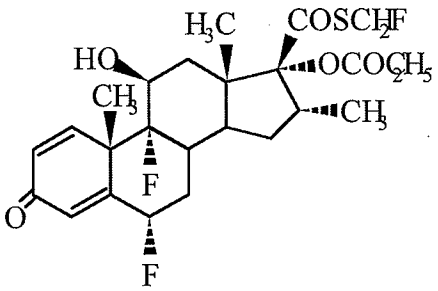
FLUTICASONE PROPIONATE Nasal Spray, 50 mcg

Rx only

For Intranasal Use Only. Shake Gently Before Use.

DESCRIPTION

Fluticasone propionate, the active component of Fluticasone Propionate Nasal Spray, is a synthetic corticosteroid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6 and the molecular formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

Fluticasone Propionate Nasal Spray, 50 mcg is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. Fluticasone Propionate Nasal Spray also contains 0.02% w/w benzalkonium chloride, dextrose, microcrystalline cellulose and carboxymethylcellulose sodium, 0.25% w/w phenylethyl alcohol, and polysorbate 80 and has a pH between 5 and 7.

It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (six actuations), each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each 16-g bottle of Fluticasone Propionate Nasal Spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be consistent and the unit should be discarded.

CLINICAL PHARMACOLOGY

Mechanism of Action

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity. *In vitro* dose response studies on a cloned human glucocorticoid receptor system involving binding and gene expression afforded 50% responses at 1.25 and 0.17 nM concentrations,

respectively. Fluticasone propionate was 3-fold to 5-fold more potent than dexamethasone in these assays. Data from the McKenzie vasoconstrictor assay in man also support its potent glucocorticoid activity.

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to the natural hormone. However, the clinical significance of these findings in relation to the low plasma levels (see Pharmacokinetics) is not known.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. In seven trials in adults, fluticasone propionate nasal spray has decreased nasal mucosal eosinophils in 66% (35% for placebo) of patients and basophils in 39% (28% for placebo) of patients. The direct relationship of these findings to long-term symptom relief is not known.

Fluticasone propionate nasal spray, like other corticosteroids, is an agent that does not have an immediate effect on allergic symptoms. A decrease in nasal symptoms has been noted in some patients 12 hours after initial treatment with fluticasone propionate nasal spray. Maximum benefit may not be reached for several days. Similarly, when corticosteroids are discontinued, symptoms may not return for several days.

Pharmacokinetics

Absorption

The activity of fluticasone propionate nasal spray is due to the parent drug, fluticasone propionate. Indirect calculations indicate that fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (50 pg/mL) only when recommended doses were exceeded and then only in occasional samples at low plasma levels. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral dosing of radiolabeled drug have demonstrated that fluticasone propionate is highly extracted from plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circulating radioactivity is due to an inactive metabolite.

Distribution

Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 91% with no obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism

The total blood clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the

cytochrome P450 3A4 pathway. This inactive metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Elimination

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations

Fluticasone propionate nasal spray was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained.

Drug Interactions

Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max}) averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and $AUC_{(0\text{-}\tau)}$ averaged 8.43 pg•hr/mL (range 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{max} and $AUC_{(0\text{-}\tau)}$ increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Pharmacodynamics

In a trial to evaluate the potential systemic and topical effects of fluticasone propionate nasal spray on allergic rhinitis symptoms, the benefits of comparable drug blood levels produced by fluticasone propionate nasal spray and oral fluticasone propionate were compared. The dosages used were 200 mcg of fluticasone propionate nasal spray, the nasal spray vehicle (plus oral placebo), and 5 and 10 mg of oral fluticasone propionate (plus nasal spray vehicle) per day for 14 days. Plasma levels were undetectable in the majority of patients after intranasal dosing, but

present at low levels in the majority after oral dosing. Fluticasone propionate nasal spray was significantly more effective in reducing symptoms of allergic rhinitis than either the oral fluticasone propionate or the nasal vehicle. This trial demonstrated that the therapeutic effect of fluticasone propionate nasal spray can be attributed to the topical effects of fluticasone propionate.

In another trial, the potential systemic effects of fluticasone propionate nasal spray on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in allergic patients. Fluticasone propionate nasal spray given as 200 mcg once daily or 400 mcg twice daily was compared with placebo or oral prednisone 7.5 or 15 mg given in the morning. Fluticasone propionate nasal spray at either dosage for 4 weeks did not affect the adrenal response to 6-hour cosyntropin stimulation, while both dosages of oral prednisone significantly reduced the response to cosyntropin.

CLINICAL TRIALS

A total of 13 randomized, double-blind, parallel-group, multicenter, vehicle placebo-controlled clinical trials were conducted in the United States in adults and pediatric patients (4 years of age and older) to investigate regular use of fluticasone propionate nasal spray in patients with seasonal or perennial allergic rhinitis. The trials included 2,633 adults (1,439 men and 1,194 women) with a mean age of 37 (range, 18 to 79 years). A total of 440 adolescents (405 boys and 35 girls) mean age of 14 (range, 12 to 17 years), and 500 children (325 boys and 175 girls), mean age of 9 (range, 4 to 11 years) were also studied. The overall racial distribution was 89% white, 4% black, and 7% other. These trials evaluated the total nasal symptom scores (TNSS) that included rhinorrhea, nasal obstruction, sneezing, and nasal itching in known allergic patients who were treated for 2 to 24 weeks. Subjects treated with fluticasone propionate nasal spray exhibited significantly greater decreases in TNSS than vehicle placebo-treated patients. Nasal mucosal basophils and eosinophils were also reduced at the end of treatment in adult studies; however, the clinical significance of this decrease is not known.

There were no significant differences between fluticasone propionate regimens whether administered as a single daily dose of 200 mcg (two 50 mcg sprays in each nostril) or as 100 mcg (one 50 mcg spray in each nostril) twice daily in six clinical trials. A clear dose response could not be identified in clinical trials. In one trial, 200 mcg/day was slightly more effective than 50 mcg/day during the first few days of treatment; thereafter, no difference was seen.

Two randomized, double-blind, parallel-group, multicenter, vehicle placebo-controlled 28-day trials were conducted in the United States in 732 patients (243 given fluticasone propionate nasal spray) 12 years of age and older to investigate "as-needed" use of fluticasone propionate nasal spray (200 mcg) in patients with seasonal allergic rhinitis. Patients were instructed to take the study medication only on days when they thought they needed the medication for symptom control, not to exceed 2 sprays per nostril on any day, and not more than once daily. "As-needed" use was prospetively defined as average use of study medication no more than 75% of study days. Average use of study medications was 57% to 70% of days for all treatment arms. The studies demonstrated significantly greater reduction in TNSS (sum of nasal congestion, rhinorrhea, sneezing, and nasal itching) with fluticasone propionate nasal spray 200 mcg compared to placebo. The relative difference in efficacy with as-needed use as compared to regularly administered doses was not studied.

Three randomized, double-blind, parallel-group, vehicle placebo-controlled trials were conducted in 1,191 patients to investigate regular use of fluticasone propionate nasal spray in patients with perennial nonallergic rhinitis. These trials evaluated the patient-rated TNSS (nasal obstruction, postnasal drip, rhinorrhea) in patients treated for 28 days of double-blind therapy and in 1 of the 3 trials for 6 months of open-label treatment. Two of these trials demonstrated that patients treated

with fluticasone propionate nasal spray at a dosage of 100 mcg twice daily exhibited statistically significant decreases in TNSS compared with patients treated with vehicle.

Individualization of Dosage

Patients should use fluticasone propionate nasal spray at regular intervals for optimal effect.

Adult patients may 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).

Individual patients will experience a variable time to onset and different degree of symptom relief. In four randomized, double-blind, vehicle placebo-controlled, parallel-group allergic rhinitis studies and two studies of patients in a outdoor "park" setting (park studies), a decrease in nasal symptoms in treated subjects compared to placebo was shown to occur as soon as 12 hours after treatment with a 200 mcg dose of fluticasone propionate nasal spray. Maximum effect may take several days. Regular-use patients who have responded may be able to be maintained (after 4 to 7 days) on 100 mcg/day (one spray in each nostril once daily).

Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of fluticasone propionate nasal spray (not to exceed 200 mcg daily) effective for symptom control (see CLINICAL TRIALS). Greater symptom control may be achieved with scheduled regular use. Efficacy of as-needed use of fluticasone propionate nasal spray has not been studied in pediatric patients under 12 years of age with seasonal allergic rhinitis, or patients with perennial allergic or nonallergic rhinitis.

Pediatric patients (4 years of age and older) should be started with 100 mcg (one spray in each nostril once daily). Treatment with 200 mcg (two sprays in each nostril once daily or one spray in each nostril twice daily) should be reserved for pediatric patients not adequately responding to 100 mcg daily. Once adequate control is achieved, the dosage should be decreased to 100 mcg (one spray in each nostril) 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.

INDICATIONS AND USAGE

Fluticasone Propionate 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.

Safety and effectiveness of Fluticasone Propionate Nasal Spray in children below 4 years of age have not been adequately established.

CONTRAINDICATIONS

Fluticasone Propionate Nasal Spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of

withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Avoid spraying in eyes.

PRECAUTIONS

General

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS: Pediatric Use).

Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of fluticasone propionate nasal spray. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticosteroids, including fluticasone propionate.

Use of excessive doses of corticosteroids may lead to signs or symptoms of hypercorticism and/or suppression of HPA function.

Although systemic effects have been minimal with recommended doses of fluticasone propionate nasal spray, potential risk increases with larger doses. Therefore, larger than recommended doses of fluticasone propionate nasal spray should be avoided.

When used at higher than recommended doses or in rare individuals at recommended doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If

such changes occur, the dosage of fluticasone propionate nasal spray should be discontinued slowly consistent with accepted procedures for discontinuing oral corticosteroid therapy.

In clinical studies with fluticasone propionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of treatment with fluticasone propionate nasal spray. Patients using fluticasone propionate nasal spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

Intranasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred.

Information for Patients

Patients being treated with fluticasone propionate nasal spray should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay.

Patients should use fluticasone propionate nasal spray at regular intervals for optimal effect. Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of 200 mcg once daily effective for symptom control (see CLINICAL TRIALS).

A decrease in nasal symptoms may occur as soon as 12 hours after starting therapy with fluticasone propionate nasal spray. Results in several clinical trials indicate statistically significant improvement within the first day or two of treatment; however, the full benefit of fluticasone propionate nasal spray may not be achieved until treatment has been administered for several days. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

For the proper use of fluticasone propionate nasal spray and to attain maximum improvement, the patient should read and follow carefully the patient's instructions accompanying the product.

Drug Interactions

Fluticasone propionate is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg; 5 times the maximum daily intranasal dose)

with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when fluticasone propionate nasal spray is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 20 times the maximum recommended daily intranasal dose in adults and approximately 10 times the maximum recommended daily intranasal dose in children on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults and approximately equivalent to the maximum recommended daily intranasal dose in children on a mcg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (approximately equivalent to and 4 times, respectively, the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis) revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 25 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis) of fluticasone propionate to the rabbit. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).

Fluticasone propionate crossed the placenta following oral administration of 100 mcg/kg to rats or 300 mcg/kg to rabbits (approximately 4 and 25 times, respectively, the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids

than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nursing Mothers

It is not known whether fluticasone propionate is excreted in human breast milk. However, other corticosteroids have been detected in human milk. Subcutaneous administration to lactating rats of 10 mcg/kg or tritiated fluticasone propionate (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis) resulted in measurable radioactivity in the milk. Since there are no data from controlled trials on the use of intranasal fluticasone propionate by nursing mothers, caution should be exercised when fluticasone propionate nasal spray is administered to a nursing woman.

Pediatric Use

Six hundred fifty (650) patients aged 4 to 11 years and 440 patients aged 12 to 17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and effectiveness of fluticasone propionate nasal spray in children below 4 years of age have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including fluticasone propionate nasal spray, should be monitored routinely (e.g. via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including fluticasone propionate nasal spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A 1-year placebo-controlled clinical growth study was conducted in 150 pediatric patients (ages 3 to 9 years) to assess the effect of fluticasone propionate nasal spray (single daily dose of 200 mcg, the maximum approved dose) on growth velocity. From the primary population of 56 patients receiving fluticasone propionate nasal spray and 52 receiving placebo, the point estimate for growth velocity with fluticasone propionate nasal spray was 0.14 cm/year lower than that noted with placebo (95% confidence interval ranging from 0.54 cm/year lower than placebo to 0.27 cm/year higher than placebo). Thus, no statistically significant effect on growth was noted compared to placebo. No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.

The potential for fluticasone propionate nasal spray to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.

Geriatric Use

A limited number of patients above 65 years of age and older (N=129) or 75 years of age and older (N=11) have been treated with fluticasone propionate nasal spray in US and non-US clinical

trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients.

ADVERSE REACTIONS

In controlled US studies, more than 3,300 patients with seasonal allergic, perennial allergic, or perennial nonallergic rhinitis received treatment with intranasal fluticasone propionate. In general, adverse reactions in clinical studies have been primarily associated with irritation of the nasal mucous membranes, and the adverse reactions were reported with approximately the same frequency by patients treated with the vehicle itself. The complaints did not usually interfere with treatment. Less than 2% of patients in clinical trials discontinued because of adverse events; this rate was similar for vehicle placebo and active comparators.

Systemic corticosteroid side effects were not reported during controlled clinical studies up to 6 months' duration with fluticasone propionate nasal spray. If recommended doses are exceeded, however, or if individuals are particularly sensitive or taking fluticasone propionate nasal spray in conjunction with administration of other corticosteroids, symptoms of hypercorticism, e.g., Cushing syndrome, could occur.

The following incidence of common adverse reactions (>3%, where incidence in fluticasone propionate-treated subjects exceeded placebo) is based upon seven controlled clinical trials in which 536 patients (57 girls and 108 boys aged 4 to 11 years, 137 female and 234 male adolescents and adults) were treated with fluticasone propionate nasal spray 200 mcg once daily over 2 to 4 weeks and two controlled clinical trials in which 246 patients (119 female and 127 male adolescents and adults) were treated with fluticasone propionate nasal spray 200 mcg once daily over 6 months. Also included in the table are adverse events from two studies in which 167 children (45 girls and 122 boys aged 4 to 11 years) were treated with fluticasone propionate nasal spray 100 mcg once daily for 2 to 4 weeks.

Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in Controlled Clinical Trials With Fluticasone Propionate Nasal Spray in Patients ≥ 4 Years With Seasonal or Perennial Allergic Rhinitis

Adverse Experience	Vehicle Placebo (N = 758) %	Fluticasone Propionate 100 mcg Once Daily (N = 167) %	Fluticasone Propionate 200 mcg Once Daily (N = 782) %
Headache	14.6	6.6	16.1
Pharyngitis	7.2	6	7.8
Epistaxis	5.4	6	6.9
Nasal burning/nasal irritation	2.6	2.4	3.2
Nausea/vomiting	2	4.8	2.6
Asthma symptoms	2.9	7.2	3.3
Cough	2.8	3.6	3.8

Other adverse events that occurred in ≤3% but ≥1% of patients and that were more common with fluticasone propionate (with uncertain relationship to treatment) included: blood in nasal

mucus, runny nose, abdominal pain, diarrhea, fever, flu-like symptoms, aches and pains, dizziness, bronchitis.

Observed During Clinical Practice

In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of intranasal fluticasone propionate in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate or a combination of these factors.

General

Hypersensitivity reactions, including angioedema, skin rash, edema of the face and tongue, pruritus, urticaria, bronchospasm, wheezing, dyspnea, and anaphylaxis/anaphylactoid reactions, which in rare instances were severe.

Ear, Nose, and Throat

Alteration or loss of sense of taste and/or smell and, rarely, nasal septal perforation, nasal ulcer, sore throat, throat irritation and dryness, cough, hoarseness, and voice changes.

Eye

Dryness and irritation, conjunctivitis, blurred vision, glaucoma, increased intraocular pressure, and cataracts.

Cases of growth suppression have been reported for intranasal corticosteroids, including fluticasone propionate nasal spray (see PRECAUTIONS: Pediatric Use).

OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS). Intranasal administration of 2 mg (10 times the recommended dose) of fluticasone propionate twice daily for 7 days to healthy human volunteers was well tolerated. Single oral doses up to 16 mg have been studied in human volunteers with no acute toxic effects reported. Repeat oral doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg daily for 14 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. Acute overdosage with this dosage form is unlikely since one bottle of fluticasone propionate nasal spray contains approximately 8 mg of fluticasone propionate.

The oral and subcutaneous median lethal doses in mice and rats were >1,000 mg/kg (>20,000 and >41,000 times, respectively, the maximum recommended daily intranasal dose in adults and >10,000 and >20,000 times, respectively, the maximum recommended daily intranasal dose in children on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION

Patients should use fluticasone propionate nasal spray at regular intervals for optimal effect.

Adults

The recommended starting dosage in **adults** is two sprays (50 mcg of fluticasone propionate each) in each nostril once daily (total daily dose, 200 mcg). The same dosage divided into 100 mcg given twice daily (e.g., 8 a.m. and 8 p.m.) is also effective. After the first few days, patients may be able to reduce their dosage to 100 mcg (one spray in each nostril) once daily for maintenance therapy. Some patients (12 years of age and older) with seasonal allergic rhinitis may find as-needed use of 200 mcg once daily effective for symptom control (see CLINICAL TRIALS). Greater symptom control may be achieved with scheduled regular use.

Adolescents and Children (4 Years of Age and Older)

Patients should be started with 100 mcg (one spray in each nostril once daily). Patients not adequately responding to 100 mcg may use 200 mcg (two sprays in each nostril). Once adequate control is achieved, the dosage should be decreased to 100 mcg (one spray in each nostril) daily.

The maximum total daily dosage should not exceed two sprays in each nostril (200 mcg/day). (See CLINICAL TRIALS: Individualization of Dosage)

Fluticasone propionate nasal spray is not recommended for children under 4 years of age.

Directions for Use

Illustrated patient's instructions for proper use accompany each package of fluticasone propionate nasal spray.

HOW SUPPLIED

Fluticasone propionate nasal spray 50 mcg is supplied in an amber glass bottle fitted with a white metering atomizing pump, white nasal adapter fitted with a clear plastic dust cap, and a green safety clip, in a box of one (NDC 0054-3270-99) with patient's instructions for use. Each bottle contains a net fill weight of 16 g and will provide 120 actuations. Each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. The correct amount of medication in each spray cannot be assured after 120 sprays even though the bottle is not completely empty. The bottle should be discarded when the labeled number of actuations have been used.

Store between 4° and 30°C (39° and 86°F).

10002064/02

Revised May 2008

Information for Patients

FLUTICASONE PROPIONATE

Nasal Spray, 50 mcg

Please read this leaflet carefully before you start to take your medicine. It provides a summary of information on your medicine. **For further information ask your doctor or pharmacist.**

WHAT YOU SHOULD KNOW ABOUT RHINITIS

Rhinitis is a word that means inflammation of the lining of the nose. If you suffer from rhinitis, your nose becomes stuffy and runny. Rhinitis can also make your nose itchy, and you may sneeze a lot. Rhinitis can be caused by allergies to pollen, animals, molds, or other materials - or it may have a nonallergic cause.

WHAT YOU SHOULD KNOW ABOUT FLUTICASONE PROPIONATE NASAL SPRAY

Your doctor has prescribed Fluticasone Propionate Nasal Spray, a medicine that can help treat your rhinitis. Fluticasone Propionate Nasal Spray contains fluticasone propionate, which is a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. When you spray fluticasone into your nose, it helps to reduce the symptoms of allergic reactions and the stuffiness, runniness, itching, and sneezing that can bother you.

THINGS TO REMEMBER ABOUT FLUTICASONE PROPIONATE NASAL SPRAY

1. Shake gently before using.
2. Use your nasal spray as directed by your doctor. The directions are on the pharmacy label.
3. Keep your nasal spray **out of the reach of children**.

BEFORE USING YOUR NASAL SPRAY

- If you are pregnant (or intending to become pregnant),
- If you are breast-feeding a baby,
- If you are allergic to Fluticasone Propionate Nasal Spray or any other nasal corticosteroids,
- If you are taking a medicine containing ritonavir (commonly used to treat HIV infection or AIDS),

TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE. In some circumstances, this medicine may not be suitable and your doctor may wish to give you a different medicine. Make sure that your doctor knows what other medicines you are taking.

USING YOUR NASAL SPRAY

- Follow the instructions shown in the rest of this leaflet. If you have any problems, tell your doctor or pharmacist.
- It is important that you use it as directed by your doctor. The pharmacist's label will usually tell you what dose to take and how often. If it doesn't, or you are not sure, ask your doctor or pharmacist.

DOSAGE

- For **ADULTS**, the usual starting dosage is ***2 sprays in each nostril once daily***. Sometimes your doctor may recommend using 1 spray in each nostril twice a day (morning and evening). You should not use more than a total of 2 sprays in each nostril daily. After you have begun to feel better, 1 spray in each nostril daily may be adequate for you.
- For **ADOLESCENTS and CHILDREN** (4 years of age and older), the usual starting dosage is ***1 spray in each nostril once daily***. Sometimes your doctor may recommend using 2 sprays in each nostril daily. Then, after you have begun to feel better, 1 spray in each nostril daily may be adequate for you.
- DO NOT use more of your medicine or take it more often than your doctor advises.
- Fluticasone Propionate may begin to work within 12 hours of the first dose, but it takes several days of regular use to reach its greatest effect. It is important that you use Fluticasone Propionate Nasal Spray as prescribed by your doctor. Best results will be obtained by using the spray on a regular basis. If symptoms disappear, contact your doctor for further instructions.
- If you also have itchy, watery eyes, you should tell your doctor. You may be given an additional medication to treat your eyes. Be careful not to confuse them, particularly if the second medication is an eye drop.
- If you miss a dose, just take your regularly scheduled next dose when it is due. DO NOT DOUBLE the dose.

HOW TO USE YOUR NASAL SPRAY

Read the complete instructions carefully and use only as directed.

BEFORE USING

1. Shake the bottle gently and then remove the dust cap and the safety clip (Figure 1).

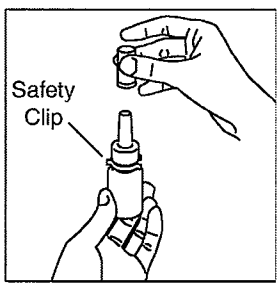


Figure 1

2. It is necessary to prime the pump into the air the first time it is used, or when you have not used it for a week or more. To prime the pump, hold the bottle as shown with the nasal applicator pointing away from you and with your forefinger and middle finger on either side of the nasal applicator and your thumb underneath the bottle. When you prime the pump for the first time, press down and release the pump six times (Figure 2).

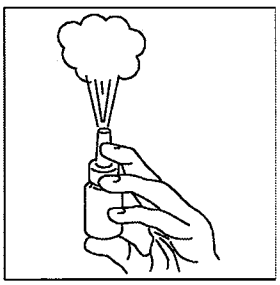


Figure 2

The pump is now ready for use. If the pump is not used for 7 days, prime until a fine spray appears.

USING THE SPRAY

3. Blow your nose to clear your nostrils.

4. Close one nostril. Tilt your head forward slightly and, keeping the bottle upright, carefully insert the nasal applicator into the other nostril (Figure 3).

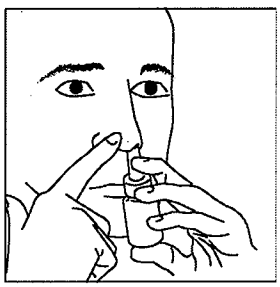


Figure 3

5. Start to breathe in through your nose, and WHILE BREATHING IN press firmly and quickly down once on the applicator to release the spray. To get a full actuation, use your forefinger and middle finger to spray while supporting the base of the bottle with your thumb. Avoid spraying in eyes. Breathe gently inwards through the nostril (Figure 4).

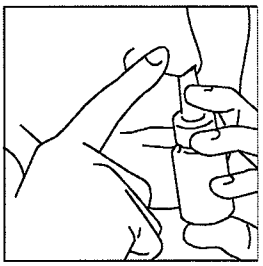


Figure 4

6. Breathe out through your mouth.
7. If a second spray is required in that nostril, repeat steps 4 though 6.
8. Repeat steps 4 through 7 in the other nostril.
9. Wipe the nasal applicator with a clean tissue and replace the dust cap and the safety clip (Figure 5).

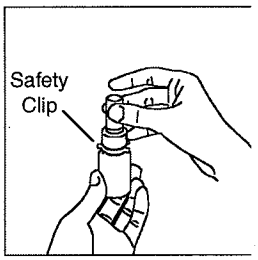


Figure 5

10. Do not use this bottle for more than the labeled number of sprays even though the bottle is not completely empty. Before you throw the bottle away, you should consult your doctor to see if a refill is needed. Do not take extra doses or stop taking Fluticasone Propionate Nasal Spray without consulting your doctor.

CLEANING

Your nasal spray should be cleaned at least once a week. To do this:

1. Remove the dust cap and then gently pull upwards to free the nasal applicator.
2. Wash the applicator and dust cap under warm tap water. Allow to dry at room temperature, then place the applicator and dust cap back on the bottle.
3. If the nasal applicator becomes blocked, it can be removed as above and left to soak in warm water. Rinse with cold tap water, dry, and refit. Do not try to unblock the nasal applicator by inserting a pin or other sharp object.

Read the complete instructions carefully and use only as directed.

STORING YOUR NASAL SPRAY

- Keep you Fluticasone Propionate Nasal Spray out of the reach of children.
- Avoid spraying in eyes.
- Store between 4° and 30°C (39° and 86°F).
- Do not use your Fluticasone Propionate Nasal Spray after the date shown as "EXP" on the label or box.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

FURTHER INFORMATION

This leaflet does not contain the complete information about your medicine. *If you have any questions, or are not sure about something, then you should ask your doctor or pharmacist.*

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

10002064/02
Revised May 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-504

LABELING REVIEWS

A1.1

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-504
Dates of Submission: October 03, 2002 (original)
Applicant's Name: Roxane labs
Established Name: Fluticasone Propionate Nasal Spray, 0.05 mg/spray

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Labeling Deficiencies:

1. **CONTAINER** (50 mcg/spray, 120 meter spray, 16 gram):

   a. Relocate the route of administration so that it appears on the front panel.

   b. Revise and relocate " 120 metered spray" to so that it appears on the front panel and reads as follows: "120 metered spray (each spray contains 50 mcg of fluticasone propionate) ".

2. **CARTON** (1x 16 gram bottles):

   a. See comments under container.

   b. Please identify the inactive ingredient and inactive ingredients by using the terms active and inactive" to proceed the ingredients.

3. **INSERT:**

[ ] b(4)

   b. Cite the manufacturer for/ by statements at the end of your professional insert. It may also appear, as seen at the end of the patient instruction sheet.

4. **PATIENT INFORMATION SHEET:**

   a. Submit a detached patient instruction sheet as does the innovator of the reference listed drug.

   b. You must also provide pictures corresponding to the numbered step. We refer you to the reference listed drug product labeling medication guide for guidance.

   c. BEFORE USING THE SPRAY- Create a new paragraph in Item 2, being with fourth sentence "The pump is now...

Please revise your labels and labeling, as instructed above, and submit 12 copies labels and labeling in final print or draft (insert and medication guide) if you prefer.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

r to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?			
Is this product a USP item? If so, USP supplement in which verification was assured. **USP 24**		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. **NONE**			

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Flonase® Nasal spray (Fluticasone Propionate Nasal Suspension) by GlaxoSimthKline (NDA 20-121/S-011, 013 and S-020; revised May 2002, Approved May 9, 2002). Medication guide revised May 2000.

2. PATENTS/EXCLUSIVITIES

   Patent Data – NDA 20-121

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4335121	November 14, 2003		Formula (Androstane cabothiates)	PIII	Same As

   Exclusivity Data– NDA 89-081

Code	Reference	Expiration	Labeling Impact
D-76	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	Mar 23, 2005	Curved Out

   [Vol. B1.1 pg.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Roxane Laboratories, Columbus, Ohio 43216
   [Vol. A40 pg. 18443]

4. CONTAINER/CLOSURE

   120 mL: amber glass bottle with a white metering atomizing pump, white nasal adapter fitted with a clear plastic dust cap and a green safety clip.[Vol. A40 pg. 18660]

5. INACTIVE INGREDIENTS

   b(4)

   and 7.

   ANDA - Same as RLD

   [ ] b(4)

6. PACKAGING CONFIGURATIONS

   RLD: Bottles of 16 g /per carton.
   ANDA: Same as RLD.
   [Vol. A1.40 pg. 18660]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Not a USP item.
RLD: Store between 4 – 30C (39-86F)
ANDA: Same as RLD.

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: Attention to pharmacist. Dispense with enclosed patient's instructions for use.
ANDA: Same as

9. BIOAVAILABILITY/BIOEQUIVALENCE: Pending

Date of Review: 1/19/03 Date of Submission: 10/03/02

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cc:

ANDA: 76-504
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
v:\firmsam\roxane\ltrs&rev\76504NA1.Lab Review

1/22/03

1/28/2003

3.1
Angela
or
Shaikh

APPROVAL SUMMARY (minor)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-504
Date of Submission	July 1, 2003
Applicant	Roxanne Lab
Drug Name	Fluticasone Propionate Nasal spray
Strength(s)	0.05 mg/spray

Approval Summary

Container Labels		**Submitted FPL**
0.05 mg	16 g	July 1, 2003 vol 3.1
Carton labeling	1 x 16 g	July 1, 2003 vol 3.1
Package Insert Labeling	#10002064/01 Rev 4/03	July 1, 2003 vol 3.1 * **will need to be revised before full approval**
Patient leaflet	#10002064/01 Rev 4/03	July 1, 2003 vol 3.1

PATENTS/EXCLUSIVITIES

Patent Data – NDA 20-121

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4335121	November 14, 2003 ped May 14, 2004		Formula (Androstane cabothiates)	PIII	Same As

Exclusivity Data– NDA 20-121

Code	Reference	Expiration	Labeling Impact
M-24/s-028	INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION	NOV 23,2005 peds, MAY 01,2006	Pediatric consult pending. (Precaution, last two paragarphs under peds section only)
D-76 ped /S-0. 23	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	Mar 23, 2005 Ped dec 1, 2006	Curved Out (Clinical Pharm.and D&A)

Reference Listed Drug

RLD on the 356(h) form	Flonase® Nasal spray
NDA Number	20-121
RLD established name	Fluticasone Propionate Nasal Suspension
Firm	GlaxoSimthKline
Currently approved PI	S-023
AP Date	5/17/02

Note. S-E/028 (approved 5/1/03) is a pediatric supplement that gained 6 months extension on patent and D-76 exclusivity. 3 year W/H may be pending. A pediatric consult may be required on S-028 (Pediatric use subsection safety information).

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?			
Is this product a USP item? If so, USP supplement in which verification was assured. **USP 24**		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. **NONE**			

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Flonase® Nasal spray (Fluticasone Propionate Nasal Suspension) by GlaxoSimthKline (NDA 20-121/S-011, 013 and S-020; revised May 2002, Approved May 9, 2002). Medication guide revised May 2000.

2. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Roxane Laboratories, Columbus, Ohio 43216

[Vol. A40 pg. 18443]

3. CONTAINER/CLOSURE

120 mL: amber glass bottle with a white metering atomizing pump, white nasal adapter fitted with a clear plastic dust cap and a green safety clip.[Vol. A40 pg. 18660]

4. INACTIVE INGREDIENTS

[ ]

USP item. This product is a suspension .

5. PACKAGING CONFIGURATIONS

RLD: Bottles of 16 g /per carton.
ANDA: Same as RLD.
[Vol. A1.40 pg. 18660]

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Not a USP item.
RLD: Store between 4 – 30C (39-86F)
ANDA: Same as RLD.

7. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: Attention to pharmacist. Dispense with enclosed patient's instructions for use.
ANDA: Same as

8. BIOAVAILABILITY/BIOEQUIVALENCE: Pending

Date of Review: 7/29/03 Date of Submission: July 1, 2003

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cc:

ANDA: 76-504
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
v:\firmsam\roxane\ltrs&rev\76504Ap.Lab Review

Grace 7/29/03
John J Grace 7/29/2003

REVIEW OF PROFESSIONAL LABELING #3 (minor)
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH
Supercedes the ap1.lab submitted on July 1, 2003
FAXed 1-12-05

ANDA Number: **76-504** Date of Submission: December 21, 2004
Applicant's Name: Roxane Labs
Established Name: Fluticasone Propionate Nasal Spray, 0.05 mg/spray

Labeling Deficiencies:

1. CONTAINER (50 mcg/spray, 120 meter spray, 16 gram): Satisfactory e-FPL.

2. CARTON (1x 16 gram bottles): Satisfactory in e- FPL.

3. INSERT:

   a. DESCRIPTION Please remove the manufacturer and product title information that intercept the continuous text in this section.

   b. PRECAUTIONS, Pediatric Use - Replace [redacted] with "Five hundred (500) patients...". b(4)

   c. DOSAGE AND ADMINISTRATION, Adults -The exclusivity for [redacted] b(4)

4. PATIENT INFORMATION SHEET: Satisfactory

Please revise your lables and labeling, as instructed above, and submit in final print according to the electronic labeling rule published December 11, 2003, (68 FR 69009) requiring submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (http://www.fda.gov/cder/guidance/5004fnl.htm). The guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html or http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-504
Date of Submission	
Applicant	Roxanne Lab
Drug Name	Fluticasone Propionate Nasal spray
Strength(s)	0.05 mg/spray

Approval Summary

Container Labels		**Submitted electronically FPL**
0.05 mg	16 g	\\CDSESUBOGD1\N76504\N_000\2004-12-21\fpl 10002063-01.pdf
Carton labeling	1 x 16 g	\\CDSESUBOGD1\N76504\N_000\2004-12-21\fpl 10002047-01.pdf
Package Insert Labeling	#10002064/01 Rev 12/04	
Patient leaflet	#10002064/01 Rev 12/04	

PATENTS/EXCLUSIVITIES

Patent Data – NDA 20-121

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4335121	November 14, 2003 ped May 14, 2004		Formula (Androstane cabothiates)	PIII	Same As

Exclusivity Data-- NDA 20-121

Code	Reference	Expiration	Labeling Impact
M-24/S-028	INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION	May 01, 2006 peds, Nov. 1, 2006	BPCA used per consult (Precaution, Pediatric subsection, final paragraph)
D-76/S-023	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	May 23, 2005 Ped Nov. 23, 2005	Carved Out (Clinical Pharm.and D&A)

Reference Listed Drug

RLD on the 356(h) form	Flonase® Nasal spray
NDA Number	20-121
RLD established name	Fluticasone Propionate Nasal Suspension
Firm	GlaxoSimthKline
Currently approved PI	S-030
AP Date	March 26, 2004

Note. S-E/028 (approved 5/1/03) is a pediatric supplement that received the 3 year W/H pediatric exclusivity. See 12/15/04 completed consult in jacket.

11 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Patent and Exclusivity Search Results from query on Appl No 020121 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020121	001	4335121	NOV 14,2003			
020121	001	4335121*PED	MAY 14,2004			

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020121	001	PED	NOV 01,2006
020121	001	PED	NOV 23,2005
020121	001	M-24	MAY 01,2006
020121	001	D-76	MAY 23,2005

Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFF 314.53(c)(3)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Orange Book Data Updated Through April, 2004
Orange Book Patent Data Only - **Daily**
Patent Data Last Updated: May 24, 2004

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?			
Is this product a USP item? If so, USP supplement in which verification was assured. **USP 24**		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert		X	

labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. **NONE**			

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Flonase® Nasal spray (Fluticasone Propionate Nasal Suspension) by GlaxoSimthKline (NDA 20-121/S-030, March 26, 2004).

2. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Roxane Laboratories, Columbus, Ohio 43216, [Vol. A40 pg. 18443]

3. CONTAINER/CLOSURE

120 mL: amber glass bottle with a white metering atomizing pump, white nasal adapter fitted with a clear plastic dust cap and a green safety clip.[Vol. A40 pg. 18660]

b(4,

accurate according to the composition statement. [Vol. A 1.40 pg. 18364] Phenylethyl alcohol is a USP item. This product is a suspension .

5. PACKAGING CONFIGURATIONS

RLD: Bottles of 16 g /per carton.
ANDA: Same as RLD.
[Vol. A1.40 pg. 18660]

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Not a USP item.
RLD: Store between 4 – 30C (39-86F)
ANDA: Same as RLD.

7. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: Attention to pharmacist. Dispense with enclosed patient's instructions for use.
ANDA: Same as

8. BIOAVAILABILITY/BIOEQUIVALENCE:

Date of Review: 1/03/05 Date of Submission: Dec. 21, 2004

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cc: ANDA: 76-504
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
v:\firmsnz\roxane\ltrs&rev\76504na2.Lab Review
Supercedes "ap1.lab"

EDR: FPL
\\CDSESUBOGD1\N76504\N_000\2004-12-21\fpl 10002063-01.pdf container
\\CDSESUBOGD1\N76504\N_000\2004-12-21\fpl 10002047-01.pdf carton

APayne 1/5/04
JGrace 1-5-04

REVIEW OF PROFESSIONAL LABELING #4
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH
Supercedes the ap1.lab and na2.lab
FAX 2-5-05

ANDA Number: **76-504** Date of Submission: January 20, 2005
Applicant's Name: Roxane Labs
Established Name: Fluticasone Propionate Nasal Spray, 0.05 mg/spray

Labeling Deficiencies:

IN [ ] :N b(4)

Please revise your lables and labeling, as instructed above, and submit in final print according to the electronic labeling rule published December 11, 2003, (68 FR 69009) requiring submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (http://www.fda.gov/cder/guidance/5004fnl.htm). The guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://www.fda.gov/cder/cdernew/listserv.html or
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

APPROVAL SUMMARY #2
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-504
Date of Submission	
Applicant	Roxanne Lab
Drug Name	Fluticasone Propionate Nasal spray
Strength(s)	0.05 mg/spray

Approval Summary

Container Labels		**Submitted electronically FPL**
0.05 mg	16 g	\\CDSESUBOGD1\N76504\N_000\2004-12-21\fpl 10002063-01.pdf
Carton labeling	1 x 16 g	\\CDSESUBOGD1\N76504\N_000\2004-12-21\fpl 10002047-01.pdf
Package Insert Labeling	#10002064/01 Rev	
Patient leaflet	#10002064/01 Rev	

PATENTS/EXCLUSIVITIES

Patent Data – NDA 20-121

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4335121	November 14, 2003 ped May 14, 2004		Formula (Androstane cabothiates)	PIII	Same As

Exclusivity Data– NDA 20-121

Code	Reference	Expiration	Labeling Impact
M-24/S-028	INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION	May 01, 2006 peds, Nov. 1, 2006	BPCA used per consult (Precaution, Pediatric subsection, final paragraph)
D-76/S-023	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	May 23, 2005 Ped Nov. 23, 2005	Carved Out (Clinical Pharm.and D&A)

Reference Listed Drug

RLD on the 356(h) form	Flonase® Nasal spray
NDA Number	20-121
RLD established name	Fluticasone Propionate Nasal Suspension
Firm	GlaxoSimthKline
Currently approved PI	S-030
AP Date	March 26, 2004 ✓ OTP 1/31/05

Note. S-E/028 (approved 5/1/03) is a pediatric supplement that received the 3 year W/H pediatric exclusivity. See 12/15/04 completed consult in jacket.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?			
Is this product a USP item? If so, USP supplement in which verification was assured. **USP 24**		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			

Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. **NONE**			

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Flonase® Nasal spray (Fluticasone Propionate Nasal Suspension) by GlaxoSimthKline (NDA 20-121/S-030, March 26, 2004).

2. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   Roxane Laboratories, Columbus, Ohio 43216, [Vol. A40 pg. 18443]

3. CONTAINER/CLOSURE

   120 mL: amber glass bottle with a white metering atomizing pump, white nasal adapter fitted with a clear plastic dust cap and a green safety clip.[Vol. A40 pg. 18660]

4. INACTIVE INGREDIENTS

[ ] 5 b(4)

accurate according to the composition statement. [Vol. A1.40 pg. 18664] Phenylethyl alcohol is a USP item. This product is a suspension .

5. PACKAGING CONFIGURATIONS

RLD: Bottles of 16 g /per carton.
ANDA: Same as RLD.
[Vol. A1.40 pg. 18660]

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Not a USP item.
RLD: Store between 4 – 30C (39-86F)
ANDA: Same as RLD.

7. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: Attention to pharmacist. Dispense with enclosed patient's instructions for use.
ANDA: Same as

8. BIOAVAILABILITY/BIOEQUIVALENCE:

Date of Review: 1/31/05 Date of Submission: Jan. 20, 2005

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cc: ANDA: 76-504
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
v:\firmsnz\roxane\ltrs&rev\76504na3.Lab Review
Supercedes "ap1.lab" and Na2.lab

EDR: FPL
\\CDSESUBOGD1\N76504\N_000\2004-12-21\fpl 10002063-01.pdf container
\\CDSESUBOGD1\N76504\N_000\2004-12-21\fpl 10002047-01.pdf carton

Grace 1/31/05
Grace 1/31/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-504

CHEMISTRY REVIEWS

ANDA 76-504

Fluticasone Propionate Nasal Spray, 50 mcg

Roxane Laboratories, Inc.
Columbus, OH

Mujahid L. Shaikh

Division Of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-504

2. REVIEW #: 1

3. REVIEW DATE: January 9-27, 2003 (Revised on February 12, 2003 & March 10, 2003)

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	10-3-02

Note: This ANDA is accepted for filing on October 4, 2002 and Acknowledgement letter is issued to the firm on November 13, 2002.

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road, Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

Note: Roxane Laboratories, Inc, OH is a company of Boehringer Ingelheim Pharmaceuticals.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Fluticasone Propionate Nasal Spray, 50 mcg

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug (RLD): FLONASE® (Fluticasone Propionate) Nasal Spray, 50 mcg and it is approved for GlaxoSmithKline (NDA 20121).

Patent Certification: Roxane certifies per Paragraph III Certification that U.S. Patent # 4,335,121 will expire on November 14, 2003 based on their best knowledge.

Based on the information published in Approved Drug Products with Therapeutic Equivalence Evaluation, the reference drug is entitled to marketing exclusivity for an indication that the ANDA will not claim till May 23, 2005.

The indications the proposed drug product is going to be used for, active ingredient, route of administration, dosage form, strength and labeling is same as listed drug product.

10. PHARMACOLY CATEGORY:

To manage the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: 50 mcg

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _X__Rx ___OTC

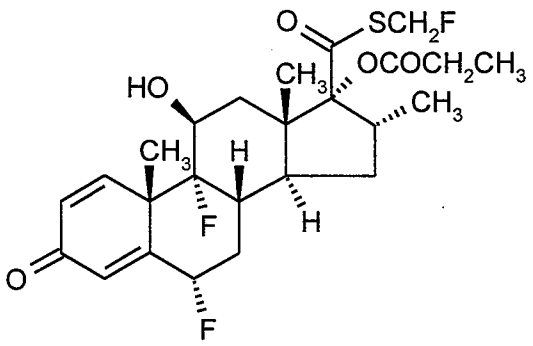
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Fluticasone Propionate
Chemical name: S-fluoromethyl 6(alpha),9(alpha)-difluoro- 11(beta)-hydroxy-16(alpha)-methyl-3-oxo-17(alpha)- propionyloxyandrosta-1,4- diene-17(beta)-carbothioate [80474-14-2].



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETE	COMMENTS
							b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Will be Requested later		
Labeling	Deficient	1/28/03	A.Payne
Bioequivalence	Pending Review		
EA	Adequate	1-15-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 76-504

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Not Approved. NA (Minor) Letter

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None identified at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The proposed drug product is Fluticasone Propionate Nasal Spray, 50 mcg.

The Reference Listed Drug is Flonase® (Flutocasone Propionate) Nasal Spray (NDA 20-121) and it is approved for GlaxoSmithKline.

Drug Substance: The active ingredient in this drug product is Fluticasone Propionate. It is a non-USP material and its acceptance specifications are based on its manufacturer. The manufacturer has stated that their acceptance specifications are based on BP.

B. Description of How the Drug Product is Intended to be Used:

Fluticasone Propionate has been used for many years for treatment of patients with seasonal and perennial allergic and non-allergic rhinitis in adults and young patients and historically has been found to be safe and efficacious. It is used as nasal spray.

C. Basis for Approvability or Not-Approval Recommendation

Based on this CMC review for this ANDA, a not approvable letter with **minor** amendment is being sent to the firm including deficiencies identified for release and stability specifications.

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-625/MShaikh/3/10/03 Mustafa Shaikh 3/24/03
HFD-625/MSmela/ M Smela 3/25/03
HFD-617/PChen/ for 3/19/03
V:/Firmsnz/Roxane/ltrs&rev/76504.R01.doc

C. CC: **ANDA 76-504**
Division File
DUP Jacket
Field Copy

41 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1a

ANDA DUP
Division File
Field Copy

Endorsements :

HFD-625 /M. Shaikh /3/10/03 Muqaddas Shaikh 3/24/03
HFD-6 25 /M. Smela /3/10/03
HFD-6 17 / PChen /3/12/03 Peter Chen 3/24/03 for 3/24/03
F/t by: gp/3/13/03
V:\FIRMSNZ\Roxane\LTRS&REV\76504.R01.doc

NOT APPROVABLE – MINOR

M Shaikh
3/25/03

ANDA 76-504

Fluticasone Propionate Nasal Spray, 50 mcg

Roxane Laboratories, Inc.
Columbus, OH

Mujahid L. Shaikh

Division Of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-504

2. REVIEW #: 2

3. REVIEW DATE: August 18, 2003 (Revised on August 25, 2003)

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original submission	10-3-02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	7/1/03

Note: This ANDA was accepted for filing on October 4, 2002 and Acknowledgement letter was issued to the firm on November 13, 2002.

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road, Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

Note: Roxane Laboratories, Inc, OH is a company of Boehringer Ingelheim Pharmaceuticals.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Fluticasone Propionate Nasal Spray, 50 mcg

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug (RLD): FLONASE® (Fluticasone Propionate) Nasal Spray, 50 mcg and it was approved for GlaxoSmithKline (NDA 20121).

10. PHARMACOLY CATEGORY:

To manage the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: 50 mcg

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _X__Rx ___OTC

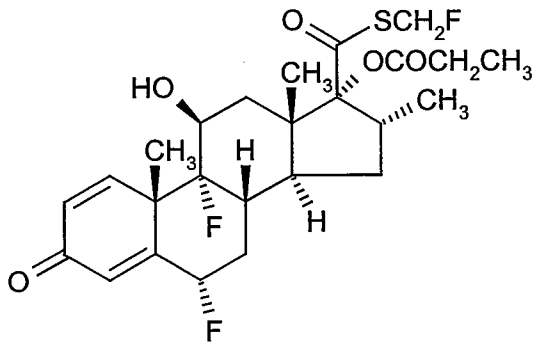
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____X_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Fluticasone Propionate
Chemical name: S-fluoromethyl 6(alpha),9(alpha)-difluoro- 11(beta)-hydroxy-16(alpha)-methyl-3-oxo-17(alpha)- propionyloxyandrosta-1,4- diene-17(beta)-carbothioate [80474-14-2].



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Inadequate	8-18-03	

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	6-2-03	J. D Ambrogio
Methods Validation	Will request later		
Labeling	Pending Review		
Bioequivalence	Pending Review		
EA	Adequate	1-15-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __ Yes __X__ No If no, explain reason(s) below: Minor amendment

The Chemistry Review for ANDA 76-504

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Not Approved. NA (Minor) Letter . In-Vitro and In-Vivo bio data have not yet been reviewed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None identified at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The proposed drug product is Fluticasone Propionate Nasal Spray, 50 mcg.

The Reference Listed Drug is Flonase® (Flutocasone Propionate) Nasal Spray (NDA 20-121) and it is approved for GlaxoSmithKline.

Drug Substance: The active ingredient in this drug product is Fluticasone Propionate. It is a non-USP material and its acceptance specifications are based on its manufacturer. The manufacturer has stated that their acceptance specifications are based on BP.

B. Description of How the Drug Product is Intended to be Used:
Fluticasone Propionate has been used for many years for treatment of patients with seasonal and perennial allergic and non-allergic rhinitis in adults and young patients and historically has been found to be safe and efficacious. It is used as nasal spray.

C. Basis for Approvability or Not-Approval Recommendation
Based on this CMC review for this ANDA, a not approvable letter with **minor** amendment is being sent to the firm based on inadequate status of the DMFs and other CMC issues.

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-625/MShaikh/8/25/03 mshaikh 9/3/03
HFD-625/MSmela/8/29/03
HFD-617/PChen/
V:/Firmsnz/Roxane/ltrs&rev/76504.R02.doc

C. CC: **ANDA 76-504**
Division File
DUP Jacket
Field Copy

33 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2a

ANDA 76-504

Fluticasone Propionate Nasal Spray, 50 mcg

Roxane Laboratories, Inc.
Columbus, OH

Mujahid L. Shaikh

Division Of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-504

2. REVIEW #: 3

3. REVIEW DATE: January 20, 2004 (Revised on February 2, 2004)

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original submission	10-3-02
Minor Amendment	7-1-03

6. SUBMISSION(S) BEING REVIEWED*:

Submission(s) Reviewed	Document Date
* NC (Pump site inquiry)	5-8-03
NC (BIO)	8-28-03
* Minor Amendment	11-11-03
Amendment (Bio)	12-19-03

Note: This ANDA was accepted for filing on October 4, 2002 and Acknowledgement letter was issued to the firm on November 13, 2002.

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road, Columbus, OH 43228
Representative:	Elizabeth Ernst

Telephone: 614-272-4785

Note: Roxane Laboratories, Inc, OH is a company of Boehringer Ingelheim Pharmaceuticals.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Fluticasone Propionate Nasal Spray, 50 mcg

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug (RLD): FLONASE® (Fluticasone Propionate) Nasal Spray, 50 mcg and it was approved for GlaxoSmithKline (NDA 20121).

10. PHARMACOLY CATEGORY:

To manage the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: 50 mcg

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

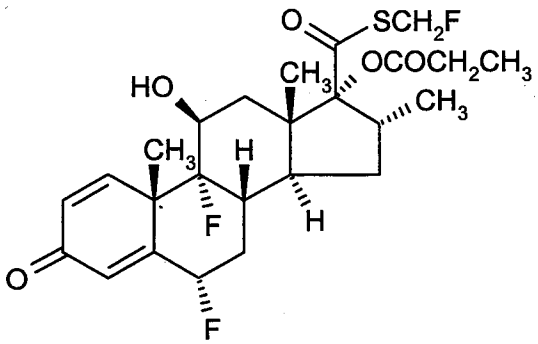
_____SPOTS product – Form Completed

____X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Fluticasone Propionate
Chemical name: S-fluoromethyl 6(alpha),9(alpha)-difluoro- 11(beta)-hydroxy-16(alpha)-

methyl-3-oxo-17(alpha)- propionyloxyandrosta-1,4- diene-17(beta)-carbothioate [80474-14-2].



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12-8-03	J. D Ambrogio
Methods Validation	Requested	2-2-04	M. Shaikh
Labeling	Acceptable	7-29-03	A. Payne/John Grace
Bioequivalence	Pending		
EA	Adequate	1-15-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __ Yes __X__ No If no, explain reason(s) below: Minor amendment

The Chemistry Review for ANDA 76-504

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approved. NA (Minor) Letter .

In-Vitro and In-Vivo bio data is deficient as of review completed on 12-2-03. Roxane submitted a bio amendment dated 12-19-03, and review is pending. Review of Clinical Study still pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None identified at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The proposed drug product is Fluticasone Propionate Nasal Spray, 50 mcg.

The Reference Listed Drug is Flonase® (Flutocasone Propionate) Nasal Spray (NDA 20-121) and it is approved for GlaxoSmithKline.

Drug Substance: The active ingredient in this drug product is Fluticasone Propionate. It is a non-USP material and its acceptance specifications are based on its manufacturer. The manufacturer has stated that their acceptance specifications are based on BP.

B. Description of How the Drug Product is Intended to be Used:

Fluticasone Propionate has been used for many years for treatment of patients with seasonal and perennial allergic and non-allergic rhinitis in adults and young patients and historically has been found to be safe and efficacious. It is used as nasal spray.

C. Basis for Approvability or Not-Approval Recommendation

Based on this CMC review for this ANDA, a not approvable letter with **minor** amendment is being sent to the firm based on inadequate status of the DMFs and other CMC issues.

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-625/MShaikh/2/2/04
HFD-625/MSmela/
HFD-617/PChen/
V:/Firmsnz/Roxane/ltrs&rev/76504.R03.doc

C. CC: **ANDA 76-504**
Division File
DUP Jacket
Field Copy

28 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 3 a

ANDA 76-504

Fluticasone Propionate Nasal Spray, 50 mcg

Roxane Laboratories, Inc.
Columbus, OH

Mujahid L. Shaikh

Division Of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-504

2. REVIEW #: 4

3. REVIEW DATE: March 29, 2004

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original submission	10-3-02
Minor Amendment	7-1-03
NC (Pump site inquiry)	5-8-03
NC (BIO)	8-28-03
Minor Amendment	11-11-03
Amendment (Bio)	12-19-03

6. SUBMISSION(S) BEING REVIEWED*:

Submission(s) Reviewed	Document Date
Gratuitous Amendment	1-27-04
Minor Amendment (Reply to February 10, 2004 NA letter)	2-27-04

Note: This ANDA was accepted for filing on October 4, 2002 and Acknowledgement letter was issued to the firm on November 13, 2002.

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road, Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

Note: Roxane Laboratories, Inc, OH is a company of Boehringer Ingelheim Pharmaceuticals.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Fluticasone Propionate Nasal Spray, 50 mcg

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug (RLD): FLONASE® (Fluticasone Propionate) Nasal Spray, 50 mcg and it was approved for GlaxoSmithKline (NDA 20121).

10. PHARMACOLY CATEGORY:

To manage the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: 50 mcg

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _X__Rx ___OTC

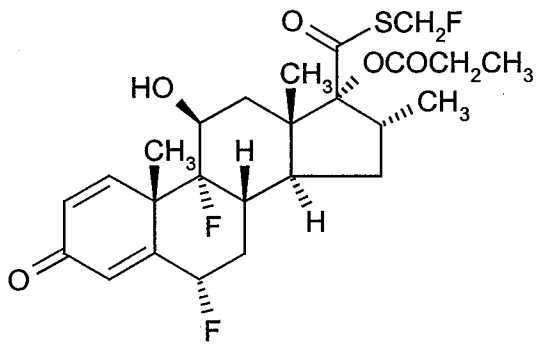
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____X_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Fluticasone Propionate
Chemical name: S-fluoromethyl 6(alpha),9(alpha)-difluoro- 11(beta)-hydroxy-16(alpha)-methyl-3-oxo-17(alpha)- propionyloxyandrosta-1,4- diene-17(beta)-carbothioate [80474-14-2].



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12-8-03	J. D Ambrogio
Methods Validation	Requested	2-2-04	M. Shaikh
Labeling	Acceptable	7-29-03	A. Payne/John Grace
Bioequivalence	Under Review		
EA	Adequate	1-15-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __ Yes __X__ No If no, explain reason(s) below: Minor amendment

cc: ANDA: 76-504
ANDA DUP
Division File
Field Copy

Endorsements :

HFD-625 /M. Shaikh / 3/29/04 3/31/04
HFD-6 25 /M. Smela /3/30/04 3/31/04
HFD-6 17 / PChen /3/30/04 3/31/04
F/t by: ard/3/30/04

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NOT APPROVABLE – MINOR

The Chemistry Review for ANDA 76-504

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approved. NA (Minor) Letter .

In-Vitro and In-Vivo bio data is deficient as of review completed on 12-2-03. Roxane submitted a bio amendment dated 12-19-03, and review is pending. Review of Clinical Study still pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None identified at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The proposed drug product is Fluticasone Propionate Nasal Spray, 50 mcg.

The Reference Listed Drug is Flonase® (Flutocasone Propionate) Nasal Spray (NDA 20-121) and it is approved for GlaxoSmithKline.

Drug Substance: The active ingredient in this drug product is Fluticasone Propionate. It is a non-USP material and its acceptance specifications are based on its manufacturer. The manufacturer has stated that their acceptance specifications are based on BP.

B. Description of How the Drug Product is Intended to be Used:

Fluticasone Propionate has been used for many years for treatment of patients with seasonal and perennial allergic and non-allergic rhinitis in adults and young patients and historically has been found to be safe and efficacious. It is used as nasal spray.

C. Basis for Approvability or Not-Approval Recommendation

Based on this CMC review for this ANDA, a not approvable letter with **minor** amendment is being sent to the firm based on inadequate status of the DMF and acceptance specifications for Fluticasone Propionate.

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-625/MShaikh/3/29/04 mujahid shaikh 3/31/04
HFD-625/MSmela/3/20/04
HFD-617/PChen/
V:/Firmsnz/Roxane/ltrs&rev/76504.R04.doc

C. CC: **ANDA 76-504**
Division File
DUP Jacket
Field Copy

18 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 4a

ANDA 76-504

Fluticasone Propionate Nasal Spray, 50 mcg

Roxane Laboratories, Inc.
Columbus, OH

Mujahid L. Shaikh

Division Of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-504

2. REVIEW #: 5

3. REVIEW DATE: June2, 2004

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original submission	10-3-02
Minor Amendment	7-1-03
NC (Pump site inquiry)	5-8-03
NC (BIO)	8-28-03
Minor Amendment	11-11-03
Amendment (Bio)	12-19-03
Gratuitous Amendment	1-27-04
Minor Amendment (Reply to February 10, 2004 NA letter)	2-27-04

6. SUBMISSION(S) BEING REVIEWED*:

Submission(s) Reviewed	Document Date
*Minor Amendment (Reply to March 31, 2004 NA letter)	4-15-04
* Telephone Amendment	5-20-04

Note: This ANDA was accepted for filing on October 4, 2002 and Acknowledgement letter was issued to the firm on November 13, 2002.

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road, Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

Note: Roxane Laboratories, Inc, OH is a company of Boehringer Ingelheim Pharmaceuticals.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Fluticasone Propionate Nasal Spray, 50 mcg

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug (RLD): FLONASE® (Fluticasone Propionate) Nasal Spray, 50 mcg and it was approved for GlaxoSmithKline (NDA 20121).

10. PHARMACOLY CATEGORY:

To manage the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: 50 mcg

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _X__Rx ___OTC

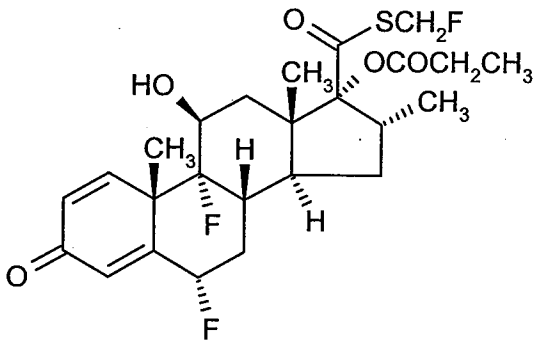
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____X_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Fluticasone Propionate
Chemical name: S-fluoromethyl 6(alpha),9(alpha)-difluoro- 11(beta)-hydroxy-16(alpha)-methyl-3-oxo-17(alpha)- propionyloxyandrosta-1,4- diene-17(beta)-carbothioate [80474-14-2].



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12-8-03	J. D Ambrogio
Methods Validation	Satisfactory	5-20-04	M. Shaikh
Labeling	Acceptable	7-29-03	A. Payne/John Grace
Bioequivalence	Under Review		
EA	Adequate	1-15-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __ Yes __X__ No If no, explain reason(s) below: Minor amendment

The Chemistry Review for ANDA 76-504

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Chemistry Completed.

In-Vitro and In-Vivo bio data are under review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None identified at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The proposed drug product is Fluticasone Propionate Nasal Spray, 50 mcg.

The Reference Listed Drug is Flonase® (Flutocasone Propionate) Nasal Spray (NDA 20-121) and it is approved for GlaxoSmithKline.

Drug Substance: The active ingredient in this drug product is Fluticasone Propionate. It is a non-USP material and its acceptance specifications are based on its manufacturer. The manufacturer has stated that their acceptance specifications are based on BP.

B. Description of How the Drug Product is Intended to be Used:

Fluticasone Propionate has been used for many years for treatment of patients with seasonal and perennial allergic and non-allergic rhinitis in adults and young patients and historically has been found to be safe and efficacious. It is used as nasal spray.

C. Basis for Approvability or Not-Approval Recommendation

Based on this CMC review for this ANDA, acceptance specifications for Fluticasone Propionate, labeling, release and stability and DMF are satisfactory and they are acceptable.

Bio status: Pending

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

Mujahid Shaikh 6/2/04

HFD-625/MShaikh/
HFD-625/MSmela/
~~HFD-617/PChen/~~
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C. CC: **ANDA 76-504**
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DUP Jacket
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M Smela 6/2/04

15 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry 5a

cc: ANDA: 76-504
ANDA DUP
Division File
Field Copy

Endorsements:
HFD-625/M. Shaikh /11/3/04
HFD-6 25/M. Smela /11/3/04
HFD-6 17/ PChen /
F/t by: ard/11/5/04

11/8/04
11/8/04
11/8/04

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NOT APPROVABLE – MAJOR

ANDA 76-504

Fluticasone Propionate Nasal Spray, 50 mcg

Roxane Laboratories, Inc.
Columbus, OH

Mujahid L. Shaikh

Division Of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-504

2. REVIEW #: 6

3. REVIEW DATE: March 7, 2005 (Revised on March 14, 2005)

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original submission	10-3-02
Minor Amendment	7-1-03
NC (Pump site inquiry)	5-8-03
NC (BIO)	8-28-03
Minor Amendment	11-11-03
Amendment (Bio)	12-19-03
Gratuitous Amendment	1-27-04
Minor Amendment (Reply to February 10, 2004 NA letter)	2-27-04
Minor Amendment (Reply to March 31, 2004 NA letter)	4-15-04
Telephone Amendment	5-20-04

6. SUBMISSION(S) BEING REVIEWED*:

Submission(s) Reviewed	Document Date
Bio Amendment	8-17-04
NC (Bio)	10-29-04
Amendment (labeling)	12-21-04
Amendment (labeling)	1-20-05
*Minor Amendment (Response to November 9, 2004 minor amendment	2-1-05
Amendment (Labeling)	2-18-05

Note: This ANDA was accepted for filing on October 4, 2002 and Acknowledgement letter was issued to the firm on November 13, 2002.

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road, Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

Note: Roxane Laboratories, Inc, OH is a company of Boehringer Ingelheim Pharmaceuticals.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Fluticasone Propionate Nasal Spray, 50 mcg

9. LEGAL BASIS FOR SUBMISSION:

Reference Listed Drug (RLD): FLONASE® (Fluticasone Propionate) Nasal Spray, 50 mcg and it is approved for GlaxoSmithKline (NDA 20121).

10. PHARMACOLY CATEGORY:

To manage the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: 50 mcg

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _X__Rx ___OTC

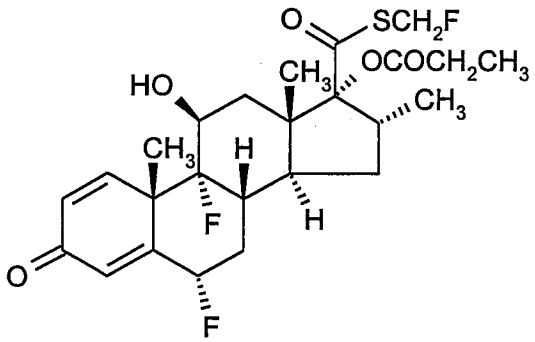
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Fluticasone Propionate
Chemical name: S-fluoromethyl 6(alpha),9(alpha)-difluoro- 11(beta)-hydroxy-16(alpha)-methyl-3-oxo-17(alpha)- propionyloxyandrosta-1,4- diene-17(beta)-carbothioate [80474-14-2].



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
1							

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12-8-03	J. D Ambrogio
Methods Validation	Satisfactory	5-20-04	M. Shaikh (See CR # 5)
Labeling	Acceptable	3-2-05	A. Payne/John Grace
Bioequivalence*	Deficient	10-18-04	Z. Z. Wahba
EA	Adequate	1-15-03	M. Shaikh
Radiopharmaceutical	N/A		

* Review of comparative clinical study is also pending.

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __ Yes __X__ No If no, explain reason(s) below: Minor amendment

The Chemistry Review for ANDA 76-504

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NA (minor)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Request is being made for commitment on limits. b(4)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The proposed drug product is Fluticasone Propionate Nasal Spray, 50 mcg.

The Reference Listed Drug is Flonase® (Flutocasone Propionate) Nasal Spray (NDA 20-121) and it is approved for GlaxoSmithKline.

Drug Substance: The active ingredient in this drug product is Fluticasone Propionate. It is a currently non-USP material and its acceptance specifications are based on its manufacturer. The manufacturer has stated that their acceptance specifications are based on DS is in USP 28 as of April 1, 2005. b(4)

B. Description of How the Drug Product is Intended to be Used:

Fluticasone Propionate has been used for many years for treatment of patients with seasonal and perennial allergic and non-allergic rhinitis in adults and young patients and historically has been found to be safe and efficacious. It is used as nasal spray.

C. Basis for Approvability or Not-Approval Recommendation

Based on this CMC review for this ANDA, acceptance specifications for Fluticasone Propionate needs revision. FPL is acceptable. Revision and commitment regarding release and stability specifications is required.

Bio status: Pending Firm

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-625/MShaikh/3/14/05 Mujahid Shaikh 3/21/05
HFD-625/MSmela/3/14/05

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C. CC: **ANDA 76-504**
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cc: ANDA: 76-504
ANDA DUP
Division File
Field Copy

Endorsements:
HFD-625/M. Shaikh /3/14/05
HFD-6 25/M. Smela /3/14/05
HFD-6 17/ PChen /3/16/05
F/t by: ard/3/17/05

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NOT APPROVABLE – MINOR

19 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 6a

2. The USP methods for the drug substance are regulatory in case of a dispute.

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

ANDA 76-504

Fluticasone Propionate Nasal Spray, 50 mcg

Roxane Laboratories, Inc.
Columbus, OH

Mujahid L. Shaikh

Division Of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-504

2. REVIEW #: 7

3. REVIEW DATE: August 2, 2005

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	10-3-02
Minor Amendment	7-1-03
NC (Pump site inquiry)	5-8-03
NC (BIO)	8-28-03
Minor Amendment	11-11-03
Amendment (Bio)	12-19-03
Gratuitous Amendment	1-27-04
Minor Amendment (Reply to February 10, 2004 NA letter)	2-27-04
Minor Amendment (Reply to March 31, 2004 NA letter)	4-15-04
Telephone Amendment	5-20-04
Bio Amendment	8-17-04
NC (Bio)	10-29-04
Amendment (labeling)	12-21-04
Amendment (labeling)	1-20-05
Minor Amendment (Response to November 9, 2004 minor amendment	2-1-05
Amendment (Labeling)	2-18-05

6. SUBMISSION(S) BEING REVIEWED*:

Submission(s) Reviewed	Document Date
* Minor Amendment	5-25-05
Bio amendment (Response to bio deficiency letter dated October 8, 2004)	6-6-05
* Telephone Amendments	7-22-05 and 8-5-05

Note: This ANDA was accepted for filing on October 4, 2002 and Acknowledgement letter was issued to the firm on November 13, 2002.

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road, Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

Note: Roxane Laboratories, Inc, OH is a company of Boehringer Ingelheim Pharmaceuticals.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Fluticasone Propionate Nasal Spray, 50 mcg

9. LEGAL BASIS FOR SUBMISSION:
Reference Listed Drug (RLD): FLONASE® (Fluticasone Propionate) Nasal Spray, 50 mcg and it is approved for GlaxoSmithKline (NDA 20121).

10. PHARMACOLY CATEGORY:
To manage the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: 50 mcg

13. ROUTE OF ADMINISTRATION: Nasal

14. Rx/OTC DISPENSED: _X__Rx ___OTC

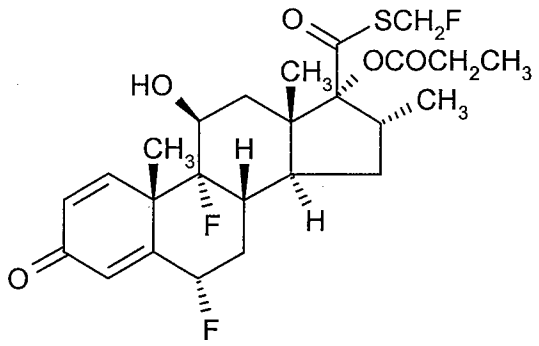
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NAME: Fluticasone Propionate
Chemical name: S-fluoromethyl 6(alpha),9(alpha)-difluoro- 11(beta)-hydroxy-16(alpha)-methyl-3-oxo-17(alpha)- propionyloxyandrosta-1,4- diene-17(beta)-carbothioate [80474-14-2].



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
							b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	12-8-03	J. D Ambrogio
Methods Validation	Satisfactory	5-20-04	M. Shaikh (See CR # 5)
Labeling	Acceptable	3-2-05	A. Payne/John Grace
Bioequivalence	Pending		
EA	Adequate	1-15-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __ Yes __X__ No If no, explain reason(s) below: Minor amendment

The Chemistry Review for ANDA 76-504

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry completed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

b(4)

Commitment on [redacted] its to be finalized by [redacted] after 20 batches has been made. Commitment for CBE-0 for 1st batch DP manufactured with Process 3 DS has been made.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: The proposed drug product is Fluticasone Propionate Nasal Spray, 50 mcg.

The Reference Listed Drug is Flonase® (Flutocasone Propionate) Nasal Spray (NDA 20-121) and it is approved for GlaxoSmithKline.

Drug Substance: The active ingredient in this drug product is Fluticasone Propionate. It is a USP material and its acceptance specifications are based on its manufacturer. The manufacturer has stated that their acceptance specifications are based on BP. The DS is in USP 28 as of April 1, 2005.

B. Description of How the Drug Product is Intended to be Used:

Fluticasone Propionate has been used for many years for treatment of patients with seasonal and perennial allergic and non-allergic rhinitis in adults and young patients and historically has been found to be safe and efficacious. It is used as nasal spray.

C. Basis for Approvability or Not-Approval Recommendation

Based on this CMC review for this ANDA, acceptance specifications for Fluticasone Propionate became acceptable.

Release and stability specifications became acceptable in this review.

Bio status: Pending

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-630/MShaikh/ Mujahid Shaikh 8/9/05
HFD-625/MSmela/ M Smela 8/9/05

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C. CC: **ANDA 76-504**
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No new amendments to DMF or ANDA. Bio acceptable 8/30/05. ANDA is approvable.
M Smela
9/14/05

20 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 7a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-504

BIOEQUIVALENCE REVIEWS

Review of a Bioequivalence Study with Clinical Endpoints

ANDA 76-504	
Drug Product:	**Fluticasone Propionate Nasal Spray, 50 mcg**
Sponsor:	Roxane Laboratories, Inc.
Reference Listed Drug:	Flonase® Nasal Spray, 50 mcg, NDA 20-121, GlaxoSmithKline
Reviewer:	Carol. Y. Kim, Pharm.D.
Submission date:	October 4, 2002
Date of Review:	May 9, 2005

V:/firmsnz/roxane/ltrs&rev/76504A.1002.mor

I. Introduction

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 may 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.

II. Background

The following submissions have been reviewed by the OGD for other generic sponsor's fluticasone propionate nasal spray:

1. Control Documents

Submission date	OGD document no.	Sponsor
1/21/00	[redacted]	[redacted]
8/16/00		
6/21/01		
7/20/01		
6/12/02		
6/14/02		

b(4)

7/26/02
9/12/02
10/28/02
2/14/03
5/12/03
6/13/03

2. ANDA submissions for same product

Submission date	Application number	Sponsor
3/3/03		
4/25/03		

Roxane's clinical endpoint studies for Fluticasone Propionate Nasal Spray

On 10/17/00, Roxane submitted an original protocol for a bioequivalence study with clinical endpoints on fluticasone nasal spray. Following the review of this protocol, the OGD responded on 2/14/01 (OGD#00-447) that the proposed baseline lead-in period should be no longer than 2 to 4 days and suggested that the sponsor may include a placebo during the baseline run-in period.

On 4/2/01, the OGD recommended (OGD#00-447) the following: 1) The endpoint (reflective score or instantaneous score) should be the average of arithmetic mean of the daily Total Nasal Symptom Score (TNSS) over the full treatment period compared to baseline. 2) The baseline should be the arithmetic mean over the full pre-treatment period. 3) The endpoint (change from baseline) should be calculated as the mean over the full treatment period subtracted from the baseline mean, and 4) The endpoint should be analyzed using an analysis of variance (ANOVA) model.

On 9/ 4/2001, the sponsor submitted their proposals in response to the OGD comments previously issued on 2/14/01 and 4/2/01 as follows:

- The sponsor proposed to maintain a 7-day baseline lead-in period. The sponsor stated that it is appropriate to conduct a 7-day lead-in period because the majority of published fluticasone propionate aqueous nasal spray (FP ANS) studies were performed with 7-day lead in periods.
- Because patients with a history of allergic rhinitis frequently recognize the RLD product, the OGD recommended maintaining treatment blinded to patients. In response to this recommendation, the sponsor claimed that the bottle and actuator used by the RLD are proprietary making it impossible to truly blind it to patients. Therefore, the sponsor proposed to designate a "dispenser" to be responsible for dispensing and receiving the returned study drug. The blind was to be maintained for the study coordinator and investigator.
- The sponsor claimed that an analysis of co-variance (ANCOVA) model is preferred over the OGD's recommended analysis of variance (ANOVA) model for this type of study because it generally yields smaller variability of response than ANOVA. Therefore, the

sponsor proposed to use Feiller's approach with the adjusted means from the ANCOVA model.

Both the original protocol and the sponsor's proposals as mentioned above dated 9/4/01 were reviewed by a working group refining the CDER guidance for bioequivalence studies of nasal steroid drug products. Based on their recommendations, the OGD recommended (OGD #01-457, November 20, 2001) the following to the sponsor: 1) Consider applying a protective cover to all of the products to maintain the blind. 2) For baseline lead-in period, use both AM and PM measurements for the 3 days immediately prior to initiation of treatment. And 3) The analysis should include baseline as a covariate.

On 10/4/02, Roxane submitted the ANDA for review. This is a potential first generic application for Fluticasone Propionate Nasal Spray.

III. Study Information

Protocol Number: RTRFLT-001

Title: A Double-Blind Randomized, Parallel Group, Placebo Controlled Study Comparing the Efficacy and Safety of Generic Fluticasone Propionate Aqueous Nasal Spray Versus FLONASE® Nasal Spray Versus Placebo Nasal Spray in Subjects with Seasonal Allergic Rhinitis

Objectives:

1. To evaluate the therapeutic equivalence of Roxane Laboratories, Inc. fluticasone propionate aqueous nasal spray and Flonase nasal spray in the treatment of seasonal allergic rhinitis as measured by patient-rated Total Nasal Symptom Score (TNSS).
2. To compare the safety among the treatment groups.

Study Design:

This is a multi-center, three-arm, placebo-controlled, parallel group, randomized, double-blind clinical bioequivalence study designed to assess the bioequivalence of 200 mcg once-daily doses (two 50 mcg sprays in each nostril) of Roxane's Fluticasone Nasal Spray and Flonase® in the treatment of seasonal allergic rhinitis as measured by patient rated TNSS during spring allergy season. After 7-day untreated baseline lead-in period, patients were randomized to receive one of the following treatments for a 14-day treatment period:

1. Test: Fluticasone propionate (50 mcg/spray), 2 sprays in each nostril, once daily; Lot number: C049983
2. Reference: Flonase® nasal spray, (50 mcg/spray), 2 sprays in each nostril, once daily; Lot number: 019032A
3. Placebo: Roxane's Placebo nasal spray, 2 sprays in each nostril, once daily; Lot number: 019035A.

A study design schematic is presented below as follows:

Study Design

Visit 1 (Screening)	Visit 2 (Treatment)	Visit 3 (Treatment)	Visit 4 (End of Treatment/ Early Discontinuation)
Baseline Lead-in ← 7 ± 1 Days →	Double-Blind Medication ← 7 ± 1 Days → Placebo once daily, **or** Study Drug once daily, **or** Flonase once daily	Double-Blind Medication ← 7 ± 1 Days → Placebo once daily, **or** Study Drug once daily, **or** Flonase once daily	

Reviewer's Comments: *The latest CDER Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, posted April 2003, recommends a 7-day placebo run-in period to establish a baseline TNSS and eliminate placebo responders. Placebo responders are to be excluded from the treatment phase of the study to increase the sensitivity of the study to discern a difference between the test and reference products. The sponsor's proposed study design, which has been previously accepted by the OGD, is not consistent with the current CDER Draft Guidance because it uses an untreated run-in baseline period instead of a placebo run-in period. The study using a baseline run-in period without placebo treatment is less likely to demonstrate superiority of active treatments over the placebo group because more placebo responders are included in the treatment period. Furthermore, the inclusion of potential placebo responders in the active treatment groups is likely to decrease any difference in response and make the test and reference results appear more alike.*

Study Population:

Male or female patients over the age of 12 years old with a diagnosis of Seasonal Allergic Rhinitis (SAR) must meet the following criteria:

Inclusion Criteria

1. Females with non-childbearing potential (pre-menarcheal, 1-year post menopausal, or surgically sterile), or with childbearing potential who are non-pregnant/non-lactating and use acceptable contraceptive measures.

2. History (written or verbal medical confirmation) of SAR for the previous 2 spring allergy seasons. The specific allergen the subject was allergic to must have been indigenous to the study site area.

3. Positive skin test response to at least one spring allergen with a wheal diameter of at least 3 mm (prick) or 5 mm (intradermal) greater than diluent within 15 minutes after beginning of the test at Visit 1.

4. The four nasal symptoms assessed by the patient were as follows:
    - Sneezing;
    - Rhinorrhea;
    - Nasal pruritis (itching);
    - Nasal congestion.

    The patient was to self-evaluate each symptom on the following severity scale (0-3):

    0= Absent, none present
    1=Mild, clearly present but minimal awareness that is bothersome but tolerable
    2=Moderate, definite awareness which was bothersome but tolerable
    3=Severe, hard to tolerate, interfere with activities of daily living and/or sleeping.

5. To be eligible for randomization into the study (at Visit 2), the patient's morning and evening reflective symptom assessments obtained during the 7-day baseline period must meet the following two criteria:

    - A severity score must be recorded on the patient's diary for each of the 4 nasal symptoms on 6 or more morning and evening reflective assessments during the baseline period;
    - A sum of the morning and preceding evening reflective TNSS ≥12 (of a maximum 24) on at least 4 of the last 7 summed scores during the baseline period with at least 1 of these summed scores within 2 summed scores of Visit 2. The evening reflective TNSS should be summed with the morning reflective TNSS of the following day to form a summed score.

6. Able to give signed written informed consent prior to study entry. If the patient was a minor, he/she must have given assent to study participation and a parent or legal guardian must have signed written informed consent prior to study entry.

Exclusion Criteria

1. Females who were pregnant, lactating, or were likely to become pregnant, during the study. Sexually active females of child-bearing potential were expected to use one of the following contraceptive regimens throughout the study:

    - Systemic contraceptive (oral, implant, injection);
    - Diaphragm with intravaginal spermicide;
    - Cervical cap;
    - Intrauterine device (IUD);
    - Condom with intravaginal spermicide;
    - Abstinence.

If it became known that a female patient was pregnant during the study, study medication was to be discontinued and the patient was to be followed to determine the pregnancy outcome.

2. Upper respiratory tract infection within 30 days prior to Visit 1.

3. Evidence of sinusitis within 30 days prior to Visit 1.

4. Any of the following underlying conditions known or suspected to be present:

   - Malnutrition;
   - Blood dyscrasia;
   - Renal or hepatic insufficiency;
   - Chronic infection;
   - Current drug abuse or alcoholism;
   - Malignancy;
   - Malabsorption;
   - Rhinitis medicamentosa.

5. Clinically significant cardiovascular, hepatic, neurologic, endocrine, or other major systemic disease or laboratory abnormality making implementation of the protocol or interpretation of the study outcome difficult.

6. Nasal polyp(s), significantly displaced nasal septum (>50% obstruction), history of glaucoma, history of nasal septal surgery or nasal septal perforation.

7. Mental capacity limited to the extent the patient would not be able to provide legal consent or information regarding efficacy, and side effects/tolerance of drug.

8. Patients receiving immunotherapy except those on stable maintenance therapy for at least 1 month prior to Visit 1.

9. Known hypersensitivity to fluticasone propionate or other inhaled corticosteriods.

10. Use of an investigational drug within 30 days prior to Visit 1.

11. Patients with asthma who require medication other than inhaled and/or oral beta agonists.

12. Patients with planned travel outside the study area for a substantial portion of the study period.

13. Use of any of the following prohibited drugs within the time indicated prior to Visit 1:

Drug	Time Prior to Visit 1
Intramuscular/articular, inhaled, intranasal, oral, intravenous, and/or potent or super-potent topical corticosteroids	≤30 days
Nedocromil or comolyn sodium	≤14 days
Astemizole	≤50 days
Loratadine	≤7 days
Terfenadine	≤7 days
Fexofenadine	≤7 days
Cetirizine	≤7 days
Other (QD/BID dosing) Antihistamines	≤7 days
Other (TID/QID dosing) Antihistamines	≤3 days
Oral decongestants, decongestant nasal sprays or drops, including all OTC preparations - cough/cold preparations and sleep aids	≤3 days
Hydroxyzine	≤3 days
Anticholinergic agents	≤ 3 days

Removal of Patients from Therapy or Assessment

Patient participation was terminated at any time for any of the following reasons:

- Intolerable treatment emergent AE as determined by the investigator and/or patient;
- Failure to return to the study site for scheduled visits;
- Patient elected to discontinue study;
- Clinically significant abnormal laboratory values that may jeopardize the patient's safety.

If possible, patients withdrawn from the study after randomization, but prior to the end of the study, have completed all events scheduled for Visit 4. Patients who discontinued prematurely were not replaced.

Blinding/Unblinding

To ensure blinding (Flonase® containers differ slightly in shape from placebo and Roxane's Fluticasone propionate containers), a study drug dispenser at each study site provided the study medication to patients. The study drug dispenser at each site was partially unblinded to study treatment identification because of the differences in medication container shapes. The study drug dispenser was not able to distinguish between Roxane's product and placebo aqueous nasal spray. With the exception of the study drug dispenser, the investigator and/or other study site personnel directly involved with the study were not permitted to view the study medication at any time during the study. The study drug dispenser always met privately with the patient to dispense or collect study medication.

Placebo nasal spray is identical in appearance to Roxane's product bottle, pump, and actuator. Since the innovator's bottle and actuator are proprietary, the original label of Flonase® nasal spray was covered by the study medication label.

Study Procedures:

Eligible Patients were instructed to administer two 50 mcg sprays into each nostril once daily in the morning for a 14-day treatment period. The following Schedule of Study Events summarizes

the frequency and timing of the safety and efficacy measurements.

Schedule of Study Events

Study Procedure	Visit				
	1	*2*	*3*	*4*	***Early Discontinuation[1]***
Informed Consent	X				
Demographics	X				
Medical History	X				
Skin Test	X				
Entrance Criteria	X	X			
Medical History	X				
Vital Signs	X	X	X	X	X
Physical Examination	X[2]			X	X
Clinical Labs	X			X	X
Pregnancy Test	X[3]			X[4]	X[4]
Subject-Qualifying-SAR Assessment for Double-Blind Medication		X			
Daily Symptom Diary Issued	X	X	X		
Study Medication Dispensed		X[5]			
Concomitant Medications Assessment		X	X	X	X
Collect Symptom Diary		X	X	X	X
Determine Study Drug Compliance			X	X	X
Adverse Event Assessment		X	X	X	X

[1] Not required if subject was not randomized to study medication
[2] Including an examination of the nose
[3] Serum pregnancy test
[4] Urine pregnancy test
[5] First dose of study medication was administered in the clinic under supervision of the study drug dispenser.

Visit 1 (Day -7 to -1); Screening and baseline lead-in period

- Patients were instructed to read and sign an informed consent form. Screening evaluations included collection of demographic information, relevant medical history, vital signs, laboratory samples (chemistry, hematology and urinalysis, pregnancy test), and recording of any concomitant medication use. A physical examination was performed including examination of the nose.
- An epicutaneous or intradermal skin test was performed to test for a positive allergic response to spring allergens.
- Patients were provided with a baseline period symptom diary card and instructed on when and how to complete the diary. The patient was instructed to begin recording symptom assessments in the evening of this clinic visit. On the following days they completed symptom assessments twice a day (in the morning at 7 AM [±1 hour] and in the evening at 7 PM [±1 hour]). At both assessment times, the patient completed both an instantaneous (evaluation of symptoms at that moment in time) and reflective (evaluation of symptoms during the period of time since the last assessment) symptom assessment.

Visit 2 (Day 1); Randomization Visit

Seven days after the screening visit, patients returned to the clinic with their baseline period symptom diary card. The patient's symptom diary card was reviewed to determine if the patient qualified for the treatment phase of the study. Any new concomitant medications or adverse events (AEs) since visit 1 were recorded and vital signs were measured.

The following criteria were required for randomization:

- The patient recorded all morning and evening symptoms (i.e., a severity score must have been recorded in the patient's diary for each of the 4 nasal symptoms on 6 or more morning and evening reflective assessments during the baseline period);

- The patient met all inclusion/exclusion criteria;

- The patient was symptomatic during the baseline period with a sum of the morning and preceding evening reflective TNSS ≥12 (of a maximum 24) on at least 4 of the last 7 summed scores during the baseline period with at least 1 of these summed scores within 2 summed scores of Visit 2. The evening reflective TNSS was to be summed with the morning reflective TNSS of the following day to form a summed score.

If the patient qualified for randomization, the treatment period Week 1 symptom diary card was dispensed. The patient was instructed to begin recording symptom assessments on the treatment period Week 1 symptom diary card in the evening of this clinic visit. On the following days they completed symptom assessments twice a day (in the morning just prior to study medication dosing and in the evening at 7 PM [± 1 hour]). At both assessment times, the patient completed both instantaneous and reflective symptom assessments.

Following instruction on the use of the diary card, the study drug dispenser met privately with the patient to dispense study medication. One container of study medication was dispensed for the entire 2-week treatment period. The study drug dispenser witnessed the initial dose of study medication in the clinic. The patient was instructed to self-administer the second dose of study medication the next morning at 7 AM (± 1 hour), immediately after completing their symptom evaluations, and once per day each morning thereafter.

Visit 3 (Day 14); Treatment Visit

Seven days following Visit 2, patients returned to the clinic with their treatment period Week 1 symptom diary card. Upon return to the clinic, the patient's symptom diary card was reviewed for compliance by the study site coordinator. Patients were instructed not to bring their study medication to this visit. In addition, vital signs were obtained and any AEs or new concomitant medications since Visit 2 were recorded. The patient was provided with the treatment period Week 2 symptom diary card and given instructions for completion of the diary.

Visit 4 (Day 21); End of Treatment Visit or Early Discontinuation Visit

Seven days following Visit 3, patients returned to the clinic with their treatment period Week 2 symptom diary card. In order to maintain the blind, patients were instructed to return their study medication only to the study drug dispenser. The study drug dispenser was required to be present at this clinic visit in order to collect the study drug. Study drug was not collected by the study coordinator or investigator. If it was known in advance that the study drug dispenser was not available at Visit 4, the patient was to be contacted and instructed not to bring his/her study medication to Visit 4. If this was the case, at Visit 4, the patient was provided with a pre-addressed and pre-stamped envelope for return of the study drug to the study drug dispenser. Following study drug collection by the study drug dispenser, the patient's symptom diary card was collected and reviewed for compliance by the study coordinator. Vital signs were obtained and any AEs or new concomitant medications since Visit 3 were recorded. In addition, a physical examination was performed, vital signs were measured, and laboratory samples (chemistry, hematology and urinalyses, and urine pregnancy test) were collected.

Safety:

Safety was assessed and evaluated by monitoring adverse events, laboratory measurements, and vital signs.

Statistical Plan:

Primary Endpoint

All patients who were considered eligible for randomization were included in the primary endpoint analysis. The primary symptom assessment was an average of the summed morning and prior evening reflective assessments.

The primary endpoint for this product is the change in the average reflective TNSS of the baseline period compared to the average reflective TNSS of the 14-day treatment period in the evaluable population. Secondary parameters include the average morning and evening instantaneous TNSS of the baseline period compared to the same measure for the treatment period.

The sponsor's TNSS was defined as the sum of patient-rated severity scores for the following four allergy symptoms: sneezing, rhinorrhea, nasal prurits (itching), and nasal congestion. The severity score for each symptom was based on a 4-point scale (0=none, 1=mild, 2=moderate, and 3=severe).

Two patient populations were defined by the sponsor as follows:

Intent-to-treat (ITT) Population
- randomized into the study
- received at least one dose of study medication

Evaluable (EP) Population
- randomized into the study (met all entry criteria and exclusion criteria)
- had no major protocol violations or other events considered to bias the study outcome

Other events considered to bias the study outcome included:

- Did not have at least 6 acceptable reflective daily assessments during baseline, week 1 and week 2. A patient's daily reflective data are considered acceptable for any given day in which the morning medication dose was taken between 5:00 AM and 9:00 AM and the morning reflective daily assessments preceded the morning dose or were recorded within 30 minutes of when the dose was taken and the previous days' evening reflective assessments were recorded within 5:00 PM to 9:00 PM.
- Received prohibited concomitant medications without adequate washout period.
- Had other major protocol violations (e.g., patients met the study inclusion/exclusion criteria at the time the information was obtained but were later found to have violated some of these criteria).

Sample Size

The sample size of 450 patients was initially planned, 180 in each active group and 90 in Placebo group. According to the sponsor's analysis, this sample size yields 90% power to detect a difference in means (active versus placebo) of 0.8 points assuming a common standard deviation of 1.9 points using a two-group t-test with a 0.05 two-sided significance level. The sponsor believed that a coefficient of variation (CV) of 0.58 requires 150 evaluable patients for each active group to have approximately 90% power for the 90% confidence interval (CI) of the ratio (of the active treatment means) to be contained within ± 20% (e.g., 0.80 to 1.25).

However, the number of patients to be randomized into the study (450 subjects), as described in the protocol, was exceeded by 116 patients due to the severity of the allergy season resulting in rapid enrollment. The total number of patients randomized was 566.

Analysis

The clinical model sensitivity was assessed using the primary efficacy parameter and analyzed using an Analysis of Covariance (ANCOVA) model. The ANCOVA model included the change in the patient's average reflective TNSS of the baseline period compared to the average reflective TNSS of the treatment period as the outcome and treatment, investigative site and average baseline TNSS as predictor variables. Using the ANCOVA model, the (adjusted) means of the treatments were statistically compared to assess statistical significance.

The primary test of bioequivalence was the statistical comparison of Roxane's fluticasone propionate aqueous nasal spray 200 mcg versus Flonase® nasal spray 200 mcg. Using the ANCOVA model, the (adjusted) means of the treatments were statistically compared to assess clinical equivalence.

The comparison of therapeutic equivalence of Roxane's fluticasone propionate and Flonase® nasal spray in the Evaluable Population was conducted by constructing a 90% confidence interval (CI) for the ratio of the treatment group means from the ANCOVA model using Fieller's method. Therapeutic equivalence between the two active treatments was declared if the 90% CI limits for the ratio were contained within ± 20 percent, or (0.80, 1.25), inclusive.

The two comparisons of efficacy (active versus placebo) were each conducted with the Intent-to-Treat Population as two-sided tests of significance at the α=0.05 level.

No adjustments were made to the type I error (α=0.05) to correct for multiple comparisons because each of the two comparisons must be successful. The treatment-by-site interaction and the treatment-by-baseline interaction were tested at the α=0.10 level of significance and explored graphically (if necessary). These analyses were only used to evaluate the robustness of the primary ANCOVA model.

The secondary efficacy parameters were analyzed using the same approach as described for the primary efficacy parameter. If the distribution of the change in the average reflective or instantaneous individual symptom scores was found to violate the ANCOVA assumptions of normality or homogeneous variance, then Cochran-Mantel-Haenszel (CMH) procedures were used to compare the treatment groups. The secondary analyses were conducted using the Evaluable Population or the ITT Population.

Reviewer's Comment: *A statistical review was requested to verify the sponsor's analysis. See the summary of statistical review below for details.*

IV. RESULTS

CRO: [redacted] b(4)

Study Period: February 18, 2002 to May 30, 2002

Study Centers/Investigators:

The study was planned at 35 sites in the United States; of these, two sites were closed without having enrolled a patient. Thirty-three investigational sites enrolled patients in this study.

Investigator

b(4)

Site #	# patients
Site 1	27
Site 2	17
Site 3	14
Site 4	9
Site 5	17
Site 6	X
Site 7	35
Site 8	22
Site 9	23
Site 10	13
Site 11	3
Site 12	23
Site 13	17
Site 14	15
Site 15	14
Site 16	29
Site 17	9
Site 18	14

X: Did not enroll patients

Investigator

b(4)

Site #	# patients
Site 19	31
Site 20	11
Site 21	14
Site 22	6
Site 23	5
Site 25	15
Site 26	27
Site 27	2
Site 28	30
Site 29	22
Site 30	12
Site 31	20
Site 32	26
Site 33	17
Site 34	7
Site 35	X
Site 36	20

Patient Enrollment:

Of eight hundred (800) patients initially screened, 694 patients were enrolled into the study. Of these, 128 patients did not meet the randomization criteria. Five hundred sixty–six (566) patients who met the randomization criteria were treated with the study drugs. Two hundred thirty patients (230) in the reference group, 226 patients in the test group, and 110 patients in the placebo group used the study medication as directed.

A total of 539 patients completed the study and 27 patients discontinued prematurely from the study. The most frequent reason for early discontinuation from the study was due to adverse events. The incidence of discontinuations due to adverse events was similar between the test and reference products. One patient, #05-0024 (Ref), experienced sinusitis (possibly drug related) after receiving the study medication. All other withdrawals from the study due to adverse events were considered not related to study medication. The sponsor's patient disposition for the Intent-to-Treat Population per treatment arm is shown in Table I.

TABLE I. Subject Disposition (Intent-to-Treat Population) per sponsor

Disposition	Placebo N (%)	Test 200 mcg N (%)	Flonase 200 mcg N (%)	Total N (%)
Intent-to-Treat	110 (100.0)	230 (100.0)	226 (100.0)	566 (100.0)
Completed	106 (96.4)	220 (95.7)	213 (94.2)	539 (95.2)
Discontinued	4 (3.6)	10 (4.3)	13 (5.8)	27 (4.8)
Primary Reason for Discontinuation				
Adverse Event	0 (0.0)	7 (3.0)	5 (2.2)	12 (2.1)
Protocol Violation	0 (0.0)	0 (0.0)	5 (2.2)	5 (0.9)
Subject Voluntarily Withdrew	1 (0.9)	2 (0.9)	1 (0.4)	4 (0.7)
Lost to Follow-up	1 (0.9)	1 (0.4)	1 (0.4)	3 (0.5)
Other	2 (1.8)	0 (0.0)	1 (0.4)	3 (0.5)
Evaluable	82 (74.5)	158 (68.7)	161 (71.2)	401 (70.8)
Primary Reason for Non-Evaluable				
Non-Compliance	25 (22.7)	63 (27.4)	56 (24.8)	144 (25.4)
Took Prohibited Medication*	4 (3.6)	12 (5.2)	15 (6.6)	31 (5.5)*
Inclusion/Exclusion Violation	0 (0.0)	2 (0.9)	1 (0.4)	3 (0.5)
Baseline Symptomatic Assessment Violation	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Other	1 (0.9)	0 (0.0)	2 (0.9)	3 (0.5)

Note: Denominators were based on the number of Intent-to-Treat subjects.
A subject may have had more than one reason for not completing the study and for not being evaluable.
Non-compliance = Individual subjects were considered non-compliant if they did not have at least 6 acceptable reflective daily assessments during baseline, week 1 and week 2. Daily reflective data were considered acceptable if for any given day the morning medication dose was taken between 5:00 AM and 9:00 AM and the morning reflective daily assessments preceded the morning dose or was recorded within 30 minutes of when the dose was taken and the previous days' evening reflective assessments were recorded between 5:00 PM to 9:00 PM.

**Reviewer's Comment:* Review of these patients suggest that only 1 (test group) of these medications was used as rescue treatment for signs of allergic rhinitis in any treatment group.

Reviewer's Comments:

- *One patient from each study group discontinued the study because increasing allergic symptoms or symptoms were not controlled by the study drug. The sponsor considered these patients as non-compliant and excluded them from the EP population. Since they discontinued the study due to lack of treatment effect/treatment failures, they should be included and evaluated in the EP population analysis. Since the primary endpoint of this study is not a dichotomized success/failure outcome, a statistical review is requested to appropriately analyze these patients in the evaluable population.*

Site	*Patient number*	*Study Drug*
5	*0019*	*Reference*
5	*0006*	*Test*

- *The sponsor excluded one patient (#0034, site 29, test) from the EP population because this patient received prohibited medication (Sudafed) during the study. Since this patient took the medication to relieve allergy symptoms, this patient should be included in the evaluable population as treatment failure and analyzed accordingly.*

Demographics:

Of the 566 treated patients, 446 (78.8%) were Caucasian, 57 (10.1%) were Black, 47 (8.3%) were Hispanic, 13 (2.3%) were Asian, and 3 (0.5%) were classified as other races. Baseline demographics, age, and race were comparable in three treatment groups. The mean age was 35.2 (12-72), 34.9 (12-69), and 34 (12-66) years in the test, reference, and placebo groups, respectively. See Table II for the reported demographic characteristics for all treated patients (ITT population).

Table II. Demographic characteristics for Intent-to-Treat patients (per sponsor)

Subject Demographics and Baseline Characteristics

Characteristic		Placebo (N=110)	Test 200 mcg (N=230)	Reference 200 mcg (N=226)	Total (N=566)
Gender N(%)	Male	40 (36.4)	78 (33.9)	68 (30.1)	186 (32.9)
	Female	70 (63.6)	152 (66.1)	158 (69.9)	380 (67.1)
Race N(%)	Caucasian	90 (81.8)	175 (76.1)	181 (80.1)	446 (78.8)
	Black	7 (6.4)	27 (11.7)	23 (10.2)	57 (10.1)
	Asian	2 (1.8)	7 (3.0)	4 (1.8)	13 (2.3)
	Hispanic	10 (9.1)	20 (8.7)	17 (7.5)	47 (8.3)
	Other	1 (0.9)	1 (0.4)	1 (0.4)	3 (0.5)
Age (Yrs)	N	110	230	226	566
	Mean (SD)	34.0 (13.62)	35.2 (12.78)	34.9 (12.02)	34.9 (12.64)
	Median	33.0	34.5	34.5	34.0
	Min, Max	12, 66	12, 72	12, 69	12, 72
Age Group N(%)	12-17	17 (15.5)	21 (9.1)	16 (7.1)	54(9.5)
	18-64	92 (83.6)	203 (88.3)	208 (92.0)	503 (88.9)
	>=65	1 (0.9)	6 (2.6)	2 (0.9)	9 (1.6)

Baseline TNSS Severity:

The sponsor tabulated patient baseline characteristics for the ITT and EP populations. The baseline characteristics for each parameter were similar in three treatment groups in the ITT population as shown in Table III. All evaluated baseline characteristics were comparable in two active treatment groups and placebo for the ITT and EP populations.

Table III. Baseline TNSS Severity for Intent-to-Treat Patients (per sponsor)

Characteristic		Placebo (N=110)	Test 200 mcg (N=230)	Flonase 200 mcg (N=226)	Total (N=566)
Baseline Instantaneous TNSS	N	109	230	226	565
	Mean (SD)	17.16 (3.795)	16.96 (4.203)	16.83 (3.885)	16.94 (3.996)
	Median	17.14	17.38	16.86	17.14
	Min, Max	8.7,24.0	5.9,24.0	6.3,24.0	5.9,24.0
Baseline Reflective TNSS	N	110	230	226	566
	Mean (SD)	18.19 (3.310)	18.22 (3.493)	17.87 (3.375)	18.08 (3.410)
	Median	18.36	18.57	18.15	18.38
	Min, Max	11.4,24.0	10.1,24.0	10.6,24.0	10.1,24.0
Baseline Instantaneous Sneezing	N	109	230	226	565
	Mean (SD)	3.14 (1.735)	3.19 (1.705)	3.18 (1.697)	3.18 (1.705)
	Median	3.14	3.43	3.43	3.43
	Min, Max	0.0, 6.0	0.0, 6.0	0.0, 6.0	0.0, 6.0
Baseline Reflective Sneezing	N	110	230	226	566
	Mean (SD)	3.71 (1.403)	3.85 (1.381)	3.73 (1.398)	3.78 (1.391)
	Median	3.79	4.00	3.86	3.86
	Min, Max	0.3, 6.0	0.1, 6.0	0.0, 6.0	0.0, 6.0
Baseline Instantaneous Runny Nose/Post Nasal Drip	N	109	230	226	565
	Mean (SD)	4.65 (1.123)	4.54 (1:228)	4.56 (1.181)	4.57 (1.189)
	Median	4.86	4.71	4.67	4.71
	Min, Max	1.6, 6.0	0.3, 6.0	0.5, 6.0	0.3, 6.0

Characteristic		Placebo (N=110)	Test 200 mcg (N=230)	Flonase 200 mcg (N=226)	Total (N=566)
Baseline Reflective Runny Nose/Post Nasal Drip	N	110	230	226	566
	Mean (SD)	4.84 (0.923)	4.78 (1.058)	4.73 (1.070)	4.77 (1.037)
	Median	5.00	5.00	4.86	5.00
	Min, Max	2.5, 6.0	0.9, 6.0	0.9, 6.0	0.9, 6.0

Baseline Instantaneous Itchy Nose	N	109	230	226	565
	Mean (SD)	4.40 (1.160)	4.33 (1.328)	4.24 (1.346)	4.31 (1.304)
	Median	4.57	4.54	4.38	4.43
	Min, Max	1.8, 6.0	0.1, 6.0	0.1, 6.0	0.1, 6.0
Baseline Reflective Itchy Nose	N	110	230	226	566
	Mean (SD)	4.53 (1.149)	4.58 (1.152)	4.42 (1.255)	4.51 (1.193)
	Median	4.57	4.71	4.57	4.57
	Min, Max	2.0, 6.0	0.3, 6.0	0.3, 6.0	0.3, 6.0
Baseline Instantaneous Nasal Congestion	N	109	230	226	565
	Mean (SD)	4.96 (0.972)	4.89 (1.040)	4.84 (1.025)	4.89 (1.021)
	Median	5.00	5.07	5.00	5.00
	Min, Max	2.0, 6.0	1.1, 6.0	0.1, 6.0	0.1, 6.0
Baseline Reflective Nasal Congestion	N	110	230	226	566
	Mean (SD)	5.10 (0.933)	5.02 (0.951)	4.99 (1.029)	5.02 (0.979)
	Median	5.29	5.29	5.15	5.29
	Min, Max	1.6, 6.0	1.6, 6.0	0.1, 6.0	0.1, 6.0

Efficacy Outcomes:

The primary efficacy parameter (average reflective TNSS) was computed as follows:

(1) Sum the Day 1 evening reflective TNSS of the period with the morning reflective TNSS from Day 2 of the period. This process was continued for each day in the period. If either the morning or evening assessment was missing, then the sum was considered missing.
(2) Average the daily sums of the reflective TNSS of the baseline period to obtain the average reflective TNSS of the baseline period.
(3) Average the daily sums of the reflective TNSS of the treatment period to obtain the average reflective TNSS of the treatment period. Additionally, only the symptom scores recorded during the last 7 days of the baseline period and the first 14 days of the treatment period were used in computation of the average scores (i.e., some patients may have returned >7 days of diary recordings during the baseline period and/or >14 days of diary recordings during the treatment period).

The change in the patient's average reflective TNSS was computed for each patient by subtracting his or her average reflective TNSS of the baseline period from his or her average reflective TNSS of the treatment period. Therefore, negative values for the change in the patient's average reflective TNSS represent an improvement in the patient's symptom severity (i.e., they have, on average, less severe symptoms during the treatment period than they did

during the baseline period). The morning and prior evening reflective symptom severity scores used to compute the TNSS were obtained from the patient's daily diary cards.

Reviewer's comments: *The sponsor stated that missing TNSS was not replaced. No Last-Observation-Carried Forward (LOCF) method was used for both the EP and ITT population analyses.*

The sponsor's primary efficacy analysis is shown in Table IV.

IV. Primary Efficacy Analysis: Change from Baseline in Reflective TNSS (per sponsor)

A. Reflective TNSS Change from Baseline During the Treatment Period for the Active Treatment Groups Summary and Comparison (Evaluable Population)

Treatment	Test 200 mcg (N=158)		Flonase 200 mcg (N=161)			90% Confidence Interval For the Ratio	
Variable	LSMean	SE	LSMean	SE	Ratio (%) of LSMeans	Low (%)	High (%)
First Treatment Week	-6.09	0.385	-5.36	0.397	113.67	101.08	126.25
Second Treatment Week	-8.45	0.467	-7.92	0.481	106.73	96.77	116.70
Combined Treatment Period	-7.24	0.403	-6.62	0.415	109.51	99.06	119.95

B. Reflective TNSS During the Treatment Period (Evaluable Population)

Reflective TNSS		Placebo (N=82)	Test 200 mcg (N=158)	Flonase 200 mcg (N=161)
Baseline	N	82	158	161
	Mean (SD)	18.21 (3.354)	18.38 (3.324)	18.15 (3.419)
	Median	18.64	18.57	18.57
	Min, Max	11.9, 24.0	10.1, 24.0	11.3, 24.0
First Treatment Week	N	82	158	161
	Mean (SD)	13.98 (4.917)	12.31 (5.190)	12.91 (4.762)
	Median	13.86	11.64	13.00
	Min, Max	2.6, 24.0	1.4, 22.9	0.7, 24.0
Second Treatment Week	N	82	158	161
	Mean (SD)	12.93 (5.395)	9.96 (5.863)	10.45 (5.430)
	Median	13.14	9.29	10.14
	Min, Max	0.8, 24.0	0.0, 24.0	0.0, 24.0
Combined Treatment Period	N	82	158	161
	Mean (SD)	13.48 (4.894)	11.17 (5.340)	11.70 (4.802)
	Median	13.31	10.69	11.57
	Min, Max	2.6, 24.0	1.3, 23.4	1.2, 24.0

C. Primary Efficacy Endpoint Analysis: Change from Baseline in reflective TNSS for the Two-Week Treatment Period - Intent-to-Treat Population

Parameter	Placebo N = 110	Test N = 230	Flonase N = 226
LS Mean ± SE[1]	-5.02 ± 0.45	-7.05 ± 0.33	-6.62 ± 0.33
P-value vs. Placebo[2]	-	<0.001	0.002

[1]LS Mean ± standard error.
[2]ANCOVA test of placebo vs. active drug.

Reviewer's comments:

1. *Although the FDA had originally recommended the use of ANOVA for the statistical analyses, the final OGD response on 11/20/01 stated that the analysis should include baseline as a covariate. The sponsor used ANCOVA. A statistical consultation was requested to review the analysis method and evaluate its acceptability.*

2. *According to the sponsor's analysis, the study demonstrates that the 90% CI of the test/reference ratio of mean change from baseline reflective TNSS [averaged reflective TNSS over the entire untreated 7-day baseline run-in period] to the average reflective TNSS over the 14-day treatment period is within 0.80 and 1.25.*

   The sponsor's analysis also shows the mean change from average baseline reflective TNSS to the average reflective TNSS over the 14-day treatment period for both active treatment groups in the ITT population to be superior to placebo group. A statistical review was requested to verify the sponsor's results.

   The baseline reflective TNSS score was computed by adding the evening and morning reflective TNSS score for each day of the entire baseline period (e.g. the evening reflective TNSS from Day 1 plus the morning reflective TNSS from Day 2). The average of the daily sums of the entire untreated baseline period was used to calculate the baseline TNSS score. Likewise, the reflective TNSS of the treatment period was obtained by averaging daily sums of the evening and morning reflective TNSS of the entire 14-days of treatment. For missing morning or evening assessment, the sum was considered missing. A statistical analysis was requested to verify the sponsor's calculations.

3. *The above mentioned the CDER Draft Guidance recommends that the baseline TNSS score be calculated by averaging the reflective AM and PM scores on Days 5, 6, and 7 of the placebo run-in period and the AM score (prior dosing) on Day 1 of the active treatment period. Since the sponsor did not use placebo run-in period, it is appropriate to compute baseline TNSS by averaging the daily sums over the entire 7-day run-in period instead of the last 7 scores. The Division of Pulmonary and Allergy Drug Products concurs that this deviation from the CDER Draft Guidance is acceptable.*

Adverse Events:

No serious adverse event or death was reported in the study. Forty six patients (20%) in the test group, 53 patients (23.5%) in the reference group, and 18 patients (26.4%) in the placebo group experienced at least one adverse event. Of these, 8 patients (4 in the test and 4 in the reference) reported severe adverse events that were considered not related to study drugs. One patient (13-0010, Test) experienced severe fatigue that was assessed as probably related to study medication by the investigator. No additional treatment was provided for this adverse event, and the patient completed the study without further complication. Headache was the most commonly reported adverse event in both active treatment groups (3% in the test and 4% in the reference). The sponsor's frequency analysis of adverse events is shown below in Table V and VI.

Table V
Overall Summary of Treatment Period Adverse Events in the ITT Population (per sponsor)

		Placebo (N=110)	Test 200 mcg (N=230)	Flonase 200 mcg (N=226)
Body System		N (%)	N (%)	N (%)
Adverse Events Per Subject	0	92 (83.6)	184 (80.0)	173 (76.5)
	1	13 (11.8)	28 (12.2)	34 (15.0)
	2	4 (3.6)	13 (5.7)	12 (5.3)
	3	0 (0.0)	2 (0.9)	6 (2.7)
	>=4	1 (0.9)	3 (1.3)	1 (0.4)
Maximum Severity of Adverse Events	No adverse Events	92 (83.6)	184 (80.0)	173 (76.5)
	Mild	11 (10.0)	25 (10.9)	25 (11.1)
	Moderate	7 (6.4)	16 (7.0)	24 (10.6)
	Severe	0 (0.0)	5 (2.2)	4 (1.8)
Subjects with Serious Adverse Events		0 (0.0)	0 (0.0)	0 (0.0)

VI. Frequency of Adverse Events during the Treatment Period (ITT Population)

		Placebo (N=110)		GFP 200 mcg (N=230)		Flonase 200 mcg (N=226)	
		Subjects	Events	Subjects	Events	Subjects	Events
Body System	Preferred Term	N (%)	N	N (%)	N	N (%)	N
SUBJECTS WITH AT LEAST 1 ADVERSE EVENT		18 (16.4)	26	46 (20.0)	78	53 (23.5)	81
BODY AS A WHOLE	OVERALL	9 (8.2)	10	22 (9.6)	24	29 (12.8)	36
	HEADACHE	1 (0.9)	1	7 (3.0)	8	9 (4.0)	10
	ACCIDENTAL INJURY	1 (0.9)	1	4 (1.7)	4	4 (1.8)	4
	BACK PAIN	1 (0.9)	1	3 (1.3)	3	2 (0.9)	2
	INFECTION	0 (0.0)	0	3 (1.3)	3	3 (1.3)	3
	PAIN	5 (4.5)	5	2 (0.9)	2	7 (3.1)	7

	ASTHENIA	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
	FEVER	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
	MUCOUS MEMBRANE DISORDER	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
	VIRAL INFECTION	1 (0.9)	1	1 (0.4)	1	1 (0.4)	1
	ABDOMINAL PAIN	1 (0.9)	1	0 (0.0)	0	1 (0.4)	1
	ALLERGIC REACTION	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	CELLULITIS	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	CHILLS	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	HALITOSIS	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	INFECTION FUNGAL	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	NECK PAIN	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	NECK RIGIDITY	0 (0.0)	0	0 (0.0)	0	2 (0.9)	2
CARDIOVASCULAR SYSTEM	OVERALL	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
	VASCULAR PURPURA	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
DIGESTIVE SYSTEM	OVERALL	2 (1.8)	2	6 (2.6)	7	7 (3.1)	10
	DIARRHEA	0 (0.0)	0	4 (1.7)	4	2 (0.9)	2
	TOOTH CARIES	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
	ULCERATIVE STOMATITIS	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
	VOMITING	0 (0.0)	0	1 (0.4)	1	2 (0.9)	2
	DRY MOUTH	1 (0.9)	1	0 (0.0)	0	0 (0.0)	0
	GASTRITIS	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	LIVER FUNCTION TESTS ABNORMAL	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	NAUSEA	1 (0.9)	1	0 (0.0)	0	3 (1.3)	4
HEMIC AND LYMPHATIC SYSTEM	OVERALL	2 (1.8)	2	2 (0.9)	3	0 (0.0)	0
	LEUKOPENIA	0 (0.0)	0	1 (0.4)	2	0 (0.0)	0
	ANEMIA	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
	LYMPHADENOPATHY	2 (1.8)	2	0 (0.0)	0	0 (0.0)	0
METABOLIC AND NUTRITIONAL DISORDERS	OVERALL	0 (0.0)	0	0 (0.0)	0	2 (0.9)	2
	HYPERGLYCEMIA	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	THIRST	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
MUSCULOSKELETAL SYSTEM	OVERALL	0 (0.0)	0	2 (0.9)	2	1 (0.4)	1
	BONE PAIN	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
	MYALGIA	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
	TENDON DISORDER	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
NERVOUS SYSTEM	OVERALL	2 (1.8)	2	1 (0.4)	1	3 (1.3)	4
	NERVOUSNESS	0 (0.0)	0	1 (0.4)	1	2 (0.9)	2
	AGITATION	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	HYPERKINESIA	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1

	HYPERTONIA	1 (0.9)	1	0 (0.0)	0	0 (0.0)	0
	PARESTHESIA	1 (0.9)	1	0 (0.0)	0	0 (0.0)	0
RESPIRATORY SYSTEM	OVERALL	6 (5.5)	8	16 (7.0)	31	15 (6.6)	19
	EPISTAXIS	1 (0.9)	1	6 (2.6)	8	3 (1.3)	3
	PHARYNGITIS	2 (1.8)	2	4 (1.7)	8	4 (1.8)	4
	ASTHMA	0 (0.0)	0	3 (1.3)	4	0 (0.0)	0
	COUGH INCREASED	0 (0.0)	0	3 (1.3)	3	3 (1.3)	3
	LARYNGITIS	0 (0.0)	0	2 (0.9)	3	0 (0.0)	0
	LUNG DISORDER	0 (0.0)	0	2 (0.9)	2	2 (0.9)	2
	PNEUMONIA	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
	RHINITIS	3 (2.7)	5	1 (0.4)	1	2 (0.9)	2
	SINUSITIS	0 (0.0)	0	1 (0.4)	1	5 (2.2)	5
SKIN AND APPENDAGES	OVERALL	0 (0.0)	0	1 (0.4)	1	4 (1.8)	5
	CONTACT DERMATITIS	0 (0.0)	0	1 (0.4)	1	2 (0.9)	2
	ACNE	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	PRURITUS	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	SKIN DISORDER	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
SPECIAL SENSES	OVERALL	1 (0.9)	1	5 (2.2)	6	0 (0.0)	0
	CONJUNCTIVITIS	0 (0.0)	0	4 (1.7)	4	0 (0.0)	0
	EAR DISORDER	1 (0.9)	1	1 (0.4)	2	0 (0.0)	0
UROGENITAL SYSTEM	OVERALL	1 (0.9)	1	2 (0.9)	2	3 (1.3)	4
	DYSMENORRHEA	0 (0.0)	0	1 (0.4)	1	1 (0.4)	2
	URINARY TRACT INFECTION	0 (0.0)	0	1 (0.4)	1	0 (0.0)	0
	HEMATURIA	1 (0.9)	1	0 (0.0)	0	0 (0.0)	0
	KIDNEY CALCULUS	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
	VAGINAL MONILIASIS	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1

Adverse Events, within a Body System Class, are ordered by decreasing frequency for the GFP 200 mcg treatment group. GFP = Generic Fluticasone Propionate.

Reviewer's Comment: *The incidence of adverse events was similar between the test and reference treatment groups, with headache being the most commonly reported adverse event.*

V. Formulation

Ingredients	Test Product (Amount/Unit Weight)	*Flonase® (%w/w)
[redacted]		

b(4)

*per Bioequivalence Checklist for First Generic ANDA

Reviewer's Comment: *The test product is qualitatively and quantitatively the same as the reference product.*

VI. Review of Division of Scientific Investigation (DSI) report (5/26/04)

Of four sites (#1, 13, 27, and 28) inspected, the DSI issued a Form FDA 483 at one site (#27) only because the investigator failed to conduct the study in accordance with the protocol. This site enrolled two patients and only one patient (#0005, ITT) had the objectionable finding from the DSI. The investigator stated that this site was unable to provide a written or verbal confirmation of this patient's history of SAR (violation of inclusion criteria). However, the investigator confirmed that this patient's allergen skin test was positive prior to entry.

The DSI also stated that all four inspected sites failed to comply with the current rule for retention of bioavailability (BA) and bioequivalence (BE) testing samples because each clinical site was instructed by the sponsor to send all randomly selected reserve samples back to a third party storage facility, [redacted] mples were collected on these inspected sites.

The DSI commented that [redacted] should not have retained the study reserve samples because [redacted] was involved in the packaging and distribution of the study medication to these sites. Since this sponsor's study was conducted at the time the storage requirements of the testing samples were not clearly defined by the Agency, the DSI recommended accepting data from these inspected sites. The DSI also recommended that the study reserve samples should not be transferred by the testing facility back to an SMO (site management organizations) or any other organization that deals with packaging the test articles and reference standards for storage.

Reviewer's Comments: *It is the sponsor's responsibility to assure that the clinical sites for all future BE studies comply with the current requirements for retention of study drugs for each shipment as per 21 CFR 320.38 and 320.63. As described in the CDER Guidance for Industry: Handling and Retention of BA and BE Testing Samples, posted 5/25/04, the study reserve samples should not be transferred by the testing facility back to an SMO (site management organizations) or any other organization that deals with packaging the test articles and reference standards for storage. 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.*

The sponsor included patient #0005 in the ITT population but excluded from the EP because this patient had less than 6 days of valid scores (considered as major protocol violation). Based on the DSI final report, no further adjustment for the ITT and evaluable population is needed.

VII. Review of the FDA Statistical Report (4/19/05)

The conclusion of the FDA statistical analysis confirms the 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 for the guidance-based evaluable population is (0.965, 1.216), which is within the bioequivalence limits of 0.80 and 1.25. 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 provided the summary of the equivalence test for the evaluable population as shown below, and their conclusion is as follows:

Point estimates and 90% confidence intervals calculated for baseline = sample median baseline in the GPP – Reflective assessments**

endpoint	week	sample median baseline	point estimate	90% confidence interval	falls within [0.80, 1.25]?
TNSS	**overall***	**9.429**	**1.082**	**0.965, 1.216**	**Yes**
	1	9.429	1.123	0.984, 1.287	No
	2	9.429	1.057	0.944, 1.185	Yes
Itchy Nose	overall	2.429	1.049	0.930, 1.186	Yes
	1	2.429	1.091	0.947, 1.261	No
	2	2.429	1.023	0.908, 1.154	Yes
Runny Nose	overall	2.571	1.094	0.968, 1.239	Yes
	1	2.571	1.139	0.987, 1.319	No
	2	2.571	1.066	0.944, 1.206	Yes
Nasal Congestion	overall	2.714	1.169	1.024, 1.340	No
	1	2.714	1.207	1.037, 1.416	No
	2	2.714	1.144	1.004, 1.310	No
Sneezing	overall	2.000	1.021	0.903, 1.157	Yes
	1	2.000	1.059	0.913, 1.231	Yes
	2	2.000	0.998	0.884, 1.126	Yes

*scores averaged over both treatment weeks
**Guidance-based per protocol population

The summary of the FDA statistical comments are listed as follows:

1. Sponsor's defined variables vs. the April 2003 *CDER Draft Guidance for Industry- Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* defined variables

    - The sponsor defined the baseline average TNSS as the average (arithmetic mean) of the baseline day 1 through 7 TNSS sums. 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.

- The use of AM and PM sums by the sponsor appears to reflect a desire to balance any effect of morning vs. evening. An effect of using sums is to double the possible range of the outcome variables. However, the results of the statistical analyses would have been unaffected by such a division by 2. Therefore, the doubling of the possible range by using sums does not warrant a statistical issue.

2. Baseline assessment based on a placebo run-in period vs. untreated period

- The sponsor collected baseline TNSS from untreated baseline period. The draft guidance recommends placebo run-in baseline assessments from days 5, 6, and 7 (plus the AM assessment from day 8) and all placebo responders were to be excluded. Since the baseline period was not treated, all baseline days may be regarded as the same. Thus, the sponsor's use of all baseline days for defining the average baseline TNSS is acceptable.

3. Sponsor's per protocol (SPP) vs. Guidance-based per protocol (GPP) population analyses

- The FDA statistician excluded seven patients (34, 17, 5, 9, 10, 43, 1) from the SPP population and labeled it as a GPP population due to insufficient instantaneous assessments.
- Since four patients (19 at site 5, 6 at site 5, 6 at site 18, and 29 at site 34) discontinued the study due to lack of efficacy response, this reviewer asked the FDA statistician to evaluate the study outcome with or without them. Because the outcome of this study is not based on a dichotomous endpoint (cure/ no cure, success/failure), the evaluated endpoints do not allow coding as "treatment failure". Therefore, the FDA statistician performed equivalence analyses with and without these four patients. Whether they are included or excluded from the GPP population analysis, the study outcome remains the same.

4. Statistical model

- The sponsor used a general linear model, including baseline as a linear covariate for the efficacy and equivalence analyses. This is consistent with currently recommended statistical approach by the working group refining the CDER guidance for bioequivalence studies for nasal steroid drug products. In this statistical model, the mean change from baseline is a linear function of baseline. Therefore, the difference between the test and reference means as a proportion of the reference product mean is closer to zero for higher values of baseline. This suggests that for higher values of baseline, the ratio of the test and reference means is closer to one. Thus, the possibility may exist that the two products could be inequivalent (have a ratio of means less than 0.80 or greater than 1.25) for a given value of baseline, but equivalent for a higher value of baseline. Therefore, the FDA statistician concluded that equivalence must be demonstrated for values of baseline greater than or equal to the average value of baseline observed in the study.
- Based on the skewed distribution of sample baseline values in this study, the median (the value such that half the distribution is above it and half is below it) was selected

as a more meaningful measurement than the mean. Therefore, for all FDA statistical analyses, the sample mean and median values for reflective TNSS baseline scores were calculated from the data on all treatment groups (test, reference, and placebo). The 90% confidence intervals were calculated using data from the test and reference groups only.

5. Equivalence Results

- The FDA statistical review concluded that the 90% confidence interval for the ratio of the mean for test over the mean for reference (based on average reflective TNSS change from baseline) fell within the bioequivalence limits of (0.80 and 1.25) for all baseline values greater than or equal to 8.445 in the GPP population.
- The sample mean overall (scores averaged over both treatment weeks) average baseline reflective TNSS for the GPP was 9.252 and the sample median overall average baseline reflective TNSS for the GPP was 9.429.
- The overall change from baseline reflective TNSS in the Intent-to-Treat Population showed a statistically significant difference between both active treatments compared to the placebo group.

Reviewer's Comments: *This reviewer agrees with the FDA statistician's decision to use the median baseline values for selection of baseline covariate limit for determination of equivalence. The equivalence should be demonstrated for baseline values greater than or equal to the sample median baseline observed in the per protocol population.*

VIII. Conclusion and Recommendation

A. Conclusion

The data presented in this ANDA 76-504 demonstrate that Roxane Laboratories, Inc.'s Fluticasone Propionate Nasal Spray, 50 mcg, is bioequivalent to the reference listed drug, Flonase® Nasal Spray, 50 mcg. The FDA statistical review confirms 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 for the guidance-based evaluable population is (0.965, 1.216), which is within the bioequivalence limits of 0.80 and 1.25. The test and reference products also demonstrate superiority over Placebo.

B. Recommendations to be conveyed to Sponsor

The data submitted to ANDA 76-504, 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 guidance-based evaluable population, are adequate to demonstrate bioequivalence of Roxane Laboratories Inc.'s Fluticasone Propionate Nasal Spray, 50 mcg, with the reference listed drug, GloxoSmithKline's Flonase® Nasal Spray, 50 mcg. Both active treatments demonstrated superiority over the Placebo arm.

1. Bioequivalence of your product was demonstrated using 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.

2. The *CDER Draft Guidance for Industry-Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, posted April 2003,* 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 a placebo run-in baseline period, plus the AM TNSS from day 8 (first day of the treated period). Since your study did not use a placebo-run in baseline period, all 7 untreated baseline days were used for defining the average baseline TNSS. The average TNSS at baseline was calculated as the average (arithmetic mean) of the AM and PM TNSS as recommended in the draft guidance and not based on your proposed AM and PM sums.

3. Your proposed general linear model includes baseline as a linear covariate. This is consistent with a recommended statistical model by the CDER working group for the draft guidance. In this statistical model, the mean change from baseline is a linear function of baseline. Therefore, the difference between the test and reference means as a proportion of the reference product mean is closer to zero for higher values of baseline. Since the possibility may exist that the two products could be inequivalent (have a ratio of means less than 0.80 or greater than 1.25) for a given value of baseline, but may be equivalent for a higher value of baseline, the OGD concluded that equivalence must be demonstrated for values of baseline greater than or equal to the average value (median) of baseline observed in the study.

4. Based on the skewed distribution of sample baseline values in your study, the median (the value such that half the distribution is above it and half is below it) was selected as a more meaningful measurement than the mean. Therefore, for all FDA statistical analyses, the sample mean and median values for reflective TNSS baseline scores were calculated from the data on all treatment groups (test, reference, and placebo). The 90% confidence intervals were calculated using data from the test and reference groups only.

5. The DSI inspection revealed that all inspected sites failed to comply with the current rule for retention of bioavailability (BA) and bioequivalence (BE) testing samples because each clinical site was instructed by the sponsor to send all randomly selected reserve samples back to a third party storage facility, Almedica _____ reserve samples were collected on these sites. It is your responsibility to assure that the clinical sites for all future BE studies comply with the current requirements for retention of study drugs for each shipment as per 21 CFR 320.38 and 320.63.

6. As described in the *CDER Guidance for Industry: Handling and Retention of BA and BE Testing Samples, posted 5/25/04*, the study reserve samples should not be transferred by the testing facility back to an SMO (site management organizations) or any other organization that deals with packaging the test articles and reference standards for storage. If you fail 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.

Carol Y. Kim

5/9/05

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

Date

Dena R. Hixon M.D.

5/10/05

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

Date

5/12/05

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

Date

1.1

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-504 SPONSOR : Roxane Laboratories, Inc.

DRUG AND DOSAGE FORM : Fluticasone Propionate Nasal Spray, 50 mcg

STRENGTH(S) : 50 mcg

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status: completed on 5/26/04	Inspection results: acceptable
First Generic ____ New facility X For cause ____ other ____	Inspection requested: (date) 11/19/03 Inspection completed: (date) 5/26/04	

PRIMARY REVIEWER : Carol Y. Kim, Pharm. D.

INITIAL : CYK DATE : 5/9/05

ASSOCIATE DIRECTOR FOR MEDICAL AFFAIRS: Dena R. Hixon, M.D.

INITIAL : DRH DATE : 5/10/05

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

INITIAL : DPC DATE : 5/12/05

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-504 APPLICANT:Roxane Laboratories, 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 76-504, 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 guidance-based evaluable population, are adequate to demonstrate bioequivalence of Roxane Laboratories Inc.'s Fluticasone Propionate Nasal Spray, 50 mcg, with the reference listed drug, GloxoSmithKline's Flonase® Nasal Spray, 50 mcg. Both active treatments demonstrated superiority over the Placebo arm.

1. Bioequivalence of your product was demonstrated using 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.

2. The *CDER Draft Guidance for Industry-Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, posted April 2003,* 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 a placebo run-in baseline period, plus the AM TNSS from day 8 (first day of the treated period). Since your study did not use a placebo-run in baseline period, all 7 untreated baseline days were used for defining the average baseline TNSS. The average TNSS at baseline was calculated as the average (arithmetic mean) of the AM and PM TNSS as recommended in the draft guidance and not based on your proposed AM and PM sums.

3. Your proposed general linear model includes baseline as a linear covariate. This is consistent with a recommended statistical model by the CDER working group for the draft

guidance. In this statistical model, the mean change from baseline is a linear function of baseline. Therefore, the difference between the test and reference means as a proportion of the reference product mean is closer to zero for higher values of baseline. Since the possibility may exist that the two products could be inequivalent (have a ratio of means less than 0.80 or greater than 1.25) for a given value of baseline, but may be equivalent for a higher value of baseline, the OGD concluded that equivalence must be demonstrated for values of baseline greater than or equal to the average value (median) of baseline observed in the study.

4. Based on the skewed distribution of sample baseline values in your study, the median (the value such that half the distribution is above it and half is below it) was selected as a more meaningful measurement than the mean. Therefore, for all FDA statistical analyses, the sample mean and median values for reflective TNSS baseline scores were calculated from the data on all treatment groups (test, reference, and placebo). The 90% confidence intervals were calculated using data from the test and reference groups only.

5. The DSI inspection revealed that all inspected sites failed to comply with the current rule for retention of bioavailability (BA) and bioequivalence (BE) testing samples because each clinical site was instructed by the sponsor to send all randomly selected reserve samples back to a third party storage facility, b(4)

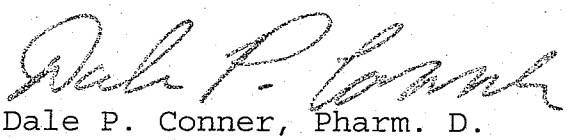
No reserve samples were collected on these sites. It is your responsibility to assure that the clinical sites for all future BE studies comply with the current requirements for retention of study drugs for each shipment as per 21 CFR 320.38 and 320.63.

6. As described in the *CDER Guidance for Industry: Handling and Retention of BA and BE Testing Samples, posted 5/25/04*, the study reserve samples should not be transferred by the testing facility back to an SMO (site management organizations) or any other organization that deals with packaging the test articles and reference standards for storage. If you fail 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.

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



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

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-504
Drug Product Name	Fluticasone Propionate Nasal Spray
Strength	50 µg/spray
Applicant Name	Roxane Laboratories
Address	Columbus, OH
Submission Date(s)	(Original application dated 10/03/02; followed by Amendment date: 12/19/2003)
Amendment Date(s)	DSI report dated: 6/21/04
Reviewer	Zakaria Z. Wahba
First Generic	No
File Location	V:\firmsnz\Roxane\ltrs&rev\76504O0604.doc

Review of a DSI Report

Executive Summary

This is a response to the Division of Scientific Investigation (DSI) audit report on Roxane's fluticasone Nasal Spray 50 µg/spray.

The original submission consisted of in vitro and in vivo bioequivalence (BE) studies. Consistent with the recommendations made in the revised Draft Nasal BA/BE guidance, the in vitro bioequivalence studies were conducted for the following tests: the single actuation content, droplet size distribution (laser diffraction and cascade impaction), spray pattern and plume geometry. The in vivo portion of this application consisted of three BE studies (PK studies #451-05, and #451-03) under fasting conditions and a Clinical End Point Rhinitis study. The in vitro and in vivo studies have been found acceptable (BDE review date: 02/11/04).

At the request of the Division of Bioequivalence (DBE), DSI conducted an audit on Roxane's fluticasone Nasal Spray 50 µg/spray, bioequivalence studies. The DSI inspection revealed some deficiencies related to quantitation of spray patterns and a Form 483 was issued. The DSI report found inconsistencies in quantitation of spray patterns. For some patterns, darker regions of the patterns were used to define images, for other patterns the gray regions were used to define the image boundaries.

DBE agrees with the DSI findings and the firm should be advised to re-submit data based on requantitation of all images using spray pattern boundaries based on the dark regions.

Background

- The firm has previously submitted in vitro and in vivo bioequivalence (BE) studies comparing its test product Roxane's fluticasone Nasal Spray 50 µg/spray to the RLD GlaxoSmithKline's Flonase® Nasal Spray, 50 µg. The submission was reviewed and was found acceptable by the Division of Bioequivalence (V:\firmsnz\Roxane\ltrs&rev\76504a1203.doc, DBE review date: 2/11/04, and V:\firmsnz\Roxane\ltrs&rev\76504n1002.doc, DBE review date: 11/24/03).

- At the request of the Division of Bioequivalence, the Division of Scientific Investigation (DSI) HFD-340 conducted an audit on Roxane's fluticasone Nasal Spray 50 µg/spray, b(4)

  483 was issued (DSI report dated: 06/21/04).

Recommendation

The DSI report found inconsistencies in quantitation of spray patterns. For some patterns, darker regions of the patterns were used to define images, for other patterns the gray regions were used to define the image boundaries.

The firm should submit data based on requantitation of all images using spray pattern boundaries based on the dark regions. The analysis should be based on actual images not photocopies. Paper copies of representative images, with defined boundaries and Dmin and Dmax axes should be submitted in the report. The defined boundaries should be representative of the true shape of the spray pattern. The application is incomplete.

Zakaria Z. Wahba, Ph.D. Zakaria Z. Wahba 7/27/04
Division of Bioequivalence
Review Branch III

RD INITIALLED YCHUANG
FT INITIALLED YCHUANG Y Chuang 7/27/2004

Concur Dale P. Conner Date: 7/27/04
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA:76-504 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg

The Division of Bioequivalence has completed its review of the Division of Scientific Investigation (DSI) report and the following deficiency has been identified:

The DSI report found inconsistencies in quantitation of spray patterns. For some patterns, darker regions of the patterns were used to define images, for other patterns the gray regions were used to define the image boundaries.

Please submit data based on requantitation of all images using spray pattern boundaries based on the dark regions. The analysis should be based on actual images not photocopies. Paper copies of representative images, with defined boundaries and Dmin and Dmax axes should be submitted in the report. The defined boundaries should be representative of the true shape of the spray pattern.

Sincerely yours,

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

CC: ANDA #76-504
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Bio Reviewer
HFD-658/ Bio Team Leader

Endorsements:
HFD-658/ Z Wahba ZW 7/27/04
HFD-658/ YC Huang YH 7/27/2004
HFD-650/ D Conner 7/27/04

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BIOEQUIVALENCE - Incomplete

U2

1. **Other (DSI)**, 06/21/04 OIC Strengths: 50 ug
[redacted] U2 document **Outcome: IC**

OUTCOME DECISIONS: IC - Incomplete

6.1

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 76-504 SPONSOR : Roxane Laboratories, Inc.
DRUG AND DOSAGE FORM : Fluticasone Propionate Nasal Spray
STRENGTH(S) : 50 mcg
TYPES OF STUDIES : In Vitro and In Vivo Studies
CLINICAL STUDY SITE(S) : ———— b(4)
ANALYTICAL SITE(S) : ————

STUDY SUMMARY : In Vitro Studies are acceptable.

DSI INSPECTION STATUS

Inspection needed:	Inspection status: Completed	Inspection results:
~~YES~~ Yes	~~Pending~~ 11/19/03	NAI
First Generic ___	Inspection requested: (date) 11/19/03	accept studies
New facility ___	Inspection completed: (date)	
For cause ___	5/25/04	
Other ___		

PRIMARY REVIEWER : ZAKARIA Z. WAHBA, Ph.D. BRANCH : III

INITIAL : ZZW DATE : 2/11/04

TEAM LEADER : GJP SINGH, Ph.D. BRANCH : III

for ~~INITIAL~~ : Per DATE : 2/11/2004

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : Gabor K. Dan DATE : 2/11/04

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-504
Drug Product Name	Fluticasone Propionate Nasal Spray
Strength	50 µg/spray
Applicant Name	Roxane Laboratories
Address	Columbus, OH
Submission Date(s)	10/03/02 (Original application)
Amendment Date(s)	12/19/2003
Reviewer	Zakaria Z. Wahba
First Generic	No
File Location	V:\firmsnz\Roxane\ltrs&rev\76504a1203.doc

I. Executive Summary

This submission is an amendment containing the firm's responses to deficiencies in the original application. All responses are acceptable.

The original submission consisted of in vitro and in vivo bioequivalence (BE) studies.

Consistent with the recommendations made in the revised Draft Nasal BA/BE guidance, the in vitro bioequivalence studies were conducted for the following tests: the single actuation content, droplet size distribution (laser diffraction and cascade impaction), spray pattern and plume geometry.

Statistical analyses of the in vitro performance data for Roxane's fluticasone Nasal Spray 50 µg/spray) and the RLD GlaxoSmithKline's Flonase® Nasal Spray, 50 µg, demonstrate acceptable performance of the test products. However, the application is incomplete due to several deficiencies cited in the deficiency section.

The in vivo portion of this application consisted of three BE studies (PK studies #451-05, and #451-03) under fasting conditions and a Clinical End Point Rhinitis study.

The firm submitted the BE study protocol #451-05 for demonstrating bioequivalence of its Fluticasone Nasal Spray 50 µg/spray to the RLD GlaxoSmithKline's Flonase® Nasal Spray, 50 µg. The study is a single dose replicate design in normal male and female subjects (n=80). The study was performed in two groups; Group 1: subjects 1-40, Group 2: subjects 41-80.

Statistical analyses of the plasma concentration data demonstrate bioequivalence in group 2 where point estimate, 90% CI are: $LAUC_t$ of 107.5%, 97.3-118.7%; $LAUC_i$ of 107.6%, 97.5-118.8% and LCmax of 108.3%, 100.2-116.9%. On the other hand fluticasone results of group 1 (point estimate, 90% CI) are: $LAUC_t$ of 128.7%, 115.4-143.6%; $LAUC_i$ of 123.1%, 106.0-142.8% and LCmax of 115.1%, 106.9-123.9%. The DBE considers the groups as two separate studies, which may have different outcomes. Therefore BE evaluation is based on group 2

(subjects 41-80) only. The 90% confidence intervals for group 2 are within the acceptable range of 80-125% for log-transformed AUCt, AUCi, and Cmax for fluticasone.

The second BE study (#451-03) is a failed study. The firm submitted the results as requested by the Division of Bioequivalence. It is a single dose replicate design in normal male and female subjects (n=28). Fluticasone results (point estimate, 90% CI) are: $LAUC_t$ of 155.0%, 130.2-184.4%; $LAUC_i$ of 126.5%, 112.2-142.6% and LCmax of 142.9%, 128.9-158.5%. The statistical analyses of the plasma concentration data did not demonstrate bioequivalence.

The Rhinitis study is a clinical end point study. It is currently under review with the OGD medical officer.

The in vitro and in vivo studies have been found acceptable. The application is now acceptable with no deficiency.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Fluticasone Propionate Nasal Spray, 50 µg
Reference Product	Flonase® Fluticasone Propionate Nasal Spray, Metered, 50 µg
RLD Manufacturer	GlaxoSmithKline
NDA No.	020-121
RLD Approval Date	10/19/94
Indication	For the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients.

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	N/A	
Single-dose fed	N/A	
Steady-state	N/A	
In vitro dissolution	N/A	
Waiver requests	No	
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies	N/A	
Amendments	Yes	1

C. Formulation

The formulation was previously submitted and reviewed (see the DBE review report dated 11/24/03 or "V:\firmsam\Roxane\ltrs&rev\76504n1002.doc)

D. In Vitro Dissolution: N/A

E. Waiver Request(s): N/A

F. Responses to Deficiency Comments Stated in the November 24, 2003 DBE Review:

FDA Deficiency Comment #1

Please provide a hard copy of the in vitro data that were submitted on August 28, 2003. This copy should include the raw data.

Firm's Response to Deficiency Comment #1

The requested hard copy of the in vitro data was submitted on August 28, 2003 (Attachment A, volume C6.1)

DBE's Comment on Deficiency #1:

The firm's response is acceptable

FDA Deficiency Comment #2

Please provide a description of the conduct of the cascade impaction studies. You should submit the relevant standard operation procedure (SOP) and include information regarding number of actuation used in each test, operating conditions, type of the atomization chamber used, and data including the mass balance estimates.

Firm's Response to Deficiency Comment #2

A description of the conduct of the cascade impaction studies is provided in the protocol entitled "Individual Project Procedure for In Vitro Bioequivalence Evaluation of Fluticasone Nasal Spray, 0.05% (w/w) for Roxane Laboratories, Inc., ORS Job No.: 151773" Effective date: 9/27/01. The analytical test method entitled "Determination of Aerodynamic Particle Size Distribution in Fluticasone Propionate Nasal Spray, 0.05% (w/w) by Cascade Impaction", Method No.: M1-FP-CI.2, Effective date: 9/27/01. The requested information is included in the above mentioned protocol (pages 359-400, volume C6.2).

DBE's Comment on Deficiency #2:

The firm's response is acceptable

FDA Deficiency Comment #3

Please provide relevant SOPs of all in vitro tests that were included in the application.

Firm's Response to Deficiency Comment #3

All relevant test methods for all of the in vitro tests that were included in the firm's amendment (pages 368-400, volume C6.2):

- Title: Delivery Testing of Fluticasone Propionate Nasal Spray, 0.05% (w/w), Method No.: M1-FP-DC.2, Effective Date: October 12, 2001
- Title: Determination of Aerodynamic Particle Size Distribution in Fluticasone Propionate Nasal Spray, 0.05% (w/w) by Cascade Impaction, Method No.: M1-FP-CI.2, Effevtive Date: 9/27/01.
- Title: Droplet Size Determination of in Fluticasone Propionate Nasal Spray, 0.05% (w/w), Method No.: M1-FP-DS.0, Effective Date: August 7, 2001.
- Title: Determination of Spray Pattern for Fluticasone Propionate Nasal Spray, 0.05% (w/w), Method No.: M1-FP-SP.1, Effective Date: September 27, 2001.
- Title: High-Speed Video Capture of the Spray Plume (Plume Geometry) for Fluticasone Propionate Nasal Spray, 0.05% (w/w), Method No.: M1-FP-PG.1, Effective Date: September 27, 2001.

DBE's Comment on Deficiency #3:

The firm's response is acceptable

FDA Deficiency Comment #4

The firm is requested to provide assay validation information on fluticasone stock stability data. The mean value for study sample set, range (minimum and maximum), precision (%CV), accuracy (%), and number of samples.

Firm's Response to Deficiency Comment #4

The data demonstrating stability of stock solutions of fluticasone propionate at -20°C for at least 65 days as follows:

Theoretical Concentration	500 pg/mL Peak Area Ratio	
	Freshly Prepared Samples	Stability Samples
Mean	2.50	2.43
% CV	2.1	1.1
% Ratio of means	-	97

n	6	6

DBE's Comment on Deficiency #4:

The firm's response is acceptable

FDA Deficiency Comment #5

Regarding samples acceptance and rejection, you have mentioned in the analytical section only the following information "per MDSPS SOP 03.01.042" without any details (see page 663, volume A2.2). Please provide the SOP(s) for describing the analytical method (sample acceptance, rejection criteria, repeat-assay, etc.) for the two bioequivalence (BE) studies (#451-05 and #451-03). The SOP number, date of SOP approved, and SOP title should be also included.

Firm's Response to Deficiency Comment #5

SOP No.	Date of SOP	SOP Title
03.01.016, issue 12	03/01/2002	Acceptance Criteria of Analytical Runs
03.01.019, issue 10	02/22/2002	Reassay Criteria and Acceptance of Reassay Results.

DBE's Comment on Deficiency #5:

The firm's response is acceptable

FDA Deficiency Comment #6

You have mentioned that some reassayed samples were reanalyzed "per client requested criteria", (for more information see page 695, volume A2.2). Please provide the rational for establishing these criteria.

Firm's Response to Deficiency Comment #6

Due to the volume of sample collected (approximately 4 mL of plasma) and the requirement of 1.0 mL per assay, reassay in triplicate is not possible. Consequently, for the purpose of this study, Roxane requested the following: Duplicate reassay should be performed for samples for which there was sufficient volume and the MDSPS SOP noted above followed to determine reportable value. If there was insufficient sample for reassay in duplicate but the same can be reassayed in singlet, then the sample was reassayed in singlet and the new value was accepted for reporting, as is, irrespective of its agreement with the original value.

DBE's Comment on Deficiency #6:

The firm's response is acceptable

FDA Deficiency Comment #7

Please provide the dates of analytical assay (from the first sample to last sample analyzed) of each study (#451-05 and #451-03).

Firm's Response to Deficiency Comment #7

The dates of analytical assay for each study are as follows.
Study 451-03: November 26, 2001 through December 10, 2001
Study 451-05: April 22, 2002 through July 29, 2002

DBE's Comment on Deficiency #7:

The firm's response is acceptable

FDA Deficiency Comment #8

Please provide the expiration dates of the reference listed drug (RLD) lots # OH704, CO19943, and CO35879.

Firm's Response to Deficiency Comment #8

The expiration dates are:
Lot OH704: expires 8/2002
Lot C019943: expires 9/2002
Lot C035879: expires 3/2003

DBE's Comment on Deficiency #8:

The firm's response is acceptable

This space is intentionally left blank

G. Recommendations

1. The *in vitro* performance data submitted by Roxane Laboratories, Inc. comparing its Fluticasone Propionate Nasal Spray (50 µg/spray) with the reference product, GlaxoSmithKline's Flonase® Nasal Spray (50 µg/spray) have been found to be acceptable by the Division of Bioequivalence. The studies demonstrate equivalent *in vitro* performance of Roxane's Fluticasone Propionate Nasal Spray (50 µg/spray), and the reference listed drug product GlaxoSmithKline's Flonase® Nasal Spray (50 µg/spray).

2. The *in vivo* performance data (single dose fasting BE study, protocol #451-05) submitted by Roxane Laboratories, Inc. comparing its Fluticasone Propionate Nasal Spray (50 µg/spray) with the reference product, GlaxoSmithKline's Flonase® Nasal Spray (50 µg/spray) have been found to be acceptable by the Division of Bioequivalence. The studies demonstrate equivalent *in vivo* performance of Roxane's Fluticasone Propionate Nasal Spray (50 µg/spray), and the reference listed drug product GlaxoSmithKline's Flonase® Nasal Spray (50 µg/spray).

3. From the bioequivalence viewpoint, the firm has met the requirements of formulation sameness, device comparability, in vitro and in vivo performance testing.

Zakaria Z Wahba Date 02/11/04

Zakaria Z. Wahba, Ph.D.,
Branch III

for RT: Date 2/11/2004

Gur Jai Pal Singh, Ph.D.,
Branch III

Concur: Barbara M Davit Date 2/11/04

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

IV. Appendix:

NA

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-504 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

Please also 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,

Barbara M Davit

for

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

CC: ANDA 76-504
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:
HFD-658/ Z. Wahba 2/11/04
for HFD-658/ GJP Singh 2/11/2004
for HFD-650/ D. Conner 2/11/04

v:\\firmsnz\Roxane\LTRS&REV\76504a1203.doc

BIOEQUIVALENCE - ACCEPTABLE

submission date: 12/19/03

1. Study Amendment (STA)

Strength: 50 mcg
Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments: Acceptable

15-1

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-504
Drug Product Name	Fluticasone Propionate Nasal Spray
Strength	50 µg/spray
Applicant Name	Roxane Laboratories
Address	Columbus, OH
Submission Date(s)	(Original application dated 10/03/02, followed by Amendment dated 12/19/2003, DSI report dated 6/21/04, and another amendment on 8/17/04)
Amendment Date(s)	6/6/2005 (Current Amendment)
Reviewer	Gur Jai Pal Singh, Ph.D.
First Generic	No
File Location	V:\firmsnz\Roxane\ltrs&rev\76504a0605.doc

Executive Summary

The original application was submitted on October 3, 2002. It referenced Flonase® (Fluticasone propionate nasal spray) manufactured by GlaxoSmithKline. The application contained (1) information supporting Q_1 and Q_2 sameness of the test and reference product formulations, (2) a clinical (rhinitis) study to document equivalence in drug delivery to the local site (nasal cavity) of action, (3) a pharmacokinetic bioequivalence (PK BE) study comparing systemic exposure from nasal administration of the test and reference products, and (4) in vitro performance studies based on the Draft Nasal BA/BE guidance.

Both the rhinitis and pharmacokinetic studies have been found acceptable in previous reviews of this application. The PK BE study compared the test and reference products at a dose of 800 µg, which exceeds the maximum labeled dose (200 µg), recommended in the April 2003 draft of the Nasal BA/BE Guidance. However it is noted, in this regard, that (1) the PK BE study was initiated before the issuance of the April 2003 draft of the guidance; it was based on the June 1999 draft of the Nasal BA/BE Guidance which provided allowance for use of doses exceeding the maximum labeled dose, and (2) the firm had obtained the Office of Generic Drugs' permission to use the 800 µg dose before initiation of the study.

The firm submitted complete sets of in vitro evaluation studies at two separate occasions. The original application contained comparative studies based on three lots of the test and reference products. However, none of procured reference lots was sufficient to support testing for all in vivo and in vitro testing. Therefore, to follow the Agency's recommendation, one of the three reference lots used for in vitro studies was replaced with another lot of the reference product that was used in all in vivo and in vitro testing,. A "bridging" in vitro performance study was performed to include the replacement lot.

All in vitro data submitted in the original application, the bridging study and the current amendment were evaluated using the Population Bioequivalence (PBE) methodology. Based on these analyses, in vitro performance of the test product is equivalent to that of the reference product.

From the bioequivalence view point, the application is complete with no deficiencies.

Background (NOT TO BE RELEASED UNDER FOI)

- The clinical (rhinitis) study submitted by the firm was previously found acceptable by the Office of Generic Drugs ((V:\firmsnz\Roxane\ltrs&rev\76504 A.1002.mor, Review Date: 5/9/2005).

- The in vitro and in vivo bioequivalence (PK BE) studies comparing Roxane's fluticasone Nasal Spray 50 µg/spray to the RLD GlaxoSmithKline's Flonase® Nasal Spray, 50 µg. were previously found acceptable by the Division of Bioequivalence (V:\firmsnz\Roxane\ltrs&rev\76504a1203.doc, DBE review date: 2/11/04, and V:\firmsnz\Roxane\ltrs&rev\76504n1002.doc, DBE review date: 11/24/03).

- At the request of the DBE, the Division of Scientific Investigations (DSI) conducted an audit on Roxane's fluticasone Nasal Spray 50 µg/spray bioequivalence studies (in vitro and in vivo studies). The DSI inspection revealed deficiencies related to quantitation of spray patterns and a Form 483 was issued (DSI report dated: 06/21/04). The DBE agreed with the DSI finding and sent a deficiency letter to the firm (DBE review date: 07/27/04). In that letter the DBE requested the firm to submit spray pattern data based on re-quantitation of all images using spray pattern boundaries based on the dark regions.

- In an amendment dated 8/17/04, the firm responded to the DBE deficiency letter and provided the requested information. On 09/21/04, the DBE held a meeting on Roxane's fluticasone Nasal Spray 50 µg/spray. The meeting included DBE Director, Deputy Director, Branch 3 Team Leader, GJP Singh and the reviewer of this submission. The purpose of the meeting was to discuss the result of the submitted spray pattern data and the method of Population Bioequivalence (PBE) with regard to nasal spray submissions. The conclusion of the meeting was that the submitted in vitro data on spray patterns are not acceptable since the data were outside the acceptable range of 0.9-1.11, the acceptance criteria in effect at that time. On October 18, 2004, the DBE communicated the following two deficiencies:

    - The spray pattern data are incomplete. The ratios of geometric means on Dmax and Dmin at the 6.5 cm distance were outside the acceptable range of 0.9-1.11 at the beginning life sector.

    - The cascade impaction data are incomplete. The ratios of the geometric means for group 2 (end sector) and group 3 (both beginning and end sectors) data were outside the acceptable limit of 0.90-1.11.

Statistical Analyses of the In Vitro Performance Data

The DBE has been evaluating in vitro studies on nasal sprays based on the ratios of geometric means (Acceptance limit: 0.9-1.11) and evidence for comparable variability of the test and reference products. On August 3, 2005, the DBE management made a decision to implement the draft Population Bioequivalence (PBE) method that was developed for evaluation of certain comparative in vitro performance studies on aerosols and nasal sprays. Information regarding the PBE methodology has been posted on the Agency website since April 11, 2003. This method uses a confidence interval approach and, as such, it imparts greater scientific validity to determination of equivalence, over assessment of equivalence based on ratios of geometric means and evaluation of comparative variability based on eyeballing of the data.

All in vitro data submitted in the original and bridging studies were evaluated using the PBE methodology (see Attachment 1). These analyses employed a $Sigma_{T0}$ of 0.1 and an Epsilon value of 0.01.

Current Amendment

In the current amendment, the firm has responded to the deficiencies cited on October 18, 2004. The reviewer's comments on the firm's responses are as follows:

1. ***Quantitation of Spray Patterns:*** Data submitted in the original application was based on manual quantitation of spray patterns. Subsequently, a DSI audit determined that measurements of spray pattern dimensions were subjective and biased. To eliminate the subjectivity and operator bias, the firm used an automated method which was not available at the time of analyses of data submitted in the original application. The automated method used EZSpray® computer software for quantitation of scanned images of the spray patterns. The images of patterns produced in the original study were re-analyzed using the automated method. Consistent with the recommendation of the April 2003 daft Nasal BA/BE guidance, the firm reported comparative data for the spray pattern area and ovality ratio.

   PBE analyses of the spray pattern area and ovality ratio data were performed (See Attachment 1). The results of these analyses showed equivalence between the test and reference products for all comparisons, except for the area at the 2.5 cm distance even though T/R ratio of geometric means for the same data was 1:00.

   An examination of the PBE analyses for the spray pattern area data indicated a $Sigma_T/Sigma_R$ ratio of 1.39 at the 2.5 cm distance compared with a $Sigma_T/Sigma_R$ ratio of 0.78 at 6.5 cm. These data indicated that the test product spray pattern was more variable than that of the reference product at the 2.5 cm distance, and at the 6.5 cm distance it was much less variable than the reference product. These results were questionable because (1) as evident from the reference product data, variability in spray pattern area generally increases with increasing distance from the orifice partly due to plume dissipation and decreased

intensity of spray patterns, and (2) relative variability of the test and reference is not expected to reverse at two distances.

An examination of the individual data (Attachment 2) revealed an aberrant value (Bottle 43) in the test product data at 2.5 cm. The area value of 147 at the 2.5 cm was 38% lower than the lowest value (237) in the remaining 2.5 cm data for the test product. However, the same bottle's performance at the 6.5 cm was 54% greater than mean value of the test product area at 6.5 cm. In addition, the aberrant value was more than 2 standard deviations lower than the mean value, and such deviation was not observed with the 6.5 cm data for the test product, or 2.5 cm and 6.5 cm data for the reference product. In the reviewer's opinion the aberrant value represents probable product malfunction. Therefore, a PBE analysis was performed without the aberrant value. The revised analysis (Attachment 1) showed $Sigma_T/Sigma_R$ ratio of 1.02 and demonstrated equivalence between the test and reference products. It is noteworthy that for great majority of the PBE analyses provided in Attachment 1, $Sigma_T/Sigma_R$ ratio was < 1.00.

2. ***Cascade Impaction Data:*** The cascade impaction data submitted in the original application and the bridging study were grouped into three groups based on the particle size cutoffs (Group 1 >9 μM, Group 2 4.7 – 9 μM , and Group 3 <4.7 μM).

The April 2003 draft of the BA/BE Guidance recommends grouping of data from all cascade impactor stages below the top stage, to compute the amount of drug delivered as particles/droplets < 9μM in diameter. The objective of this test is to ensure that fraction of the formulation delivered by the test product in droplets < 9 μM is not greater than that delivered by the reference product. Therefore, the firm pooled the data from the original study representing droplets < 9μM.

The DBE analyzed the revised Cascade Impactor data using the PBE approach. Based on these analyses, the test product is equivalent to the reference product with regard to drug below the top stage (Group 2, < 9 μM, see Attachment 1).

Recommendations

1. The formulation of the test product has been found Q_1 and Q_2 same as that of the reference product.

2. The *in vivo* rhinitis study comparing the clinical performance of Roxane's fluticasone propionate nasal spray, 50 µg/spray, and the reference listed drug Flonase® (GlaxoSmithKline) has been found acceptable.

3. The *in vivo* pharmacokinetic study comparing systemic exposure from Roxane's fluticasone propionate nasal spray, 50 µg/spray, and the reference listed drug Flonase® (GlaxoSmithKline (GlaxoSmithKline) has been found acceptable.

4. The *in vitro* performance studies conducted by Roxane comparing its fluticasone propionate nasal spray, 50 µg/spray, and the reference listed drug Flonase® (GlaxoSmithKline) have been found acceptable.

5. The firm has satisfactorily addressed a 483 issued by the Division of Scientific Investigation regarding the in vitro performance studies.

From the bioequivalence point of view, this application is complete with no deficiencies.

Gur Pal Singh Date: 8-29-05

Gur Jai Pal Singh, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

Concur: Barbara M Davit Date: 8/30/05

Barbara Davit, Ph.D.
Deputy Director
Division of Bioequivalence

Concur: Dale P. Conner Date: 8/31/05

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCE COMMENTS

ANDA:76-504 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg

The Division of Bioequivalence has completed its review of your submission(s) and has no further questions at this time.

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.
2.

Sincerely yours,

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

CC: ANDA #76-504
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-655/ Bio Team Leader

Endorsements:
HFD-655/ GJP Singh Concur 8-29-05
HFD-650/ B Davit 6 MD 8/30/05
HFD-650/ D Conner DM 8/31/05
v:\\firmsnz\Roxane\LTRS&REV\76504a00605.doc

BIOEQUIVALENCE - Complete submission date: 06-06-2005

1. Study Amendment (STA) Strength: 50 mcg
Outcome: AC

Outcome Decisions: AC
WinBio Comments: Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA#: **76-504** SPONSOR: **Roxane**
DRUG AND DOSAGE FORM: **Fluticosone Propionate Nasal Spray**
STRENGTH(S): **50 µg/Spray**
TYPES OF STUDIES: Clinical Rhinitis Study, Pharmacokinetic Study and In vitro Performance Studies
CLINICAL STUDY SITE(S)

[redacted] b(4)

ANALYTICAL SITE(S): [redacted]

STUDY SUMMARY: Both the rhinitis and PK-BE studies are acceptable
IN VITRO PERFORMANCE TESTING: Acceptable

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
First Generic __Yes_	Inspection requested: (date)	
New facility _____	Inspection completed: (date) 6/21/04	
For cause ____		
Other ____		

Proposed Dissolution Method and Spec from Prior Amendment: Not applicable

TEAM LEADER BRANCH: II: Gur-Jai Pal Singh, Ph.D.
INITIAL: GPS DATE : 8-29-05

DEPUTY DIRECTOR, DIVISION OF BIOEQUIVALENCE: Barbara Davit, Ph.D.
INITIAL: BMD DATE : 8/29/05

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.
INITIAL: DPC DATE : 8/30/05

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-504 SPONSOR : Roxane Laboratories, Inc.

DRUG AND DOSAGE FORM : Fluticasone Propionate Nasal Spray, 50 mcg

STRENGTH(S) : 50 mcg

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status: completed on 5/26/04	Inspection results: acceptable
First Generic ____ New facility X For cause ____ other ____	Inspection requested: (date) 11/19/03 Inspection completed: (date) 5/26/04	

PRIMARY REVIEWER : Carol Y. Kim, Pharm. D.

INITIAL : CYK DATE : 5/9/05

ASSOCIATE DIRECTOR FOR MEDICAL AFFAIRS: Dena R. Hixon, M.D.

INITIAL : DRH DATE : 5/10/05

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

INITIAL : DPC DATE : 5/12/05

BIOEQUIVALENCE DEFICIENCIES

ANDA:76-504 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg

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

1. The spray pattern data are incomplete. The ratios of geometric means on Dmax and Dmin at the 6.5 cm distance were outside the acceptable range of 0.9-1.11 at the beginning life sector.

2. The cascade impaction data are incomplete. The ratios of the geometric means for group 2 (end sector) and group 3 (both beginning and end sectors) data were outside the acceptable limit of 0.90-1.11.

3. Please re-submit new data on both tests for review.

Sincerely yours,

Barbara M. Saint

pp

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

CC: ANDA #76-504
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Bio Reviewer
HFD-658/ Bio Team Leader

Endorsements:
HFD-658/ Z Wahba ZW 10/13/04
HFD-658/ YC Huang YCH 10/13/2004
HFD-655/ GJP Singh
HFD-650/ D Conner BDC 10/14/04

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BIOEQUIVALENCE - Incomplete submission date: 08/17/04

1. Study Amendment (STA) 011

Strength: 50 mcg
Outcome: IC

Outcome Decisions: IC - Incomplete
WinBio Comments: Incomplete

OCT 18 2004

BIOEQUIVALENCE DEFICIENCIES

ANDA:76-504 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg

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

1. The spray pattern data are incomplete. The ratios of geometric means on Dmax and Dmin at the 6.5 cm distance were outside the acceptable range of 0.9-1.11 at the beginning life sector.

2. The cascade impaction data are incomplete. The ratios of the geometric means for group 2 (end sector) and group 3 (both beginning and end sectors) data were outside the acceptable limit of 0.90-1.11.

3. Please re-submit new data on both tests for review.

Sincerely yours,

Barbara M Savitt

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

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-504
Drug Product Name	Fluticasone Propionate Nasal Spray
Strength	50 µg/spray
Applicant Name	Roxane Laboratories
Address	Columbus, OH
Submission Date(s)	(Original application dated 10/03/02; followed by Amendment date: 12/19/2003, DSI report dated: 6/21/04)
Amendment Date(s)	08/17/04
Reviewer	Zakaria Z. Wahba
First Generic	No
File Location	V:\firmsnz\Roxane\ltrs&rev\76504a0804.doc

Executive Summary

This amendment is a response to deficiencies identified during the Division of Scientific Investigation (DSI) audit on Roxane's fluticasone Nasal Spray 50 µg/spray. The firm's response is incomplete.

The original submission consisted of in vitro and in vivo bioequivalence (BE) studies. Consistent with the recommendations made in the revised Draft Nasal BA/BE guidance, the in vitro bioequivalence studies were conducted for the following tests: the single actuation content, droplet size distribution (laser diffraction and cascade impaction), spray pattern and plume geometry. The in vivo portion of this application consisted of three BE studies (PK studies #451-05, and #451-03) under fasting conditions and a Clinical End Point Rhinitis study. The in vivo studies have been found acceptable (DBE review date: 02/11/04). The clinical end point rhinitis study is pending.

At the request of the Division of Bioequivalence (DBE), DSI conducted an audit on Roxane's fluticasone Nasal Spray 50 µg/spray. The DSI inspection revealed some deficiencies related to quantitation of spray patterns and a Form 483 was issued. The DSI report found inconsistencies in quantitation of spray patterns. For some patterns, darker regions of the patterns were used to define images, for other patterns the gray regions were used to define the image boundaries

In this amendment, the firm resubmitted spray pattern data based on requantitation of all images using boundaries based on the dark regions. The resubmitted data on spray patterns were reviewed and were found not acceptable to the Division of Bioequivalence (DBE). The ratios of the geometric mean (test/reference) for the spray pattern data (Dmax and Dmin at the 6.5 cm distance for the beginning life sector and Dmin at the 6.5 cm for the end life sector) were outside the acceptable limit of 0.90-1.11. During an internal review in the DBE, it is noted that the ratios of geometric means for the cascade impaction data for group 2 (end stage) and 3 (both beginning

and end stages) were also outside the acceptable limit of 0.90-1.11. Therefore, the originally submitted cascade impaction data were failed to meet the acceptable limit of 0.9-1.11.

The application is incomplete due to the deficiency regarding spray pattern and cascade impaction data. The firm is requested to resubmit new data on spray pattern and droplet size distribution using cascade impaction.

Background (NOT TO BE RELEASED UNDER FOI)

- The firm has previously submitted in vitro and in vivo bioequivalence (BE) studies comparing its test product Roxane's fluticasone Nasal Spray 50 µg/spray to the RLD GlaxoSmithKline's Flonase® Nasal Spray, 50 µg. The submission was reviewed and was found acceptable by the Division of Bioequivalence (V:\firmsnz\Roxane\ltrs&rev\76504a1203.doc, DBE review date: 2/11/04, and V:\firmsnz\Roxane\ltrs&rev\76504n1002.doc, DBE review date: 11/24/03).

- At the request of the DBE, the DSI (HFD-340) conducted an audit on Roxane's fluticasone Nasal Spray 50 µg/spray, bioequivalence studies (in vitro and in vivo studies) at _____ The DSI inspection revealed some deficiencies related to quantitation of spray patterns and a Form 483 was issued (DSI report dated: 06/21/04). b(4)

- The DBE agreed with the DSI finding and sent a deficiency letter to the firm (DBE review date: 07/27/04). In the letter the DBE requested the firm to resubmit spray pattern data based on requantitation of all images using spray pattern boundaries based on the dark regions.

- In this amendment, the firm has responded to the DBE deficiency letter and provided the requested information.

- On 09/21/04, DBE held a meeting on Roxane's fluticasone Nasal Spray 50 µg/spray. The meeting included DBE Director, Deputy Director, Branch 3 Team Leader, Dr. Singh and the reviewer of this submission. The purpose of the meeting was to discuss the result of the submitted spray pattern data and the method of Population Bioequivalence (PBE) with regard to nasal spray submissions. The conclusion of the meeting was that the submitted in vitro data on spray patterns are not acceptable since the data were outside the acceptable range of 0.9-1.11. Currently, the PBE approach should not be applied in the regulatory decision of in vitro nasal spray testing. Furthermore, it was recommended that the firm should resubmit new droplet size distribution data using cascade impaction method.

The firm's Response to the DBE Deficiency Comment
The deficiency comment is as stated in the DBE Review (review date 07/27/04):

FDA Deficiency Comment

The DSI report found inconsistencies in quantitation of spray patterns. For some patterns, darker regions of the patterns were used to define images, for other patterns the gray regions were used to define the image boundaries.

Please submit data based on requantitation of all images using spray pattern boundaries based on the dark regions. The analysis should be based on actual images not photocopies. Paper copies of representative images, with defined boundaries and Dmin and Dmax axes should be submitted in the report. The defined boundaries should be representative of the true shape of the spray pattern.

Firm's Response to the Deficiency Comment

(The submitted information is included in volumes A8.1 and A8.2).

The spray pattern data were requantitated and were stored as electronic images which were printed and processed to determine the Dmax and Dmin. The firm submitted spray pattern data at three distances (2.5, 4.5 and 6.5 cm) from TLC plate at beginning life sector and end life sector for the test product and the reference products. It provided individual results of spray pattern determination in term of longest diameter (D_{max}), shortest diameter (D_{min}) and ovality ratio (D_{max}/D_{min}).

A summary of the spray pattern data based on the reviewer's calculations is presented in Tables I and II.

Table I
Spray Pattern Data – Test Product (Beginning Life Sector)

PROD.	Sector	Distance	Parameter	Mean	Variability (%CV)			TEST/REF		P value
					Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	
				(N = 30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
		2.5	Long. Diam	23.90	4.39-8.89	2.05	6.42	1.01	1.01	0.540
		2.5	Short. Diam	20.77	3.23-6.39	4.52	6.35	0.99	0.99	0.568
		2.5	Oval. Ratio	1.15	4.43-7.53	2.35	6.29	1.02	1.02	0.326
		4.5	Long. Diam	29.63	13.81-26.91	9.52	21.42	0.95	0.94	0.264
TEST	BEG	4.5	Short. Diam	22.94	14.06-27.13	7.12	20.61	0.93	0.93	0.123
		4.5	Oval. Ratio	1.30	13.45-17.24	2.30	14.87	1.01	1.01	0.779
		6.5	Long. Diam	35.48	14.50-27.18	14.80	24.63	1.19	1.18	0.004
		6.5	Short. Diam	22.19	10.11-23.12	12.80	22.43	1.15	1.15	0.025
		6.5	Oval. Ratio	1.62	12.81-27.11	9.04	20.85	1.02	1.03	0.656

Spray Pattern Data – Reference Product (Beginning Life Sector)

PROD.	Sector	Distance	Parameter	Mean	Variability (%CV) Within-Lot	Between-lot	Total
				(N = 30)	(N=10)	(N=3)	(N=30)
		2.5	Long. Diam	23.61	6.04-8.96	5.96	8.94
		2.5	Short. Diam	21.01	4.18-11.39	2.52	9.02
		2.5	Oval. Ratio	1.23	3.64-12.70	0.05	10.11
		4.5	Long. Diam	31.31	14.18-22.10	12.05	19.48
Ref.	BEG	4.5	Short. Diam	24.79	15.21-30.13	11.77	22.53
		4.5	Oval. Ratio	1.29	10.50-21.28	2.55	17.37
		6.5	Long. Diam	29.81	15.83-25.59	1.51	19.59
		6.5	Short. Diam	19.25	13.85-21.09	11.53	19.61
		6.5	Oval. Ratio	1.58	15.12-25.26	14.16	23.17

Table II
Spray Pattern Data – Test Product (End Life Sector)

PROD.	Sector	Distance	Parameter	Mean	Variability (%CV) Within-Lot	Between-lot	Total	TEST/REF Arith Mean	Geo Mean	P value
				(N = 30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
		2.5	Long. Diam	25.70	4.28-7.44	3.00	6.66	1.02	1.02	0.53953
		2.5	Short. Diam	21.91	2.83-8.13	1.48	6.12	1.00	1.01	0.88585
		2.5	Oval. Ratio	1..18	5.04-14.09	2.06	10.29	1.02	1.02	0.57154
		4.5	Long. Diam	33.18	11.83-31.77	5.07	22.66	1.06	1.06	0.30503
TEST	End	4.5	Short. Diam	25.90	16.08-29.45	8.05	22.61	1.03	1.04	0.65382
		4.5	Oval. Ratio	1.29	13.40-21.03	3.24	16.37	1.01	1.02	0.86708
		6.5	Long. Diam	38.07	17.61-21.48	19.70	24.94	1.09	1.09	0.13265
		6.5	Short. Diam	24.28	20.11-28.02	30.66	35.55	1.12	1.12	0.11508
		6.5	Oval. Ratio	1.65	13.58-27.14	9.03	23.34	0.96	0.97	0.53646

Spray Pattern Data – Reference Product (End Life Sector)

PROD.	Sector	Distance	Parameter	Mean	Variability (%CV) Within-Lot	Between-lot	Total
				(N = 30)	(N=10)	(N=3)	(N=30)
		2.5	Long. Diam	25.18	2.30-10.56	4.78	9.13
		2.5	Short. Diam	21.85	6.25-11.99	0.13	8.57
		2.5	Oval. Ratio	1.16	10.50-11.27	5.03	11.29
		4.5	Long. Diam	31.32	14.07-32.00	10.03	22.88
Ref.	End	4.5	Short. Diam	25.12	19.00-32.61	2.65	24.72
		4.5	Oval. Ratio	1.28	9.54-29.56	14.34	25.30

6.5	Long. Diam	35.04	13.67-31.56	14.32	27.08
6.5	Short. Diam	21.70	22.05-37.34	19.18	36.14
6.5	Oval. Ratio	1.71	24.55-27.21	18.77	29.87

Comments

- The ratios of geometric means of test/reference for beginning life sector for the parameters Dmax, Dmin and Ovality were within the acceptable range of 0.9-1.11 at 2.5 and 4.5 cm distance.
- For the 6.5 cm distance, the ovality ratio (T/R) was within the acceptable range of 0.9-1.11. However, the ratios of geometric means on Dmax and Dmin at the same distance (6.5 cm) were outside the acceptable range of 0.9-1.11.
- The current guidance (the April 2003 revised Draft Guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action") recommends testing for spray pattern at the beginning life sector only. The results showed that Dmax and Dmin data at the 6.5 cm distance failed to meet the acceptance criterion for the beginning life sector.
- It is noted that the previous draft of the same guidance recommended evaluation of spray pattern at both beginning and end sectors. Since the firm provided spray pattern for end sector, the reviewer analyzed the data on both sectors. Based on the reviewer's analysis for the end sector, the ratios of geometric means of test/reference for Dmax, Dmin and Ovality were within the acceptable range of 0.9-1.11 at 2.5, 4.5 and 6.5 cm distances, except for the Dmin at the 6.5 cm distance the geometric mean ration was outside the acceptable range.
- In conclusion: The submitted spray pattern data do not meet the acceptance criterion for beginning sector as recommended in the current guidance or the beginning and end sectors as recommended in the previous draft of the same guidance. Therefore, the spray pattern test is incomplete. Therefore, the firm response to the spray pattern deficiency is not acceptable.

Deficiencies

1. The spray pattern data are not acceptable. The ratios of geometric means on Dmax and Dmin at the 6.5 cm distance for beginning life sector were outside the acceptable range of 0.9-1.11.

2. The droplet size distribution data using cascade impaction method are not acceptable. The submitted data on group 2 and 3 data were outside the acceptable limit of 0.90-1.11 (end sector for group-2, and beginning and end sectors for group-3).

3. The firm is requested to re-submit new data on both tests for review.

Recommendation

The *in vitro* performance data submitted by Roxane Laboratories, Inc. comparing its Fluticasone Propionate Nasal Spray (50 µg/spray) with the reference product, GlaxoSmithKline's Flonase®

Nasal Spray (50 µg/spray) have been found to be incomplete due to the deficiencies cited above (items 1-3).

Zakaria Z. Wahba 10/13/04

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED YCHUANG
FT INITIALLED YCHUANG Y Chuang 10/13/2004

Concur: Barbara M. Davit Date: 10/14/04
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

ANDA 76-504 (Fluticasone Propionate Nasal Spray – Roxane)

DEC - 2 2003

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-504 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg

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

In Vitro Section

1. Please provide a hard copy of the in vitro data that were submitted on August 28, 2003. This copy should include the raw data.

2. Please provide a description of the conduct of the cascade impaction studies. You should submit the relevant standard operation procedure (SOP) and include information regarding (a) number of actuation used in each test, (2) operating conditions, (c) type of the atomization chamber used, and (d) data including the mass balance estimates.

3. Please provide relevant SOPs of all in vitro tests that were included in the application.

In Vivo Section (PK Study)

4. Please provide assay validation information on fluticasone stock stability data is requested. The mean value for study sample set, range (minimum and maximum), precision (%CV), accuracy (%), and number of samples.

5. Regarding samples acceptance and rejection, you have mentioned in the analytical section only the following information "per MDSPS SOP 03.01.042" without any details (see page 663, volume A2.2). Please provide the SOP(s) for describing the analytical method (sample acceptance, rejection criteria, repeat-assay, etc.) for the two bioequivalence (BE) studies (#451-05 and #451-03). The SOP number, date of SOP approved, and SOP title should be also included.

6. You have mentioned that some reassayed samples were reanalyzed "per client requested criteria", (for more

information see page 695, volume A2.2). Please provide the rational for establishing these criteria, as well as the date(s) for establishing it.

7. Please provide the dates of analytical assay (from the first sample to last sample analyzed) of each study (#451-05 and #451-03).

8. Please provide the expiration dates of the reference listed drug (RLD) lots # OH704, CO19943, and CO35879.

Sincerely yours,

Barbara M Davit

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

Fluticasone Propionate Nasal Spray **Roxane Laboratories**
50 µg/spray Columbus, OH
ANDA #76-504 Submission Date:
Reviewer: Z.Z. Wahba October 03, 2002
V:\firmsnz\Roxane\ltrs&rev\76504n1002.doc

REVIEW OF IN VITRO AND IN VIVO BIOEQUIVALENCE STUDY DATA

I. Executive Summary

This submission consisted of in vitro and in vivo bioequivalence (BE) studies.

Consistent with the recommendations made in the revised Draft Nasal BA/BE guidance, the in vitro bioequivalence studies were conducted for the following tests: the single actuation content, droplet size distribution (laser diffraction and cascade impaction), spray pattern and plume geometry.

Statistical analyses of the in vitro performance data for Roxane's fluticasone Nasal Spray 50 µg/spray) and the RLD GlaxoSmithKline's Flonase® Nasal Spray, 50 µg, demonstrate acceptable performance of the test products. However, the application is incomplete due to several deficiencies cited in the deficiency section.

The in vivo portion of this application is consisted of three BE studies (PK studies #451-05, and #451-03) under fasting conditions and a Clinical End Point Rhinitis study.

The firm submitted the BE study protocol #451-05 for demonstrating bioequivalence of its Fluticasone Nasal Spray 50 µg/spray to the RLD GlaxoSmithKline's Flonase® Nasal Spray, 50 µg. The study is a single dose replicate design in normal male and female subjects (n=80). The study was performed in two groups; Group 1: subjects 1-40, Group 2: subjects 41-80.

Statistical analyses of the plasma concentration data demonstrate bioequivalence in group 2 where point estimate, 90% CI are: $LAUC_t$ of 107.5%, 97.3-118.7%; $LAUC_i$ of 107.6%, 97.5-118.8% and LCmax of 108.3%, 1002-116.9%. On the other hand fluticasone results of group 1 (point estimate, 90% CI) are: $LAUC_t$ of 128.7%, 115.4-143.6%; $LAUC_i$ of 123.1%, 106.0-142.8% and LCmax of 115.1%, 106.9-123.9%. The DBE considers the groups as two separate studies, which may have different outcomes. Therefore BE evaluation is based on group 2 (subjects 41-80) only. The 90% confidence intervals for group 2 are within the acceptable range of 80-125% for log-transformed AUCt, AUCi, and Cmax for fluticasone.

The second BE study (#451-03) is a failed study. The firm submitted the results as requested by the Division of Bioequivalence. It is a single dose replicate design in normal male and female subjects (n=28). Fluticasone results (point estimate, 90% CI) are: $LAUC_t$ of 155.0%, 130.2-184.4%; $LAUC_i$ of 126.5%, 112.2-142.6% and LCmax of

142.9%, 128.9-158.5%. The statistical analyses of the plasma concentration data did not demonstrate bioequivalence.

The Rhinitis study is a clinical end point study. It is currently under review with the OGD medical officer.

The application has been found incomplete due to several deficiencies (details are given in the deficiency section).

Background

Fluticasone 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.

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity. It is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump.

The RLD Flonase ® Nasal Spray 50 mcg is supplied in an amber glass bottle fitted with a white metering atomizing pump, white nasal adapter, and green dust cover in a box of 1 (NDC 0173-0453-01) with patient's instructions for use. Each bottle contains a net fill weight of 16 g and provides 120 actuations. Each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. The correct amount of medication in each spray cannot be assured after 120 sprays even though the bottle is not completely empty. The bottle should be discarded when the labeled number of actuations has been used.

The recommended starting dosage in adults is 2 sprays (50 mcg of fluticasone propionate each) in each nostril once daily (total daily dose, 200 mcg). The same dosage divided into 100 mcg given twice daily (e.g., 8 a.m. and 8 p.m.) is also effective.

Drug Products:
(info. on page 78C, vol. C1.1)

Test: Roxane's Fluticasone Propionate Nasal Spray, 50 µg, Lots 019032A, 019033A, 019034A, and 019035A, manufacturing dates: 7/11/01, 7/12/01, 7/13/01, and 1/10/01, respectively. The test product lots were made from different lots of the drug substance, pumps and actuators (pp 18661, vol. A1.40).
Note: Lot #019032A used for pivotal pharmacokinetic and clinical endpoint study.

Reference: GlaxoSmithKline's Flonase® Fluticasone Propionate Nasal Spray, Metered, 50 µg, Lots 0H704, C019943, C035879 (expiration dates were not give) and C049983, Exp. 10/2003.

Note: Lot #C049983 used for the in vitro bridging study, and also used for the pivotal pharmacokinetic and clinical endpoint study.

Relevant DBE History

- The firm's representatives met with the Office of Generic Drugs (OGD) staff on August 29, 2000. In that meeting the firm presented a summary of preliminary data for comparative in vitro performance of the devices of the test and reference products (Minutes of the Meeting are presented on pages 198-202, vol. C1.1).

- The firm subsequently submitted (Control Doc. #00396) limited in vitro testing data for DBE comments. A review of that correspondence was completed on October 30, 2000, and the firm was informed of DBE comments.

- On November 2, 2000 the firm submitted another set of questions regarding in vitro testing. Those questions were addressed in the Agency letter of November 16, 2000.

- On December 19, 2000, the firm subsequently submitted for the Agency comments a controlled correspondence containing electronic files of a large volume of in vitro testing data and a summary of a pilot pharmacokinetic study comparing the test and reference products. The reviewer determined that additional information was required before the Agency could comment on that correspondence. The firm was informed regarding the required information in a tele-conference on April 11, 20001.

- On March 09, 2001, the firm requested the Agency's comments (Contrl Doc. #01-148) regarding (1) the use of same bottle to determine unite dose, priming, repriming, and tail off, (2) sampling for determination of droplet size distribution, and (3) Q1 and Q2 formulation of the test and reference products.

II. IN VITRO BIOEQUIVALENCE TESTING

Agency Guidance

Draft guidances "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", posted on June 1999 and April 2003.

Formulation:

Composition of the test product, fluticasone propionate nasal spray, 50 µg, is quantitatively and qualitatively the same as the reference listed drug. The formulations are provided below:

FORMULATION COMPARISON **(not for release under FOI)**

Ingredient	*Test		**RLD	
	Amount per Metered Spray	Amount/per	% W/W	Amount/ kg batch
[redacted]				

b(4)

*The information is located in page 78B, volume C1.1; and p age 18364, vol. C1.40.
**The information was taken from NDA #20-221, Chemistry Review Date January 13, 1994)
***Final concentration of benzalkonium chloride = [redacted] g/spray

Comparability of Spray Devices:
(information on pp 108, and 166, vol. C1.1)

The design of the actuator used for the RLD Flonase® is proprietary to Galaxo. The pump and actuator for the RLD is manufactured from proprietary molds, according to [redacted] Roxane therefore requested from [redacted] ne closest available pump and actuator to the RLD Flonase® designs.

The pump used by Roxane, [redacted], has a comparable internal design according to [redacted] A drawing of the pump is included as Attachment A (page 168, vol. C1.1). b(4)

The polypropylene actuator provided to Roxane, CB 18, is a comparable actuator according to [redacted] A drawing of the pump is included as Attachment B (page 170, vol. C1.1).

The oblong amber glass bottle used for Flonase® is proprietary. Roxane's bottle, from [redacted] is a 15cc round amber type 1 glass bottle with a neck finish to accommodate a crimp-on nasal pump. The diptube length for the nasal device was

designed by Valois for these bottles. A drawing of the bottle is included as Attachment C (page 172, vol. C1.1)

Procedures and Information Applicable to All Tests (p 1145, vol. C1.3):

b(4)

provided data for all tests. Statistical analyses were performed by All actuations of the nasal spray products were done using a mechanical actuator to actuate the nasal sprays in a reproducible manner. The mechanical actuator used was a proprietary unit designed by or nasal spray actuation. The actuator operating conditions were as follows:

Force Rise Time:	[ ]
Min Travel Dist (mm)2	
Min Travel Time:	
Force Fall Time:	
Hold Time:	
Actuation Force:	

Unit dose (Single Actuation Content) and uniformity of unit dose

The RLD labeled number of full medication doses per bottle is 120 sprays. According to the patient's instruction leaflet for the reference listed drug (NDA 20-121, vol. 49.1, Feb 03, 2000), each unit is primed by wasting six actuations. The instructions further state that "if the pump is not used for 7 days, prime until a fine spray appears."

Based on the RLD labeling and the patient's instructions leaflet, the firm stated that actuation no. 7, is the first actuation following priming. Since no specific number of actuations was specified for re-priming, the bioequivalence of actuation no. 120 through 125 was examined (p 971, vol. C1.3).

For each test, ten (10) units from each of the three lots of the test product and each of the three lots of the reference product were tested. Therefore, for each test a total of 30 units of the test product and 30 units of the reference product were tested. The amount of drug per spray was determined by a validated HPLC analysis of LOQ=2.982 ng/mL (p 1147, vol. C1.3).

Note: information about RLD device/dosage form performance is provided on page 159, volume C1.1.

The single dose unit summary results were at the beginning (actuation 7) and end (actuation 126) of unit life. The following table provides a summary based on the reviewer's calculations.

Table I

UNIT DOSE (UNIT SPRAY CONTENT) DATA

PROD.	SECTOR	Mean*	Variability (%CV) Within-Lot	Between-lot	Total	T/R Arith Mean	Geo Mean	p
		(N = 30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
TEST	BEG	92.76	1.86-2.79	1.08	2.40	0.95	0.95	0.000000
	END	96.65	1.91-3.71	1.74	3.00	0.96	0.96	0.000054
REF	BEG	97.32	1.12-2.97	0.93	2.2			
	END	100.19	2.07-2.37	1.83	2.6			

- *The mean unit dose data are expressed % of label claim based on arithmetic means. Outcome of the statistical analysis remains the same whether the data are expressed as % LC or amount spray.*

Re-prime Data

Product	Actuation 120	Actuation 121	Actuation 122	Actuation 123	Actuation 124	Actuation 125
Test	78.72	95.58	95.30	95.91	96.40	96.41
Reference	79.41	96.30	97.89	99.81	99.41	99.83
T/R	0.99	0.99	0.97	0.96	0.97	0.97

Comments on the Single Actuation Content Data

1. For Roxane's Fluticasone Propionate Nasal Spray, 50 mcg, the geometric mean values at actuations 7 and 126 values are similar to the corresponding reference product values. The test product exhibited similar variability (%CV) as the reference product with regard to the unit dose data.

2. The test/ref ratios are within the 90-111% limits, used by DBE for acceptance of *in vitro* performance of solution nasal spray products.

3. Based on the mean values, there was no change in the unit dose determined at the beginning and end sectors. Furthermore, the data did not show a particular trend in changes in variability through the container life.

4. The firm also submitted priming data (Based on the April 2003 draft guidance, the priming profile is not necessary). The priming characteristics of the test product were same as that of the reference product. The test product delivers an equivalent amount on the first primed action (#7).

5. The re-prime data were based on sprays #120-125 following non-use for a period of 7 days. Based on the calculated data, the test and reference products have same prime retention characteristics.

Droplet size distribution

a. Laser Diffraction:

Droplet size determination was performed on 10 units from each of the 3 unit lots of test and reference products. Each unit was tested at beginning, middle, and end sectors of unit life. At each sector of unit life, each unit was actuated at three distances (3 cm, 5 cm, and 7 cm) relative to the Malvern laser beam. At each distance, measurements were taken at three delay times. The three delay times characterize three regions in the plume life based on % transmission:

Plume Region	Transmission Characteristic
Plume formation (Initial)	Drops
Fully formed plume (Middle)	Stable
Plume dissipation (End)	Rises

Representative spray time-history plots depicting the above regions were submitted (volumes C1.8, C1.9, and C1.10). Region of the fully formed plume was characterized by duration of the stabilized low transmission of laser light.

The three separate regions constitute the sampling areas on which the droplet size distribution data are based. The delay times representing these regions vary with the actuation distances. The firm submitted D10, D50, D90 and SPAN data. Based on the revised draft of the Nasal BA/BE guidance, bioequivalence evaluation is based only on D50 and SPAN data at the fully formed plume (Middle). A summary of these data based on the reviewer's calculations is given in Table II.

Table II
Droplet Size Distribution (D50 Data) – Test Product - Stable Plume

PROD.	Sector	Distance	Plume	Mean	Variability (%CV)			TEST/REF		p
					Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	
			Formation	(N = 30)	(N=10)	(N=3)	(N=30)	N=30	N=30	
		3	Middle	63.41	5.89-12.93	6.02	10.65	0.91	0.91	0.00157039
	BEG	5	Middle	53.22	6.33-7.42	9.99	15.22	0.93	0.94	0.16674714
		7	Middle	48.48	9.81-10.06	6.44	10.81	0.92	0.93	0.04802788
		3	Middle	57.18	7.99-13.18	5.86	12.04	0.93	0.93	0.04123891
TEST	MIDDLE	5	Middle	48.53	15.99-22.04	5.03	19.72	0.93	0.93	0.15397085

		7	Middle	44.76	6.42-13.04	4.09	9.93	0.91	0.92	0.02047953
		3	Middle	59.80	9.60-13.41	3.30	16.00	0.94	0.93	0.0183486
	END	5	Middle	50.27	10.87-21.90	9.03	17.51	0.92	0.92	0.07094935
		7	Middle	46.53	6.47-21.47	8.21	15.52	0.91	0.91	0.03090686

Droplet Size Distribution (D50 Data) – Reference Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
		3	Middle	70.03	9.81-9.14	3.15	9.52
	BEG	5	Middle	57.09	16.40-18.93	9.82	19.16
		7	Middle	52.50	12.59-14.78	10.29	15.67
		3	Middle	61.41	8.74-14.47	3.84	12.19
Ref	**MIDDLE**	5	Middle	52.18	11.82-16.66	12.51	17.43
		7	Middle	48.96	8.14-15.82	9.00	15.25
		3	Middle	63.92	11.18-15.04	2.30	8.05
	END	5	Middle	54.56	11.98-17.05	6.85	15.85
		7	Middle	51.37	12.35-18.69	8.46	17.05

Droplet Size Distribution (SPAN Data) – Test Product - Stable Plume

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean N=30	Geo Mean N=30	p
		3	Middle	1.73	2.47-3.96	2.17	3.60	1.01	1.01	0.2210396
	BEG	5	Middle	1.89	3.61-5.40	2.87	5.18	1.03	1.03	0.12165706
		7	Middle	1.84	3.21-6.07	1.81	4.81	1.00	1.00	0.902701
		3	Middle	1.77	2.79-4.49	2.13	3.86	1.02	1.02	0.0432934
TEST	**MIDDLE**	5	Middle	1.89	5.18-7.56	0.66	6.00	1.01	1.01	0.64423824
		7	Middle	1.84	6.05-7.58	3.17	7.19	0.99	0.99	0.53489945
		3	Middle	1.76	3.35-5.17	1.30	4.60	1.03	1.03	0.00989337
	END	5	Middle	1.89	5.47-6.27	2.17	6.01	1.00	1.01	0.8056939
		7	Middle	1.85	3.46-6.63	3.33	6.18	0.99	0.99	0.64131427

Droplet Size Distribution (SPAN Data) – Reference Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
Ref	BEG	3	Middle	1.71	3.45-4.49	1.66	4.01
		5	Middle	1.84	5.80-8.89	1.49	7.65
		7	Middle	1.84	3.85-7.55	0.95	5.38
	MIDDLE	3	Middle	1.73	2.56-5.35	1.44	4.07
		5	Middle	1.88	4.98-5.44	3.55	5.87
		7	Middle	1.86	2.72-9.52	1.45	6.44
	END	3	Middle	1.71	1.67-3.84	1.13	3.29
		5	Middle	1.88	6.73-9.23	3.05	8.56
		7	Middle	1.86	3.36-7.62	0.95	0.10

Comments on Droplet Size Distribution

1. The ratios of the test geometric means to the reference geometric means for the fully formed (stable) plume D50 for the three distances are within the 0.91-0.94 range. For most comparisons the P values were insignificant.

2. The ratios of the test geometric means to the reference geometric means for SPAN for the three distances are within 0.99-1.03 range. For most of the comparisons the P values were insignificant.

3. For D50 and SPAN, the within-lot variability, between lot variability and total variability for the test product are comparable to that of reference product.

4. Based on the mean values:

   - The D50 decreased with increase in distance between the actuator and laser beam.

   - For the test and the reference products, total variability of D50 was generally greater than that of the SPAN.

   - Based on the geometric mean data the T/R ratio for D50 and SPAN are within the 0.9-1.11 range, used hitherto by DBE for acceptance of *in vitro* performance of solution nasal spray products.

5. Based on these data, distribution of droplets in the test product spray is similar to that of the reference product spray.

Cascade impaction *(P 4508, vol. C1.10)*

The firm submitted the following data:

Collection #	Corresponding Stages	Aerodynamic Diameter (um)
Group 1	Entry Port, Cone, Stage 0	>9.0
Group 2	Stages 1 and 2	4.7 - 9.0
Group 3	Stages 3 to 7 and Filter	<4.7

The drug deposited on corresponding stages was determined by HPLC method. For the HPLC method, the limit of quantitation (LOQ) was 4.92 ng/mL (p 4518, vol. C1.10).

Ten units from each of the 3 unit lots of test and reference products were used to obtain cascade impaction data. Each unit was tested at the beginning and end of life. In each test ten actuations of the products were used.

The firm has not submitted the SOP for this test. The HPLC method for the assay of Fluticasone Propionate Nasal Spray, 50 ug/spray was validated for precision, accuracy, specificity, linearity and recovery (Vol 1.10, pages 4518-4548).

A summary of cascade impaction data based on the reviewer calculation is presented in the Table III.

Table III
Material in ug

PROD.	SECTOR	Mean(N=30)	Variability %CV) Within-Lot	Between-lot	Total	TEST/REF Arith Mean	Geo Mean	P
		Group 1	(N=10)	(N=3)	(N=30)	N=30	N=30	
				(>9.0 um)				
TEST	BEG	45.82	1.71-2.73	0.89	2.38	0.96	0.96	0.000000533697
	END	46.36	1.72-2.96	1.99	2.84	0.97	0.97	0.00000504616
REF	BEG	47.65	1.25-2.90	1.25	2.55			
	END	47.99	2.21-3.09	0.77	2.30			

PROD.	SECTOR	Mean(N=30)	Variability (%CV)			TEST/REF		
			Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	P
		Group 2	(N=10)	(N=3)	(N=30)	N=30	N=30	
			(<9.0 ->4.7 um)					
TEST	BEG	0.109	14.65-24.17	19.37	24.60	1.07	1.09	0.418852763
	END	0.142	18.26-21.27	14.14	22.53	1.137	1.169	0.092301632
REF	BEG	0.102	18.35-39.45	15.70	33.55			
	END	0.125	24.10-31.26	22.56	32.28			

PROD.	SECTOR	Mean(N=30)	Variability (%CV)			TEST/REF		
			Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	P
		Group 3	(N=10)	(N=3)	(N=30)	N=30	N=30	
				(<4.7 um)				
TEST	BEG	0.069	16.06-29.24	21.20	29.77	1.19	1.28	0.051554245
	END	0.091	19.41-23.02	9.90	22.68	1.22	1.27	0.004785453
REF	BEG	0.057	28.05-42.63	17.67	38.99			
	END	0.074	24.41-45.66	22.27	36.29			

Comment on Cascade Impaction Data:

1. The Cascade Impaction results indicated that the amount of drug deposed in droplets >9 um is similar between test and reference products. The test/ref ratios are within the 90-111% limits, used by DBE for acceptance of *in vitro* performance of solution nasal spray products.

2. The group 2 and 3 data were separately analyzed for both the beginning and end stages. However, the revised Draft Nasal BA/BE guidance issued on April 3, 2003, recommends pooling of data below the impactor stage 1. Based on that guidance, the Agency requests cascade impaction data for only the beginning stage. Therefore, the cascade impaction data were reanalyzed. Based on that analysis for the beginning stage group 2 and 3 pooled data, the test and reference arithmetic means were 0.089 and 0.080, respectively. The geometric mean values

were 0.178 and 0.160. The T/R ratios for the arithmetic and geometric means were 1.114 and 1.152, respectively. The ratio of the geometric mean is outside the acceptable limit of 0.90-1.11.

The cascade impactor data for group 2 and 3 showed considerable difference in variability between the test and reference products. These data were therefore analyzed using the Population Bioequivalence (PBE) Methodology outlined in the June 1999 draft guidance. These analyses utilized a $Sigma_{T0}$ of 0.10 and Epsilon of 0.01. The analyses were performed keeping Group 2 and 3 data separate as well as pooling these groups (as recommended in the April 2003 draft guidance). Greater variability of the reference RLD data warranted "the reference-scaled" analysis. The results indicated equivalent performance of test and reference products based on both the individual-group and the pooled data (SAS output on page 35).

3. However, the cascade impactor data are considered incomplete because the firm did not provide (1) the mass balance data for the cascade experiments and (2) SOP describing the conduct of experiment..

Spray Pattern

The firm submitted spray pattern data at three distances (3, 5 and 7 cm) from TLC plate at beginning life sectors for the test product and the reference products. It provided individual results of spray pattern determination in term of longest diameter (D_{max}), shortest diameter (D_{min}) and ovality ratio (D_{max}/D_{min}).

The firm provided color photocopies of corresponding TLC plates with markings indicating D_{max} and D_{min} (page 5911, Vol.1.13). The staining agent (phosphomolybdic acid) that reacts with drug was used to highlight the pattern of the TLC plate. Test Method No. M1-FP-SP.1 (Spray Pattern Determination for Fluticasone Propionate Nasal Spray 50 ug/spray) can be found in Vol. 1.13, page 5878.

The TLC plates were photographed, along with a ruler in the same focal plane, using the Pulnix digital camera. After saving the digital images, printouts were obtained using the same printer, paper media, and printing parameters. Using the printout, the maximum and minimum diameters (Dmax and Dmin) were determined by measuring directly with a caliper. The conversion factor was calculated by using the same caliper to measure the scale index on the digital image and dividing by the actual length (40 mm). The Dmax and Dmin values, when multiplied by this conversion factor gave the actual measurements of Dmax and Dmin as they exist on the original TLC plate (page 5884, vol. C1.13).

A summary of the spray pattern data based on the reviewer's calculations is presented in Table IV.

Table IV
Spray Pattern Data – Test Product

PROD.	Sector	Distance	Parameter	Mean	Variability (%CV)			TEST/REF		P
					Within-Lot	Between-lot	Total	Arith Mean	Geo Mean	
				(N = 30)	(N=10)	(N=3)	(N=30)	(N=30)	(N=30)	
		3	Long. Diam	27.96	5.25-14.76	3.33	10.07	1.04	1.04	0.13214397
		3	Short. Diam	24.81	2.69-14.83	4.29	9.91	1.04	1.04	0.13774264
		3	Oval. Ratio	1.13	3.37-8.00	1.68	5.68	1.00	1.00	0.93573428
		5	Long. Diam	38.74	12.22-16.75	6.86	15.68	1.04	1.04	0.37319714
TEST	BEG	5	Short. Diam	32.03	11.17-19.49	7.25	16.75	1.05	1.05	0.30406181
		5	Oval. Ratio	1.22	5.70-12.21	0.55	8.19	0.99	0.99	0.67923083
		7	Long. Diam	49.13	7.89-24.02	7.75	16.87	1.06	1.06	0.1416093
		7	Short. Diam	37.47	12.55-21.15	11.93	18.95	1.00	1.00	0.96933029
		7	Oval. Ratio	1.33	7.15-14.98	5.58	11.97	1.06	1.06	0.07210544

Spray Pattern Data – Reference Product

PROD.	Sector	Distance	Parameter	Mean	Variability (%CV)		
					Within-Lot	Between-lot	Total
				(N = 30)	(N=10)	(N=3)	(N=30)
		3	Long. Diam	26.82	8.79-13.43	2.08	10.65
		3	Short. Diam	23.81	8.43-11.71	1.83	9.88
		3	Oval. Ratio	1.13	5.01-13.06	3.97	9.37
		5	Long. Diam	37.31	11.55-17.53	9.45	15.57
Ref.	BEG	5	Short. Diam	30.54	9.18-18.11	9.85	16.39
		5	Oval. Ratio	1.23	8.58-12.92	1.99	10.89
		7	Long. Diam	46.36	13.03-16.14	13.35	18.24
		7	Short. Diam	37.53	16.46-22.26	7.89	19.33
		7	Oval. Ratio	1.25	4.99-17.45	7.16	13.95

1. The ratios of the test geometric means to the reference geometric means for D_{max} , D_{min} and Ovality were within 1.04-1.06, 1.00-1.05 and 0.99-1.06 range, respectively at the three distances. Test/ref ratios of geometric means are within the 90-111% limits used by DBE as an acceptance criteria for the solution nasal spray drug products.

2. Total variability in the three parameters was comparable between the test and reference products.

3. The spray pattern data are acceptable.

Plume Geometry

Plume geometry is described by two side views, at 90^{O} at each other and relative to the axis of the plume, of the aerosol cloud when actuated into space.

High-speed video capture the spray plume (Plume Geometry) for Fluticasone Propionate Nasal Spray, 50 ug/spray, method #M1-FP-PG.1, page 6713, Vol.1.15.

The test consisted of using 10 units from each product lot to obtain plume geometry measurements at three times after a single actuation, the beginning (Early) of the plume, the fully formed plume (Intermediate), and the dissipation plume (End). The parameters used to characterize plume geometry are plume length (height), plume width, and plume angle (spray cone angle). Photographs of the spray plumes used to measure the plume length, width and angle are shown in Volume 1.15, page 6744.

Plume geometry measurements: A ruler was placed in the same focal plane as the nozzle tip of the nasal spray unit before taking the photographs. All measurements were made directly on the raw data (the photograph). To convert the plume height and width of each spray, a 10 inch (254 mm) portion of the ruler in the photograph was measured first with a ruler. The measured value was then used to determined the conversion factor for further measurements (page 7021, vol. C1.15).

The plume geometry results calculated by the reviewer are shown in Table V.

The Draft Nasal BA/BE guidance issued on April 3, 2003, recommends measurements of plume fully developed and while the plume is still intact with the actuator. Of the three phases of plume studied by the sponsor, the early and intermediate phases represent delay times at which the plume is still intact with actuator. Therefore, the following tables include data for these two phases only.

Table V
Plume Geometry Data (Plume Length)

			Variability (%CV)			TEST/REF		
PROD.	**Plume Stage**	**Mean (N = 30)**	**Within-Lot (N=10)**	**Between-lot (N=3)**	**Total (N=30)**	**Arith Mean (N=30)**	**Geo Mean (N=30)**	**P**
			0-Degree View					
	Early	274.47	4.84-9.13	2.88	6.99	0.96	0.96	0.0387875
TEST	Intermed	320.99	3.83-7.55	5.88	7.52	0.94	0.94	0.0007205
	Early	286.01	6.45-9.09	5.38	8.67			
REF	Intermed	341.33	4.75-7.53	5.52	7.47			
			90-Degree View					
	Early	265.41	4.88-8.66	3.25	6.91	0.91	0.91	0.0000002095

TEST	Intermed	318.39	3.64-6.81	4.37	6.22	0.96	0.96	0.0007869
	Early	291.23	4.50-5.64	5.17	6.81			
REF	Intermed	333.31	4.40-7.34	6.24	7.62			

Plume Geometry Data (Plume Width)

			Variability	(%CV)		TEST/REF		
PROD.	**Plume**	**Mean**	**Within-Lot**	**Between-lot**	**Total**	**Arith Mean**	**Geo Mean**	**P**
	Stage	**(N = 30)**	**(N=10)**	**(N=3)**	**(N=30)**	**(N=30)**	**(N=30)**	
			0-Degree	**View**				
	Early	35.87	14.25-24.27	3.09	19.47	0.97	0.96	0.49928
TEST	Intermed	52.40	12.93-23.30	6.29	18.76	1.05	1.04	0.1751383
	Early	37.01	10.80-20.64	5.31	16.06			
REF	Intermed	49.92	8.88-13.68	11.66	14.96			
			90-Degree	**View**				
	Early	37.45	12.65-14.64	3.33	13.32	0.98	0.98	0.6340782
TEST	Intermed	52.76	14.10-20.71	1.02	16.27	1.02	1.04	0.6665178
	Early	38.28	11.49-24.86	17.76	23.98			
REF	Intermed	51.63	16.06-18.17	20.11	23.76			

Plume Geometry Data (Plume Angle)

			Variability	(%CV)		TEST/REF		
PROD.	**Plume**	**Mean**	**Within-Lot**	**Between-lot**	**Total**	**Arith Mean**	**Geo Mean**	**P**
	Stage	**(N = 30)**	**(N=10)**	**(N=3)**	**(N=30)**	**(N=30)**	**(N=30)**	
			0-Degree	**View**				
	Early	28.23	11.84-19.82	3.10	16.20	0.98	0.99	0.7198203
TEST	Intermed	35.87	10.13-16.61	3.97	14.22	1.05	1.05	0.2544979
REF	Early	28.80	15.27-25.97	13.89	23.41			
	Intermed	34.20	7.71-18.33	12.81	17.83			
			90-Degree	**View**				
	Early	30.03	16.33-18.95	8.01	17.36	1.01	1.03	0.8248565
TEST	Intermed	35.48	10.37-19.17	8.33	16.64	1.00	1.01	0.9764088
	Early	29.67	13.40-30.09	17.86	27.58			
REF	Intermed	35.43	16.97-21.31	15.18	22.67			

Comments on Plume Geometry Data:

1. The mean values and variability (%CV) for angle, length and width for both views and the two plume stages are summarized in the Table above.

2. For angle, length and width, the means are comparable between the test and reference formulations. The overall variability for the test and reference products is similar for the three parameters and geometric mean ratios ranged from 0.91 to 1.05, which are within the acceptable limits of 0.9-1.11..

3. Plume Geometry Data are acceptable.

III. IN VIVO BIOEQUIVALENCE TESTING

The application contains two systemic exposure (pharmacokinetic) studies and a clinical endpoint study. This review contains information regarding the pharmacokinetic studies; and the clinical end point study is under review with the OGD medical officer.

Contents of the In Vivo study Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	2
Single-dose fed	No	
Steady-state	No	
Failed Studies	Yes	1

Pre-Study Bioanalytical Method Validation (Pre-Study, page 612, Vol. A2.2)

Number of analytes	1
Analyte name	fluticasone (parent)
Internal Standard	[redacted]
Method description	LC/MS/MS
QC range	15.0, 35.0, 75.0 png/mL (p 623, Vol. A2.2)
Standard curve range	5.0 to 100 pg/mL
Limit of quantitation	5.0 pg/mL
Average recovery of Drug (%)	59
Average Recovery of Int. Std (%)	50
Intraday precision range (%)	4.0 to 6.9
Intraday accuracy range (%)	95.3 to 98.2
Interday precision range (%)	7.0 to 10.4
Interday accuracy range (%)	90.4 to 94.30
Bench-top stability (hrs)	27
Stock stability (days)	218 hours
Processed stability (hrs)	198
Freeze-thaw stability (cycles)	6
Long-term storage stability (days)	371 days at -20^{O}C (p629, v A2.2)
Dilution integrity	N/A
Specificity	Yes
SOPs submitted	Not given
Bioanalytical method is acceptable	Yes
20% Chromatograms included	Yes

1. Single-dose Fasting Bioequivalence Study (Protocol #451-05)

Study Summary	
Study No.	451-05
Study Design	Two-treatment, four-period, two-sequence replicate design
No. of subjects enrolled	80
No. of subjects completing	78
No. of subjects analyzed	73
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 44 Female: 36
Test product	Roxane's Fluticasone Propionate Nasal Spray, 50 mcg (50 mcg/spray)
Reference product	GlaxoSmithKline's Flonase® Nasal Spray, 50 mcg (50 mcg/spray)
Strength tested	50 mcg/spray
Dose	800 mcg (400 mcg in each nostril. Eight actuations, one every 5 minutes)

Summary of Statistical Analysis (#451-05)
(Least Square Geometric Means and 90% Confidence Intervals)

Parameter	All subjects[1]		All subjects[1] (Subj #2,8,9,12,24 excluded)		Group 1 (subj 1-40)		**Group 2 (subjects 41-80)**	
	Point Estimate	90% CI	Point Estimate	90% CI	Point Estimate	90% CI	Point Estimate	**90% CI**
Ln Cmax (pg/mL)	111.8	106.3-117.5	109.6	104.1-115.3	115.1	106.9-123.9	**108.3**	**100.2-116.9**
Ln AUC0-t	117.6	109.2-126.6	112.6	104.6-121.1	128.7	115.4-143.6	**107.5**	**97.3-118.7**
Ln AUCi	113.9	104.8-123.9	108.9	100.5-117.9	123.1	106.0-142.8	**107.6**	**97.5-118.8**

[1] group*treatment term is included in the model

Reanalysis of Study Samples (#451-05):
(info pp 663 and 694, vol. A2.2)

The total number of assayed samples in this study is 5957 samples. Of the 5957 samples, a total of 546 (9.2%) samples were assayed for analytical conformation. Of these repeated samples, 81.9% (447 samples) confirmed the initial assay value within ± 20% (per MDSPS SOP 03.01.042). Of the 546 samples, a total of 23 (test = 11, ref = 12) samples were analyzed for PK reasons (differ from the initial vlaue by ± 20%). The reassayed values for these 23 samples were used as reported values.
The 23 samples represent 0.38% of total samples. The use of re-assay values did not influence the outcome of the study.

Comments on Fasting Study (#451-05): Eighty subjects received 800 mcg doses of each formulation. For logistical purposes, subjects were divided into two dosing groups of 40 subjects each. The study groups (Group 1: subjects 1-40; Group 2: subjects 41-80) were dosed on separate study periods. Therefore, the DBE considers the two groups as two separate study groups. Consequently, the data from the two groups were separately evaluated for BE evaluation. Based on group 2 data, the 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCt, AUCi, and Cmax for fluticasone. Therefore, the systemic exposure study is acceptable. However, the application is incomplete due the deficiency cited below.

2. Single-dose Non-Fasted Bioequivalence Study (Protocol #451-03)

This is a failed BE study and was submitted at the request of the DBE (Information on page 17354, C1.37).

Study No.	451-03
Study Design	Two-treatment, four-period, two-sequence replicate design
No. of subjects enrolled	28
No. of subjects completing	28
No. of subjects analyzed	28
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 9 Female: 19
Test product	Roxane's Fluticasone Propionate Nasal Spray, 50 mcg (50 mcg/spray)
Reference product	GlaxoSmithKline's Flonase® Nasal Spray, 50 mcg (50 mcg/spray)
Strength tested	50 mcg/spray
Dose	800 mcg (400 mcg in each nostril. Eight actuations, one every 5 minutes)

Summary of Statistical Analysis (#451-03)

Summary of Statistical Analysis (see p 17393, vol. C1.37) Additional Information in Appendix,		
Parameter	Point Estimate	90% Confidence Interval
AUC0-t	155.0	130.2 - 184.4
AUC∞	126.5	112.2 - 142.6
Cmax	142.9	128.9 - 158.5

Comments on second fasting study: This is a failed BE study. The firm provided the study for information only as requested by the DBE.

IV. Appendix

1. Single-dose Fasting Bioequivalence Study (#451-05)

Study Information

Study Number	451-05, project #AA00138
Clinical Site	[redacted]
Principal Investigator	[redacted] p 13, vol. A2.1)
Study/Dosing Dates	Group-1 (Period-1: 03/30/02, Period-2: 04/06/02, Period-3: 04/13/02, Period-4: 04/20/02 Group-2 (Period-1: 03/31/02, Period-2: 04/07/02, Period-3: 04/14, Period-4: 04/21/02), (info on p 277, vol A2.1)
Analytical Site	[redacted]
Analytical Director	[redacted] n.D. (p 14, vol. A2.1)
Analysis Dates	Not given
Statistical Analysis	[redacted] p 100, vol. C1.1)
Storage Period	Not give

b(4)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Roxane's Fluticasone Propionate Nasal Spray	GlaxoSmithKline's Flonase® Nasal Spray
Manufacturer	Roxane Laboratories, Inc.	Glaxo Wellcome, Inc.
Batch/Lot No.	091032A (p 304, vol. A2.1)	C049983 (p 304, vol. A2.1)
Manufacture Date	July, 11, 2001 (p 304, vol. A2.1)	N/A
Expiration Date	N/A	October 2003 (p 304, vol. A2.1)
Strength	50 mcg	50 mcg
Dosage Form	Nasal spray	Nasal spray
Dose Administered	Eight (8) 50 mcg sprays per nostril. 1 every 5 minutes for 35 minutes.	Eight (8) 50 mcg sprays per nostril. 1 every 5 minutes for 35 minutes.
Total Dose Administered	*800 mcg intranasal dose.	*800 mcg intranasal dose.
Route of Administration	Nasal	Nasal

* The April 2003 draft Nasal BA/BE Guidance recommends the use of doses which do not exceed the maximum labeled dose. The dose administered in this study exceeds the maximum labeled dose. However, it is acceptable because the study was based on the June 1999 draft Nasal BA/BE Guidance, which permitted the use of doses exceeding the labeled dose. In this regard, it is also noted that in an August 29, 2000 meeting with the OGD the firm was encouraged to (1) use a dose greater than the labeled dose, and (2) administer the successive actuations at time intervals used in this study.

No. of Sequences	2
No. of Periods	4
No. of Treatments	2
Group	Group 1 (subject #1-40), Group 2 (subject #41-80)
Balanced	Yes
Washout Period	7-day (p 13458, vol. C1.29)
Randomization Scheme	Yes (p 277, vol. A2.1)
Blood Sampling Times	0, 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours
Blood Volume Collected/Sample	2 X 4 mL
Blood Sampling Processing/Storage	In EDTA vacutainers, plasma separated after centrifuging, and stored at -20°C
IRB Approval	Yes on 03/15/02 (p 13458, vol. C1.29)
Informed Consent	Yes (p 252, vol. A2.1)
Subjects Demographics	Yes (p 13473, vol. C1.29)
Length of Fasting	Subject received a standard meal within 45 minutes prior to initiation of dosing. Thereafter, lunch, dinner, and evening snacks were at 4.5, 9.5, 13 hours post-dosing, respectively. (p 13459, vol. C1.29)
Length of Confinement	24 hours
Safety Monitoring	Vital signs (sitting blood pressure and heart rate) measured prior to dosing and at completion of the study.

Table 1. Demographics of Study Subjects (p 13473, vol. C1.29)

Age		Weight (lb)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	88
Mean	33	Mean	157.7	18-40		Male	45	Afr. Amer.	3
SD	12	SD	24.9	41-64		Female	55	Hispanic	3
Range	19-55	Range	100-213	65-75				Asian	4
				>75				Others	2

Study Results

Table 2. Dropout Information (pages 1-22, vol. A2.1).

Subject No	#2, 8, 9, 12	#68 and 78
Reason	Subjects #2, 8, 9, 12, and 24 were excluded from the statistical analysis due higher ratios (i.e. > 2) for AUCt than the subjects in Dosing Group 1 and 2.	Subjects #68 and 78 withdrew from the study after first dosing, period-1, test treatment; and period-1, reference treatment, respectively.
Replacement	No	No

Was there a difference in side effects for the test versus the reference? No

Table 3. Study Adverse Events (page 274, vol. A2.1)

Adverse Events	# in Test Group	# in Reference Group
Headache	2	7
Soft tissue injury to left foot or right thumb	1	1
Nausea	1	0
Lightheaded	1	1
Sinus congestion	0	1
Stomach cramps	0	1
Loose stool	0	1
Dry lips	0	1
Insomnia	1	1
Generalized itching	2	0
Nose bleed	0	1
Rough skin left neck area	1	0
Itching at left neck area	1	0
Brownish colored skin on left neck area	1	0
# of events	11	15

Comments: No serious adverse events were reported. The reported adverse events are not likely to compromise the integrity of study.

Table 4. Protocol Deviations (pages 306 and 308, volume A2.1)

Deviations in blood sampling times were reported and other deviations were with the use concomitant medications. The PK analysis was based on actual sample times. The reported deviations are unlikely to impact the outcome of the study

Table 5. Assay Validation – Within Study (p 745, 750, 757, vol. A2.2)

	Parent
QC Conc. (pg/mL)	15.00, 35.00, and 75.00
Inter day Precision (%CV)	8.15 - 10.78
Inter day Accuracy (%)	93.40 - 94.07
Cal. Standards Conc. (pg/mL)	5.00 - 100.00 pg/mL
Inter day Precision (%CV)	3.56 - 8.02
Inter day Accuracy (%)	97.60 - 104.18
Linearity Range (range of R^2 values)	0.994507 - 0.999536

Chromatograms: Any interfering peaks? No

Table 6. SOP's dealing with analytical repeats of study samples

The SOP was not submitted in the application (see deficiency section).

Comments on repeat assays. See repeated assay section above.

Comments on Within-Study Validation: Incomplete.

Conclusion: The analytical method is incomplete due to deficiency comments cited in the deficiency section.

Table 7. Fluticasone Pharmacokinetic Parameters (Arithmetic Mean and CV%) (Study #451-05, all subjects).

PK Parameter	Test Treatment				Reference Treatment			
	Replicate 1		Replicate 2		Replicate 1		Replicate 2	
	Mean	CV%	Mean	CV%	Mean	CV%	Mean	CV%
Cmax	28.13	40.29	28.32	31.27	26.02	60.26	24.04	47.84
AUC0-t	137.7	66.85	146.1	58.36	111.2	66.38	109.3	79.63
AUCi	169.4	64.15	170.3	57.71	145.8	58.78	145.8	70.64
Tmax	1.43	36.2	1.88	144	2.07	142	2.17	175
T1/2	4.51	54.8	4.60	54.8	4.47	64.8	4.41	75.6
Kel	0.207	56.9	0.202	64.3	0.223	61.2	0.249	64.8

MEAN1=Test, MEAN2=Reference
UNIT: AUC=PG.HR/ML CMAX=PG/ML, KE=hrs^{-1} , THALF=hrs, TMAX=hrs

Table 8. Least Square Geometric - Point Estimate and 90% Confidence Intervals (Study #451-05)

Parameter	All subjects[1]		All subjects[1] (Subj #2,8,9,12,24 excluded)		Group 1 (subj 1-40)		**Group 2 (subjects 41-80)**	
	Point Estimate	90% CI	Point Estimate	90% CI	Point Estimate	90% CI	**Point Estimate**	**90% CI**
Ln Cmax (pg/mL)	111.8	106.3-117.5	109.6	104.1-115.3	115.1	106.9-123.9	**108.3**	**100.2-116.9**
Ln AUC0-t	117.6	109.2-126.6	112.6	104.6-121.1	128.7	115.4-143.6	**107.5**	**97.3-118.7**
Ln AUCi	113.9	104.8-123.9	108.9	100.5-117.9	123.1	106.0-142.8	**107.6**	**97.5-118.8**

[1] group*treatment term is included in the model

NOTE:

Dr. Helen Li (Statistician at OGD) and the reviewer verified the accuracy of the data, and performed the analysis of variance on each pharmacokinetic parameter using SAS PROC

MIX procedure. An analysis of variance (ANOVA) was applied to log-transformed and non-transformed bioequivalence parameters to determine any statistically significant ($p<0.05$) differences between the drug formulations. The 90% confidence intervals were calculated for each bioequivalence parameter.

The reviewer calculation compares the mean plasma data of the test product replicate 1 and 2 v.s. the reference product replicate 1 and 2. The firm presented the plasma data in four sets, test product replicate 1, test product replicate 2, reference product replicate 1, and reference product replicate 2 (data are presented on pages 82-101, volume A2.1).

For calculation of AUC_{0-t} PK studies on fluticasone propionate nasal sprays, the FDA has recently provided the following recommendation.

The AUC_{0-t} 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 (BLOQ) 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 Group 2 plasma concentration data were examined to apply the above recommendation. Of the 160 plasma concentration profile comprising that group, only nine profiles showed one or more concentration beyond the first zero. The subject number and treatment designations for those profiles are 43(A), 52 (B), 52 (B), 57 (A), 63 (A), 66 (B), 68 (A), 74 (B), 74 (A), and 80 (B).

The AUC_{0-t} values for these profiles were calculated according to the above recommendation, and these analyses did not change the outcome of the study. The 90% confidence intervals remained with the acceptable range of 80-125% with or without AUC_{0-t} truncation at the first zero value specified in the above recommendation.

Comments: (on pharmacokinetic analysis)

- Ke and AUCi were determined for 108 runs out of 320 runs.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as Tmax: None
  c. first measurable drug concentration as Cmax: None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Are the 90% confidence intervals for AUCt, AUCi, Cmax within the acceptable limits of 80-125%. No for Group-1, Yes for Group-2, and No for all subjects without exclusion (see the table above).
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect. No group effect.

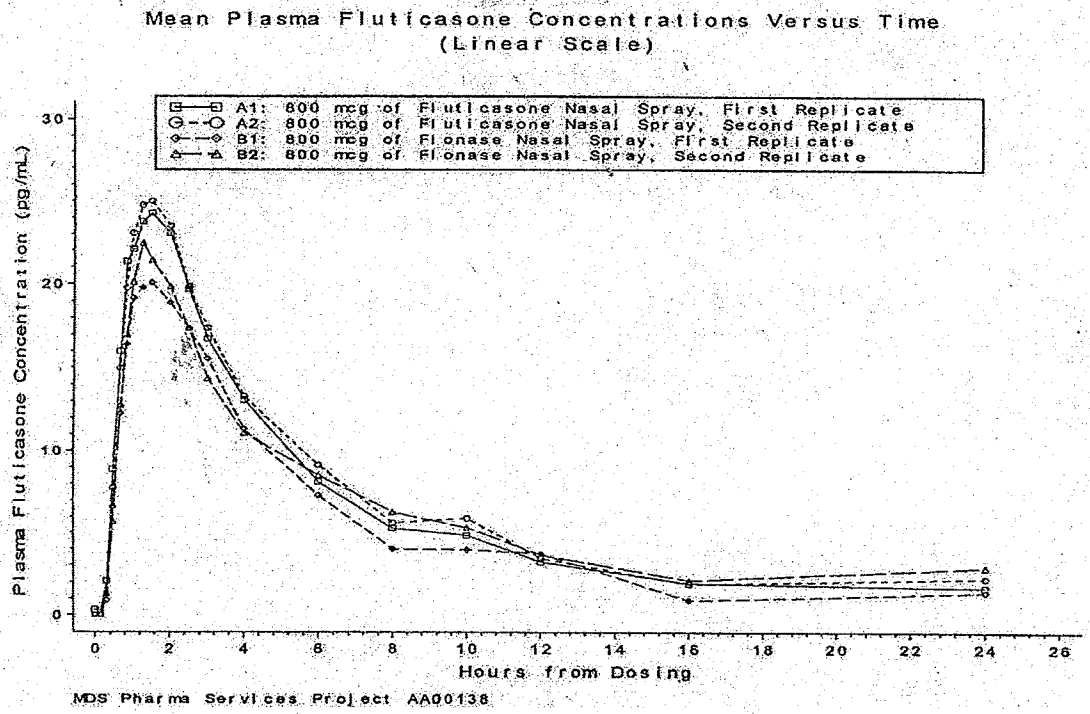
Comments on Fasting Study (#451-05): The DBE has decided that the BE evaluation should be based on group 2 (subjects 41-80). The 90% confidence intervals for group 2 are within the acceptable range of 80-125% for log-transformed AUCt, AUCi, and Cmax for fluticasone. However, the application is incomplete due the deficiency cited in the deficiency section.

Table 9. Mean Plasma Fluticasone Concentrations (pg/mL) vs Time (Study #451-05, all subjects)
(information in volume A2.1)

Time (hr)	Test Treatment				Reference Treatment			
	Replicate 1		Replicate 2		Replicate 1		Replicate 2	
	Mean	STD	Mean	STD	Mean	STD	Mean	STD
0	0.03	2.04	0.00	0.00	0.00	0.00	0.00	0.00
0.167	0.25	1.25	0.00	0.00	0.00	0.00	0.00	0.00
0.333	2.05	3.87	2.03	3.60	0.86	2.43	1.30	3.48
0.5	8.85	7.53	7.73	6.26	6.58	5.85	5.68	6.35
0.667	15.96	8.33	14.93	7.79	12.26	6.86	12.79	8.01
0.833	21.29	12.17	19.72	8.51	16.39	7.39	17.02	9.10
1	22/07	8.79	23.03	8.84	19.15	8.74	20.11	10.05
1.25	23.76	9.65	24.74	8.71	19.74	7.80	22.46	10.39
1.5	24.26	9.57	24.99	7.40	20.04	8.01	21.38	8.78
2	23.03	9.45	23.49	7.76	18.88	8.40	19.81	7.71
2.5	19.68	9.53	19.82	6.89	17.35	9.95	17.36	8.28
3	16.74	8.78	17.39	6.07	15.53	11.84	14.34	6.10
4	13.07	8.68	13.28	6.26	11.30	7.19	11.07	6.44
6	8.09	5.83	9.09	6.40	7.28	7.66	8.48	6.55
8	5.25	4.71	5.61	5.12	3.97	4.25	6.27	7.25
10	4.82	5.19	5.90	5.99	3.92	4.75	5.31	5.85
12	3.17	4.02	3.39	4.86	3.67	12.04	3.59	5.07
16	1.90	3.28	1.84	3.51	0.87	2.37	2.07	3.44
24	1.64	3.34	2.21	4.66	1.36	3.56	2.86	5.26

Figure 1. Table Mean Plasma Fluticasone Concentrations Versus Time (study #451-05)

Roxane Laboratories, Inc.
Fluticasone Propionate, Protocol 451-05
MDS Pharma Services Project AA00138
Report Addendum May 2003



2. Single-dose Fasting Bioequivalence Study (Study #451-03) (This is a failed study. The firm submitted the study as requested by DBE)

Study Information (p 17354, vol. C1.37)

Study Number	451-03
Clinical Site	
Principal Investigator	
Study/Dosing Dates	Period-1: 11/03/01, Period-2: 11/10/01, Period-3: 11/17/01, Period-4: 11/24/01 (info on p 17505, vol C1.37)
Analytical Site	
Analytical Director	
Analysis Dates	Not given
Statistical Analysis	
Storage Period	Not give

b(4)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Roxane's Fluticasone Propionate Nasal Spray	GlaxoSmithKline's Flonase® Nasal Spray
Manufacturer	Roxane Laboratories, Inc.	Glaxo Wellcome, Inc.
Batch/Lot No.	091032A (p 304, vol. A2.1)	OH704 (p 17388, vol. C1.37)
Manufacture Date	July, 11, 2001 (p 304, vol. A2.1)	N/A
Expiration Date	N/A	August 2002 (p 17388, vol. C1.37)
Strength	50 mcg	50 mcg
Dosage Form	Nasal spray	Nasal spray
Batch Size (units)	Not given	
Production size	Not given	
Potency (%)	Not given	
Content Uniformity (%)	Not given	
Dose Administered	Eight (8) 50 mcg sprays per nostril. 1 every 5 minutes for 35 minutes.	Eight (8) 50 mcg sprays per nostril. 1 every 5 minutes for 35 minutes.
Total Dose Administered	800 mcg intranasal dose.	800 mcg intranasal dose.
Route of Administration	Nasal	nasal

No. of Sequences	2
No. of Periods	4
No. of Treatments	2
Group	
Balanced	Yes
Washout Period	7-day (p 17386, C1.37)
Randomization Scheme	Yes (p 17505, vol. C1.37)

Blood Sampling Times	0, 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours
Blood Volume Collected/Sample	2 X 4 mL
Blood Sampling Processing/Storage	In EDTA vacutainers, plasma separated after centrifuging, and stored at -20°C
IRB Approval	Yes on 10/09/2001 (p 17386, vol. C1.37)
Informed Consent	Yes (p 252, vol. A2.1)
Subjects Demographics	Yes (p 13473, vol. C1.29)
Length of Fasting	Subject received a standard meal within 30 minutes prior to initiation of dosing. Thereafter, lunch, dinner, and evening snack were at 4.5, 9.5, 13 hours post-dosing, respectively.
Length of Confinement	24 hours
Safety Monitoring	Vital signs (sitting blood pressure and heart rate) measured prior to dosing and at completion of the study.

Table 10. Demographics of Study Subjects

Age		Weight (lb)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	89
Mean	30	Mean	147.8	18-40	79	Male	32	Afr. Amer.	7
SD	11	SD	26.6	41-64	22	Female	68	Hispanic	0
Range	19-55	Range	105-208	65-75	0			Asian	4
				>75	0			Others	0

Study Results

Table 11. Dropout Information: None

Was there a difference in side effects for the test versus the reference? No

Table 12. Study Adverse Events (p 17503, vol. C1.37)

Adverse Events	# in Test Group	# in Reference Group
Total:	10	18

Comments: No serious adverse events were reported. The reported adverse events are not likely to compromise he integrity of study.

Table 13. Protocol Deviations

Some deviations in blood sampling times are listed on p 17398, C1.37. The PK analysis was based on actual sample times. The reported deviations are unlikely to impact the outcome of the study

Table 14. Assay Validation – Within Study (p 17654, 17656, 17658, vol. C1.38)

	Parent
QC Conc. (pg/mL)	15.00, 35.00, and 75.00
Inter day Precision (%CV)	7.19 - 9.16
Inter day Accuracy (%)	94.86 - 95.88
Cal. Standards Conc. (pg/mL)	5.00 - 100.00 pg/mL
Inter day Precision (%CV)	4.74 - 7.83
Inter day Accuracy (%)	97.06 - 102.12
Linearity Range (range of R^2 values)	0.997169

Chromatograms: Any interfering peaks? No

Table 15. SOP's dealing with analytical repeats of study samples:
The SOP was not submitted in the application.

Comments on repeat assays. See repeated assay section above.

Comments on Within-Study Validation: acceptable.

Conclusion: The analytical method information is incomplete. However, no deficiency will be stated for this study.

Table 16. Fluticasone Pharmacokinetic Parameters (Arithmetic Mean and CV%)
(information on page 17393, volume C1.37)

PK parameter	Test Product		Reference Product	
	Mean	SD	Mean	SD
Cmax	26.90	17.73	17.33	5.71
AUC0-t	97.15	62.58	62.34	47.64
AUCi	114.95	62.83	100.17	79.76
Tmax	2.31	2.49	1.50	0.52
T1/2	2.97	1.66	4.28	6.76
Kel	0.30	0.15	0.29	0.17

MEAN1=Test, MEAN2=Reference
UNIT: AUC=PG.HR/ML CMAX=PG/ML, KE=hrs^{-1} , THALF=hrs, TMAX=hrs

Table 17. Least Square Geometric Means and 90% Confidence Intervals

Summary of Statistical Analysis (see p 17393, vol. C1.37)		
Parameter	Point Estimate	90% Confidence Interval
AUC0-t	155.0	130.2 - 184.4
AUC∞	126.5	112.2 - 142.6
Cmax	142.9	128.9 - 158.5

Comments on second fasting study: This is a failed BE study. The firm provided the study for information only, as requested by the DBE.

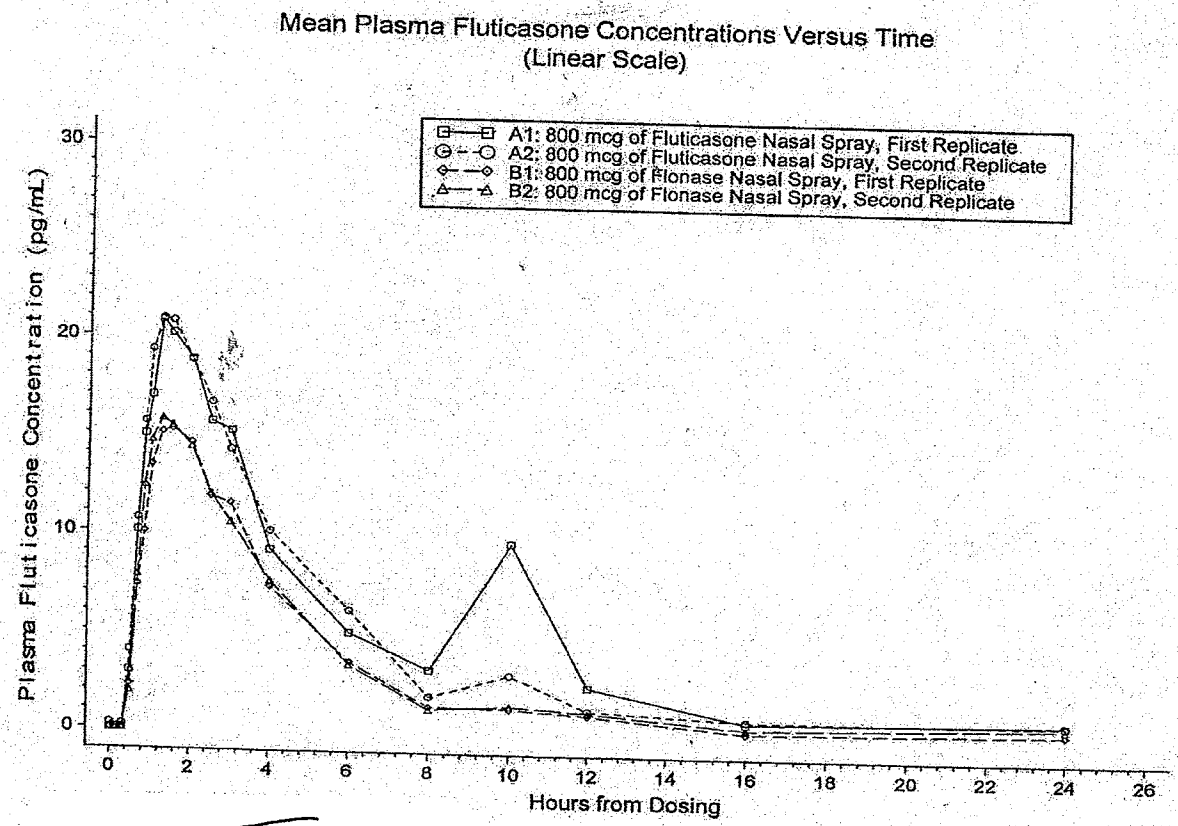
Table 18. Mean Plasma Fluticasone Concentrations (pg/mL) vs Time
For all subjects (Study #451-03)
(information on p 17402, volume C1.37)

Time (hr)	Test Treatment				Reference Treatment			
	Replicate 1		Replicate 2		Replicate 1		Replicate 2	
	Mean	STD	Mean	STD	Mean	STD	Mean	STD
0	0.00	0.00	0.24	1.26	0.00	0.00	0.00	0.00
0.167	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.333	0.00	0.00	0.19	1.01	0.00	0.00	0.00	0.00
0.5	2.95	3.95	3.99	4.61	2.23	3.42	1.91	3.44
0.667	10.05	6.63	10.70	6.40	7.32	5.74	7.84	4.69
0.833	14.96	6.83	15.60	7.14	9.98	5.67	12.37	6.62
1	16.95	5.64	19.31	8.04	13.41	5.26	14.67	5.43
1.25	20.80	7.98	20.89	7.45	15.06	4.40	15.76	6.63
1.5	20.17	7.20	20.79	7.08	15.24	4.46	15.41	6.16
2	18.82	6.92	18.80	8.30	14.55	3.92	14.36	6.66
2.5	15.66	7.13	16.65	7.67	11.85	4.21	11.99	6.04
3	15.18	7.55	14.24	7.60	11.52	5.09	10.55	5.74
4	9.17	6.59	10.12	6.82	7.33	4.28	7.61	5.39
6	5.03	4.39	6.17	5.75	3.56	4.02	3.42	4.28
8	3.22	4.31	1.86	3.47	1.33	2.61	1.19	2.62
10	9.66	27.67	3.01	6.98	1.27	2.50	1.42	3.16
12	2.46	6.92	1.25	2.46	1.01	2.22	1.14	3.09
16	0.75	2.26	0.86	2.84	0.25	1.32	0.46	1.70
24	0.92	2.71	0.86	2.86	0.43	1.56	0.75	2.22

Figure 2. Mean Plasma Fluticasone Concentrations Versus Time (study #451-03)

Roxane Laboratories, Inc.
Fluticasone, Protocol 451-03

b(4)



b(4)

Deficiencies:

In Vitro Section

1. The firm did not provide a hard copy of the in vitro data that were submitted on August 28, 2003. The requested copy should include the raw data, and calculations of all in vitro tests as outlined in the June 1999 draft Nasal BA/BE guidance.

2. The firm did not provide a description of the conduct of the cascade impaction studies. The firm should provide the relevant SOP and include information regarding (a) number of actuation used in each test, (2) operating conditions, (c) type of the atomization chamber used, and (d) data including the mass balance estimates.

2. The standard operation procedure (SOPs) of all in vitro tests that were included in the submission should be provided.

In Vivo Section (PK Study)

3 Assay validation information on fluticasone stock stability data is requested. The mean value for study sample set, range (minimum and maximum), precision (%CV), accuracy (%), and number of samples, should be provided.

4. The firm mentioned in the analytical section only the following information "per ——— 3.01.042" without any details (see p 663, vol. A2.2).The SOP for describing the analytical method (sample acceptance and rejection criteria) for the two BE studies (#451-05 and #451-03) was not provided in the submission. The SOP number, date of SOP approved, and SOP title should be also included. b(4)

5. The firm mentioned that some reassayed samples were reanalyzed "per client requested criteria", (for more information see pages 695, volume A2.2). The firm is requested to provide the rational for establishing these criteria, as well as the date (s) for establishing it.

6. The dates of analytical assay (from the first sample to last sample analyzed) of each study (#451-05 and #451-03) should be provided.

7. The expiration dates of the RLD lots # OH704, CO19943, and CO35879, were not provided in the submission.

Recommendations:

The in vitro and in vivo performance data submitted by Roxane Laboratories, Inc. for its Fluticasone Propionate Nasal Spray, 50 µg/spray is incomplete due to the deficiencies cited above.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D. Date:
Review Branch III
Division of Bioequivalence

RD INITIALLED
FT INITIALLED GJP SINGH_____ Date: 11-24-03

Concur: Barbara M Davit Date: 11/24/03
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

SAS Output

Study (pivotal)	Data (Plasma)	Data (PK parameters)	SAS Code	SAS Output
#451-05	 ft76504study45105bl.dat	 Ft76504study45105pk.dat	 ft76504study45105pk.txt	 ft76504study45105pk.txt

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

Cascade Impaction - Group: 2 and 3 comb, Stage: 1

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.6281
	CI:	-0.3587
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.1436
	CI:	0.0014
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	0.07	Mean:	0.05	Ratio:	127.85
				90% CI for ratio:		(107.7,151.7)
(log scale)	Mean:	-2.71	Mean:	-2.96	Diff:	0.25
(log scale)	CV:	-9.70	CV:	-16.62		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.263	SigmaR:	0.492	Ratio:	0.535

Class Levels (total number bottles = 57; number of sectors = 1):

Class Level Information for Input Dataset Cascade Impaction - Group: 2 and 3 com
By Product

Product	Class	Levels	Values
REF	treatment	1	REF
	container	29	1 2 5 7 9 11 15 16 20 25 33 37 40 44 64 71 77 113 124 148 154 155 160 163 164 168 169 176 178
	lot	3	C019943 C035879 C049983
TEST	treatment	1	TEST
	container	30	4 5 8 10 12 18 24 26 33 38 48 49 58 65 75 76 79 84 86 87 93 96 98 103 112 118 126 133 134 141
	lot	3	019032A 019033A 019034A

Listing of Raw Data for Cascade Impaction - Group: 2 and 3 comb, Stage: 1

Obs	lot	container	group(2+3)	ci	stage	treatment	metric	retvar
1	C019943	1	3	0.13	1	REF	-2.99573	0.08
2	C019943	7	3	0.20	1	REF	-2.65926	0.13
3	C019943	11	3	0.24	1	REF	-2.40795	0.15
4	C019943	15	3	0.27	1	REF	-2.40795	0.18
5	C019943	16	3	0.17	1	REF	-2.81341	0.11
6	C019943	20	3	0.17	1	REF	-2.81341	0.11
7	C019943	25	3	0.11	1	REF	-3.21888	0.07
8	C019943	33	3	0.05	1	REF	-4.60517	0.04
9	C019943	37	3	0.28	1	REF	-2.40795	0.19
10	C019943	40	3	0.19	1	REF	-2.65926	0.12
11	C035879	148	3	0.13	1	REF	-3.21888	0.09
12	C035879	154	3	0.16	1	REF	-2.81341	0.10
13	C035879	155	3	0.17	1	REF	-2.81341	0.11
14	C035879	160	3	0.22	1	REF	-2.40795	0.13
15	C035879	163	3	0.20	1	REF	-2.52573	0.12
16	C035879	164	3	0.16	1	REF	-2.65926	0.09
17	C035879	168	3	0.18	1	REF	-2.65926	0.11
18	C035879	169	3	0.10	1	REF	-3.50656	0.07
19	C035879	176	3	0.13	1	REF	-2.99573	0.08
20	C035879	178	3	0.17	1	REF	-2.65926	0.10
21	C049983	2	3	0.15	1	REF	-2.81341	0.09
22	C049983	5	3	0.11	1	REF	-3.21888	0.07
23	C049983	9	3	0.13	1	REF	-3.21888	0.09
24	C049983	11	3	0.19	1	REF	-2.65926	0.12
25	C049983	44	3	0.12	1	REF	-3.21888	0.08
26	C049983	64	3	0.10	1	REF	-3.50656	0.07
27	C049983	71	3	0.17	1	REF	-2.81341	0.11
28	C049983	77	3	0.08	1	REF	-3.91202	0.06
29	C049983	113	3	0.09	1	REF	-3.50656	0.06
30	C049983	124	3	0.20	1	REF	-2.65926	0.13
31	019032A	4	3	0.21	1	TEST	-2.65926	0.14
32	019032A	12	3	0.16	1	TEST	-2.81341	0.10
33	019032A	38	3	0.19	1	TEST	-2.65926	0.12
34	019032A	48	3	0.22	1	TEST	-2.52573	0.14
35	019032A	76	3	0.20	1	TEST	-2.52573	0.12
36	019032A	79	3	0.21	1	TEST	-2.65926	0.14
37	019032A	84	3	0.16	1	TEST	-2.81341	0.10
38	019032A	87	3	0.21	1	TEST	-2.65926	0.14
39	019032A	133	3	0.18	1	TEST	-2.99573	0.13
40	019032A	134	3	0.16	1	TEST	-2.81341	0.10
41	019033A	5	3	0.14	1	TEST	-2.81341	0.08
42	019033A	8	3	0.15	1	TEST	-2.99573	0.10
43	019033A	18	3	0.12	1	TEST	-3.21888	0.08
44	019033A	26	3	0.15	1	TEST	-2.81341	0.09

45	019033A	33	3	0.12	1	TEST	-2.99573	0.07
46	019033A	49	3	0.13	1	TEST	-2.99573	0.08
47	019033A	58	3	0.12	1	TEST	-2.99573	0.07
48	019033A	75	3	0.18	1	TEST	-2.52573	0.10
49	019033A	93	3	0.17	1	TEST	-2.65926	0.10
50	019033A	126	3	0.13	1	TEST	-2.99573	0.08
51	019034A	10	3	0.16	1	TEST	-2.81341	0.10
52	019034A	24	3	0.24	1	TEST	-2.40795	0.15
53	019034A	65	3	0.30	1	TEST	-2.04022	0.17
54	019034A	86	3	0.20	1	TEST	-2.52573	0.12
55	019034A	96	3	0.17	1	TEST	-2.65926	0.10
56	019034A	98	3	0.23	1	TEST	-2.20727	0.12
57	019034A	103	3	0.24	1	TEST	-2.30259	0.14
58	019034A	112	3	0.19	1	TEST	-2.65926	0.12
59	019034A	118	3	0.11	1	TEST	-2.99573	0.06
60	019034A	141	3	0.18	1	TEST	-2.65926	0.11

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for

Cascade Impaction - Group: 2 and 3 comb, Stage: 3

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.3657
	CI:	-0.1839
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0634
	CI:	0.0460
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	0.09	Mean:	0.07	Ratio:	128.52
				90% CI for ratio:		(111.7,147.9)
(log scale)	Mean:	-2.43	Mean:	-2.68	Diff:	0.25
(log scale)	CV:	-9.77	CV:	-14.69		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.237	SigmaR:	0.393	Ratio:	0.603

Class Levels (total number bottles = 56; number of sectors = 1):

Class Level Information for Input Dataset Cascade Impaction - Group: 2 and 3 com
By Product

Product	Class	Levels	Values
REF	treatment	1	REF
	container	28	1 2 5 9 11 15 16 20 21 25 37 40 42 44 64 77 113 124 148 154 155 160 163 164 169 172 176 178
	lot	3	C019943 C035879 C049983
TEST	treatment	1	TEST
	container	29	4 5 8 10 12 18 24 26 33 38 48 49 61 65 75 76 79 84 87 93 96 98 103 112 118 126 128 133 141
	lot	3	019032A 019033A 019034A

Listing of Raw Data for Cascade Impaction - Group: 2 and 3 comb, Stage: 3

Obs	lot	container	group(2+3)	ci	stage	treatment	metric	retvar
1	C019943	1	3	0.24	3	REF	-2.40795	0.15
2	C019943	9	3	0.18	3	REF	-2.81341	0.12
3	C019943	15	3	0.35	3	REF	-2.04022	0.22
4	C019943	16	3	0.28	3	REF	-2.12026	0.16
5	C019943	20	3	0.26	3	REF	-2.40795	0.17
6	C019943	21	3	0.19	3	REF	-2.65926	0.12
7	C019943	25	3	0.25	3	REF	-2.52573	0.17
8	C019943	37	3	0.29	3	REF	-2.20727	0.18
9	C019943	40	3	0.28	3	REF	-2.30259	0.18
10	C019943	42	3	0.16	3	REF	-2.65926	0.09
11	C035879	148	3	0.10	3	REF	-3.21888	0.06
12	C035879	154	3	0.19	3	REF	-2.52573	0.11
13	C035879	155	3	0.19	3	REF	-2.65926	0.12
14	C035879	160	3	0.25	3	REF	-2.30259	0.15
15	C035879	163	3	0.25	3	REF	-2.30259	0.15
16	C035879	164	3	0.16	3	REF	-2.81341	0.10
17	C035879	169	3	0.15	3	REF	-2.81341	0.09
18	C035879	172	3	0.14	3	REF	-2.99573	0.09
19	C035879	176	3	0.15	3	REF	-2.81341	0.09
20	C035879	178	3	0.14	3	REF	-2.81341	0.08
21	C049983	2	3	0.16	3	REF	-2.81341	0.10
22	C049983	5	3	0.15	3	REF	-2.99573	0.10
23	C049983	9	3	0.14	3	REF	-3.21888	0.10
24	C049983	11	3	0.27	3	REF	-2.20727	0.16
25	C049983	20	3	0.27	3	REF	-2.40795	0.18
26	C049983	44	3	0.18	3	REF	-2.65926	0.11
27	C049983	64	3	0.16	3	REF	-3.50656	0.13
28	C049983	77	3	0.11	3	REF	-3.50656	0.08
29	C049983	113	3	0.10	3	REF	-3.21888	0.06
30	C049983	124	3	0.21	3	REF	-2.40795	0.12
31	019032A	4	3	0.19	3	TEST	-2.52573	0.11
32	019032A	12	3	0.28	3	TEST	-2.12026	0.16
33	019032A	38	3	0.21	3	TEST	-2.40795	0.12
34	019032A	48	3	0.28	3	TEST	-2.30259	0.18
35	019032A	76	3	0.21	3	TEST	-2.40795	0.12
36	019032A	79	3	0.23	3	TEST	-2.40795	0.14
37	019032A	84	3	0.18	3	TEST	-2.81341	0.12
38	019032A	87	3	0.16	3	TEST	-2.81341	0.10
39	019032A	128	3	0.18	3	TEST	-2.81341	0.12
40	019032A	133	3	0.19	3	TEST	-2.65926	0.12
41	019033A	5	3	0.17	3	TEST	-2.52573	0.09
42	019033A	8	3	0.18	3	TEST	-2.65926	0.11
43	019033A	18	3	0.22	3	TEST	-2.40795	0.13
44	019033A	24	3	0.27	3	TEST	-2.20727	0.16
45	019033A	26	3	0.21	3	TEST	-2.65926	0.14

46	019033A	33	3	0.19	3	TEST	-2.65926	0.12
47	019033A	49	3	0.27	3	TEST	-2.20727	0.16
48	019033A	75	3	0.21	3	TEST	-2.40795	0.12
49	019033A	93	3	0.27	3	TEST	-2.20727	0.16
50	019033A	126	3	0.21	3	TEST	-2.40795	0.12
51	019034A	10	3	0.34	3	TEST	-2.04022	0.21
52	019034A	61	3	0.19	3	TEST	-2.65926	0.12
53	019034A	65	3	0.28	3	TEST	-2.30259	0.18
54	019034A	75	3	0.25	3	TEST	-2.12026	0.13
55	019034A	96	3	0.29	3	TEST	-2.04022	0.16
56	019034A	98	3	0.30	3	TEST	-2.30259	0.20
57	019034A	103	3	0.31	3	TEST	-2.30259	0.21
58	019034A	112	3	0.23	3	TEST	-2.40795	0.14
59	019034A	118	3	0.19	3	TEST	-2.81341	0.13
60	019034A	141	3	0.29	3	TEST	-2.20727	0.18

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-504 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Fluticasone Propionate Nasal Spray, 50 mcg

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

In Vitro Section

1. Please provide a hard copy of the in vitro data that were submitted on August 28, 2003. This copy should include the raw data.

2. Please provide a description of the conduct of the cascade impaction studies. You should submit the relevant standard operation procedure (SOP) and include information regarding (a) number of actuation used in each test, (2) operating conditions, (c) type of the atomization chamber used, and (d) data including the mass balance estimates.

3. Please provide relevant SOPs of all in vitro tests that were included in the application.

In Vivo Section (PK Study)

4. Please provide assay validation information on fluticasone stock stability data is requested. The mean value for study sample set, range (minimum and maximum), precision (%CV), accuracy (%), and number of samples.

5. Regarding samples acceptance and rejection, you have mentioned in the analytical section only the following information "per [redacted] SOP 03.01.042" without any details (see page 663, volume A2.2). Please provide the SOP(s) for describing the analytical method (sample acceptance, rejection criteria, repeat-assay, etc.) for the two bioequivalence (BE) studies (#451-05 and #451-03). The SOP number, date of SOP approved, and SOP title should be also included. b(4)

6. You have mentioned that some reassayed samples were reanalyzed "per client requested criteria", (for more

information see page 695, volume A2.2). Please provide the rational for establishing these criteria, as well as the date(s) for establishing it.

7. Please provide the dates of analytical assay (from the first sample to last sample analyzed) of each study (#451-05 and #451-03).

8. Please provide the expiration dates of the reference listed drug (RLD) lots # OH704, CO19943, and CO35879.

Sincerely yours,

Barbara M. Davit

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

CC: ANDA #76-504
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File

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Printed in final on

Endorsements: (Final with Dates)
HFD-658/ Reviewer Z. Wahba ZW 11/24/03
HFD-658/ Bio TL GJP Singh GJPS 11-24-03
HFD-650/ D. Conner BZD 11/24/03

BIOEQUIVALENCY - Incomplete submission date: 10/03/02 ✓

1. STUDY (STU) - in vitro — Strengths: 50 µg/spray; Outcome: IC
2. STUDY (STU) - in vitro — Strengths: 50 µg/spray; Outcome: IC
3. STUDY (STU) - in vitro — Strengths: 50 µg/spray; Outcome: IC
4. STUDY (STU) - in vitro — Strengths: 50 µg/spray; Outcome: IC
5. STUDY (STF) - in vivo (#451-05) — Strengths: 50 µg/spray; Outcome: IC
6. STUDY (STF) - in vivo (#451-03) — Strengths: 50 µg/spray; Outcome: IC
7. STUDY AMENDMENT (STA), 06/05/03 — Strengths: 50 µg/spray; Outcome: IC

NOTE Reviewer would receive 4 credits for reviewing nasal spray in vitro studies

Outcome Decisions: IC – Incomplete

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-504

STATISTICAL REVIEWS

ANDA 76-504

Drug Product:	Fluticasone Propionate Nasal Spray, 50 mcg
Sponsor:	Roxane Laboratories, Inc.
Reference Listed Drug:	Flonase® Nasal Spray , 50 mcg, NDA 20-121
Submission date:	October 4, 2002
Statistical Reviewer:	Donald J. Schuirmann, QMR/OB/CDER
Medical Reviewer:	Carol. Y. Kim, Pharm.D./OGD

Objectives of the study

The primary objectives of the study were to establish the bioequivalence of the test product, Roxane Laboratories, Inc. Fluticasone Propionate Nasal Spray, 50 mcg, and the reference product, Glaxosmithkline, Flonase@ Nasal Spray, 50 mcg, and to show superiority of the two active treatments to the placebo (Roxane) in the treatment of seasonal allergic rhinitis (SAR).

Data Sets submitted by the Sponsor

SAS data sets and supporting electronic documents, submitted by the Sponsor, are located in the Electronic Document Room (EDR) at \\Cdsesubogd1\N76504\N_000\2002-10-03. The submitted SAS data sets include:

diary1	individual symptom scores from each assessment
diaryss	individual AM and PM symptom score sums (ITT)
ediaryss	individual AM and PM symptom score sums (evaluable)
drytnss	average total nasal symptom score sums (all ITT patients)
edrytnss	average total nasal symptom score sums (evaluable patients and assessments)
treat	treatment (placebo, test product, or reference product) assignments for each patient

Study Design

This was a multicenter, three-arm, parallel group, double-blind, randomized study with a 7-day (with some variation) untreated baseline lead-in period followed by a 14-day (with some variation) treatment period. 566 patients were randomized to treatment. The three treatments studied were

1. Test: Roxane's fluticasone propionate (50 mcg/spray), 2 sprays in each nostril, once daily; Lot number: C049983
2. Reference: Flonase® nasal spray, (50 mcg/spray), 2 sprays in each nostril, once daily; Lot number: 019032A

3. Placebo: Roxane's Placebo nasal spray, 2 sprays in each nostril, once daily; Lot number: 019035A.

As described in the Sponsor's report, four visits were scheduled:

Visit 1 – Screening Visit - To obtain informed consent and assess subject eligibility.

Visit 2 - Randomization Visit - Seven days after the Screening Visit, subjects returned to the clinic with their baseline period symptom diary card (see below.) Those eligible for randomization were randomized to one of the three treatment groups.

Visit 3 - Treatment Visit - Seven days after Visit 2, subjects returned to the clinic with their treatment period Week 1 symptom diary card. Upon return to the clinic, the subject's symptom diary card (see below) was reviewed for compliance by the study site coordinator.

Visit 4 - End of Treatment or Early Discontinuation Visit - Seven days after Visit 3, subjects were to return to the clinic with their treatment period Week 2 symptom diary card and study medication.

At Visit 1, subjects were given a baseline period symptom diary card. During the untreated baseline period (after Visit 1 through the morning of Visit 2), subjects were to assess their symptoms in the morning (AM assessment, to be carried out at 7:00AM ± 1 hour) and in the evening (PM assessment, to be carried out at 7:00PM ± 1 hour.) Based on the Sponsor's report, it appears that that the permissible window around the nominal assessment times was relaxed to ± 2 hours for both assessments. Symptom assessments were to be recorded on the symptom diary card. Four allergy nasal symptoms were assessed:

1. Sneezing
2. Rhinorrhea (Runny Nose)
3. Nasal pruritis (Itchy Nose)
4. Nasal congestion

The severity score for each symptom was based on a 4-point scale:

0 = none
1 = mild
2 = moderate
3 = severe

At each assessment, subjects were to complete two types of symptom assessments, an *instantaneous* assessment of symptoms (i.e., evaluation of symptoms at that moment in time) and a *reflective* assessment of symptoms (i.e., evaluation of symptoms during the period of time since the last assessment.)

For each assessment, the *Total Nasal Symptom Score* (TNSS) was defined as the sum of the symptom scores for the four symptoms. As such, an individual TNSS could vary from 0 to 12.

Outcome Variables

For each patient in the study, there were to be several symptom assessments. As planned, there would be seven PM assessments (day 1 through day 7 of the baseline period) and seven AM assessments (day 2 through day 7 of the baseline period, plus the AM assessment on the morning of Visit 2.) As planned, during the treated period (weeks 2 and 3 of the study) there would be fourteen PM assessments (day 1 of the treated period (the evening of Visit 2) through day 14 of the treated period) and fourteen AM assessments (day 2 of the treated period through the morning of day 15 of the treated period.) As the study was actually conducted, some patients had more than seven days in their baseline period and some had fewer. Similarly, some patients had more than 14 days (plus the morning of the fifteenth day) in the treated period and some had fewer. Each assessment produced an individual TNSS.

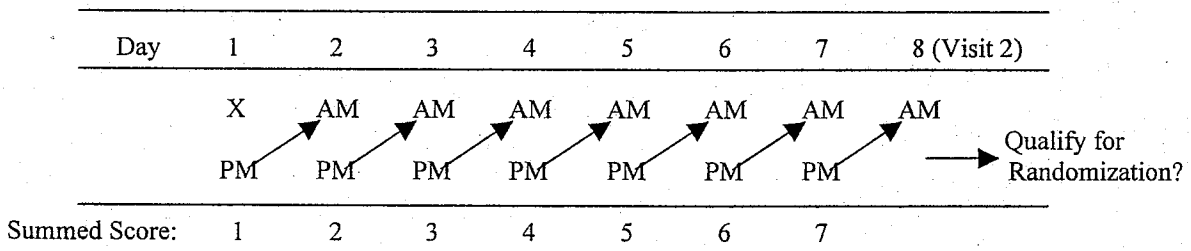
Outcome variables were based on averaged (arithmetic mean) TNSS's over the baseline period and over the treated period. The response of interest was *change from baseline*, defined as

(baseline average TNSS) – (average TNSS under treatment)

Since patients were expected to improve (resulting in lower symptom scores) over the treated period, compared to the baseline period, defining change from baseline in this way ensures that most change from baseline values are positive, though a few are negative.

Sponsor's outcome variables: The Sponsor has chosen to base their outcome variables on TNSS AM and PM *sums*. Each AM TNSS was summed with the previous evening's PM TNSS. The Sponsor provided the following schematic for the baseline period:

Baseline Period Symptom Scores



A similar summing scheme was used for the treated period (weeks 2 and 3), with the day 8 (Visit 2, day 1 of the treated period) PM TNSS summed with the day 9 AM TNSS, etc., through the day 21 (day 14 of the treated period) PM assessment summed with the day 22 AM TNSS. If either an AM or a PM TNSS was missing, the sum was considered missing. Since individual TNSS's may range from 0 to 12, it is apparent that these TNSS sums may range from 0 to 24.

The Sponsor defined the baseline average TNSS as the average (arithmetic mean) of the baseline day 1 through 7 TNSS sums. If a patient provided assessments earlier than seven days before Visit 2, those assessments were not used. Only one out of seven baseline TNSS sums could be missing for the patient's results to be included in the evaluable (PP, i.e. per protocol) analysis data set. Similarly, the Sponsor defined the average TNSS under treatment as the average (arithmetic mean) of the day 8 through day 21 (days 1 through 14 of the treated period) TNSS sums. If a patient provided assessments beyond the AM assessment on day 22, those assessments were not used. Only one out of seven TNSS sums could be missing from week 1 of the treated period (days 8 through 14 of the study) and only one out of seven TNSS sums could be missing from week 2 of the treated period (days 15 through 21 of the study) for the patient's results to be included in the evaluable (PP, i.e. per protocol) analysis data set.

Guidance-based outcome variables: The April 2003 CDER draft guidance document "Guidance for Industry – Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" calls for a *placebo* baseline run-in period of seven days, rather than the untreated baseline run-in period used by the Sponsor. 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 (Visit 2, first day of the treated period.) Thus, seven individual TNSS's – four AM and three PM – are to be averaged. Also, the draft guidance calls for defining the average TNSS under treatment as the average (arithmetic mean) of the PM TNSS from day 8 plus the AM and PM TNSS's from days 9 through 14 of the study (i.e. days 2 through 14 of the treated period.) Thus, twenty seven individual TNSS's – fourteen AM and thirteen PM – are to be averaged. It is apparent that these guidance-based average TNSS's may only range from 0 to 12.

For individual symptoms (e.g. sneezing), the Sponsor's and guidance-based outcome variables are defined similarly, using only the symptom scores for that symptom. Individual symptom scores may only range from 0 to 3, and individual symptom AM and PM sums may only range from 0 to 6. This affects the possible range of the individual symptom outcome variables.

Some discussion of Sponsor's vs. guidance-based outcome variable definitions: An effect of using sums is to double the possible range of the outcome variables. A baseline of, say, 16 for average TNSS sums corresponds to a baseline of 8 if individual TNSS's had been averaged. If the Sponsor had divided each of the AM and PM sums by 2 before taking the average over different days, the possible range would have corresponded to the guidance-based outcome variables. Furthermore, the results of the statistical analyses would have been unaffected (provided one kept track of what baseline values for sums correspond to what baseline values for averages) by such a division by 2, since the statistical methods used are invariant to this sort of scale change. So the doubling of the possible range by using sums is not an important issue, in this reviewer's opinion.

The use of AM and PM sums by the Sponsor appears to reflect a desire to balance any effect of morning vs. evening. The guidance-based average TNSS's are unbalanced with respect to morning vs. evening. Morning is over-represented in the baseline averages (4 AM vs. 3 PM assessments, 57.14% AM), while evening is over-represented in the averages under treatment (14 PM vs. 13 AM assessments, 51.85% PM.)

In one analysis that I carried out of the reflective TNSS's from Roxane's evaluable subjects (subjects classified as non-evaluable were excluded), there does appear to be an overall (averaged over the three treatments) morning vs. evening effect for reflective TNSS at both baseline (p=0.0001) and under treatment (p=0.0099.) For instantaneous TNSS, there is no evidence of a morning vs. evening effect at baseline (p=0.6534) but there is evidence of such an effect under treatment (p=0.0006.) However, these findings were not consistent across treatments, and further analysis would be needed in order to adopt a general policy.

The draft guidance recommendation to use only baseline assessments from days 5, 6, and 7 of the baseline period (plus the AM assessment from day 8) makes sense under the assumption that a placebo run-in baseline period would be used. It is expected that placebo will provide some clinical benefit, and the draft guidance recommendation allows the first four days of the baseline period for the participants to achieve their placebo symptom level (Note that, under the draft guidance recommended design with a placebo baseline period, if patients improve *too much* under placebo they are to be excluded as "placebo responders." However, the draft guidance does not define any criteria for determining how much improvement is "too much.") On the other hand, with an untreated baseline period, as was used in the Sponsor's study, all baseline days might be regarded as being more or less the same (unless one wants to allow time for the participants to get used to self-assessing their symptoms.) So, under an untreated baseline period, the Sponsor's decision to use assessments from all baseline days to define the average baseline TNSS may be reasonable.

Endpoints

The primary endpoint for the study is average (the mean over both treatment weeks) reflective TNSS change from baseline.

Secondary endpoints for the study include

1. average instantaneous TNSS change from baseline
2. average reflective TNSS change from baseline for week 1 of the treated period
3. average reflective TNSS change from baseline for week 2 of the treated period
4. average instantaneous TNSS change from baseline for week 1 of the treated period
5. average instantaneous TNSS change from baseline for week 2 of the treated period
6. similar scores to those described above, for each individual symptom

Thus, there is one primary endpoint and 29 secondary endpoints.

Analysis Data Sets

Two analysis data sets were defined by the Sponsor:

Intent-To-Treat Subjects (ITT): Intent-to-Treat subjects were defined as all randomized subjects who received at least one dose of study drug. ITT subjects were used to compare each active treatment to placebo and were used to compare safety among the treatments.

Evaluable Subjects (PP, i.e. per protocol): Evaluable subjects were defined as all Intent-to-Treat subjects who additionally had no major protocol violations or other events considered to bias their study outcome. Criteria for protocol violations/bias include:

- Not symptomatic at baseline.
- Did not meet inclusion and exclusion criteria.
- Did not have at least 6 acceptable reflective daily assessments during baseline, week 1 and week 2. A subject's daily reflective data are considered acceptable for any given day in which the morning medication dose was taken between 5:00 AM and 9:00 AM and the morning reflective daily assessments preceded the morning dose or were recorded within 30 minutes of when the dose was taken and the previous days' evening reflective assessments were recorded between 5:00 PM to 9:00 PM. [*Reviewer's note*: During the baseline period, morning assessments were apparently considered acceptable if they took place between 5:00 AM and 9:00 AM.]
- Received prohibited concomitant medications without adequate washout period.
- Had other major protocol violations (e.g., subjects met the study inclusion/exclusion criteria at the time the information was obtained but were later found to have violated some of these criteria).

These analysis data sets will be called the SITT (Sponsor's intent-to-treat) and the SPP (Sponsor's per protocol.)

In addition to the SITT and SPP analysis data sets, I constructed two *guidance-based analysis data sets.* These were based on the draft guidance recommendation that the baseline average TNSS should include the average of the AM and PM TNSS's from baseline days 5, 6, and 7, plus the AM TNSS from study day 8 (visit 2, day 1 of the treated period), and that the average TNSS under treatment should include the average of the AM and PM TNSS's from study days 9-21 (days 2-14 of the treated period), plus the PM TNSS from study day 8 (visit 2, day 1 of the treated period.) I arbitrarily adopted a rule that to be usable for the per protocol analysis data set, there could be no more than one AM and one PM assessment missing from the relevant days of the baseline period, no more than one AM and one PM assessment missing from week 1 of the treated period, and no more than one AM and one PM assessment missing from week 2 of the treated period. These analysis data sets will be called the GITT (guidance-based intent-to-treat) and the GPP (guidance-based per protocol.)

The same subjects who had been excluded by the Sponsor from the SPP were excluded from the GPP. However, the Sponsor and I sometimes differed in our decisions regarding which

individual assessments to include or exclude. As a result, one subject (subject number 34 at site 28) included in the SPP for reflective assessments was excluded from the GPP for reflective assessments because this subject did not appear to have any AM reflective baseline assessments that fell within the allowable time window. It is possible that the Sponsor examined the assessments for this subject, and satisfied themselves that he actually did do his AM reflective assessments within the allowable window, in spite of what was written on his diary card (his AM *instantaneous* assessments appear to have been within the allowable window, based on his diary card), but I decided to exclude this subject from the GPP for reflective endpoints. Also, there are 6 subjects (subject 17 at site 8, subject 5 at site 10, subject 9 at site 11, subject 10 at site 25, subject 43 at site 29, and subject 1 at site 33) who were included in the SPP for instantaneous assessments whom I excluded from the GPP for instantaneous assessments because they did not appear to have sufficient instantaneous assessments within the allowable time windows.

It is not my intention to modify the SPP to eliminate assessments that appear to violate the inclusion/exclusion criteria (e.g. that appear to fall outside allowable time windows.) Rather, I intend to use the GITT and the GPP as the primary data sets for this review, with the SITT and SPP used *as is* as supporting information.

Statistical Analysis Methods

The statistical model used to carry out the efficacy and equivalence analyses was a general linear model including treatment and site as factors, and including baseline as a linear covariate. This model has been recommended by the CDER working group for the draft guidance, and is also the model chosen by the Sponsor. Computations were carried out using SAS PROC GLM, with supporting calculations done using other software.

Efficacy analyses used the ITT analysis data sets (GITT and SITT.) In the comparison of the active treatments (Test and Reference) against Placebo, each analysis used only data from the two treatments being compared (that is, in the comparison of Test and Placebo, no data from Reference were used, and in the comparison of Reference and Placebo, no data from Test were used.

Equivalence analyses used the PP analysis data sets (GPP and SPP.) In the equivalence comparison of Test vs. Reference, data from Placebo were not used.

Implications of the statistical model

In the assumed statistical model, the mean (suitably defined) response ("response" in this case is mean change-from-baseline) for a given product is a linear function of baseline. If the slope relating response to baseline is positive, this means that for higher values of baseline the mean response is higher (since the estimated slope has been positive in all data sets that I have analyzed, I will assume a positive slope from here on.) Under the assumed model, the *difference* between the mean response to the Test product and the mean response to the Reference product is constant, independent of baseline. Therefore, the difference between the Test and Reference

means *as a proportion of the Reference product mean* is closer to zero for higher values of baseline. Equivalently, for higher values of baseline, the *ratio* of the Test and Reference means is closer to one. The possibility exists that the products could be *inequivalent* (have a ratio of means less than 0.80 or greater than 1.25) for a given value of baseline, but *equivalent* for a higher value of baseline. We therefore must address the regulatory question of "For which values of baseline must equivalence be demonstrated?" One possible answer is that equivalence must be demonstrated for values of baseline greater than or equal to the average (suitably defined) value of baseline seen in the study.

Since the assumed statistical model also includes a factor for site, we must specify what *weights* are to be given to each site in order to define what we mean by "product means". Although the Sponsor does not address this question explicitly, their choice of statistical methods (based on "least square means" as computed by SAS PROC GLM and PROC MIXED) implicitly puts *equal* weight on each site. I have used equal weights in my analyses (reported below.) For this submission, conclusions for the primary endpoint, at least, are not changed under other choices of weights. However, the question of what weighting scheme should be used in general for bioequivalence studies of nasal sprays still needs to be addressed.

Statistical Analysis Results

A total of 566 patients were enrolled and randomly assigned to the three treatment groups in the study. However, two patients – subject 17 at site 10 and subject 33 at site 29 – had no usable data under treatment.

33 study sites contributed usable data. However, site 27 contributed no usable data toward the GPP or SPP analysis data sets. The number of patients per site ranged from 2 (site 27) to 35 (site 7).

The following tables give the numbers of patients available for analysis for each endpoint ("overall" refers to assessments averaged over both treated weeks.)

SITT

	Reflective assessment endpoints				Instantaneous assessment endpoints			
	T	R	P	total	T	R	P	total
overall	230	224	110	564	230	224	109	563
week 1	229	224	110	563	229	224	109	562
week 2	222	218	108	548	222	218	107	547

GITT

	Reflective assessment endpoints				Instantaneous assessment endpoints			
	T	R	P	total	T	R	P	total
overall	230	224	110	564	230	224	109	563
week 1	230	224	110	564	230	224	109	563
week 2	227	219	109	555	226	219	108	553

SPP

	Reflective assessment endpoints				Instantaneous assessment endpoints			
	T	R	P	total	T	R	P	total
overall	158	161	82	401	158	161	82	401
week 1	158	161	82	401	158	161	82	401
week 2	158	161	82	401	158	161	82	401

GPP

	Reflective assessment endpoints				Instantaneous assessment endpoints			
	T	R	P	total	T	R	P	total
overall	158	160	82	400	154	160	81	395
week 1	158	160	82	400	157	160	81	398
week 2	158	160	82	400	155	161	81	397

Demographics

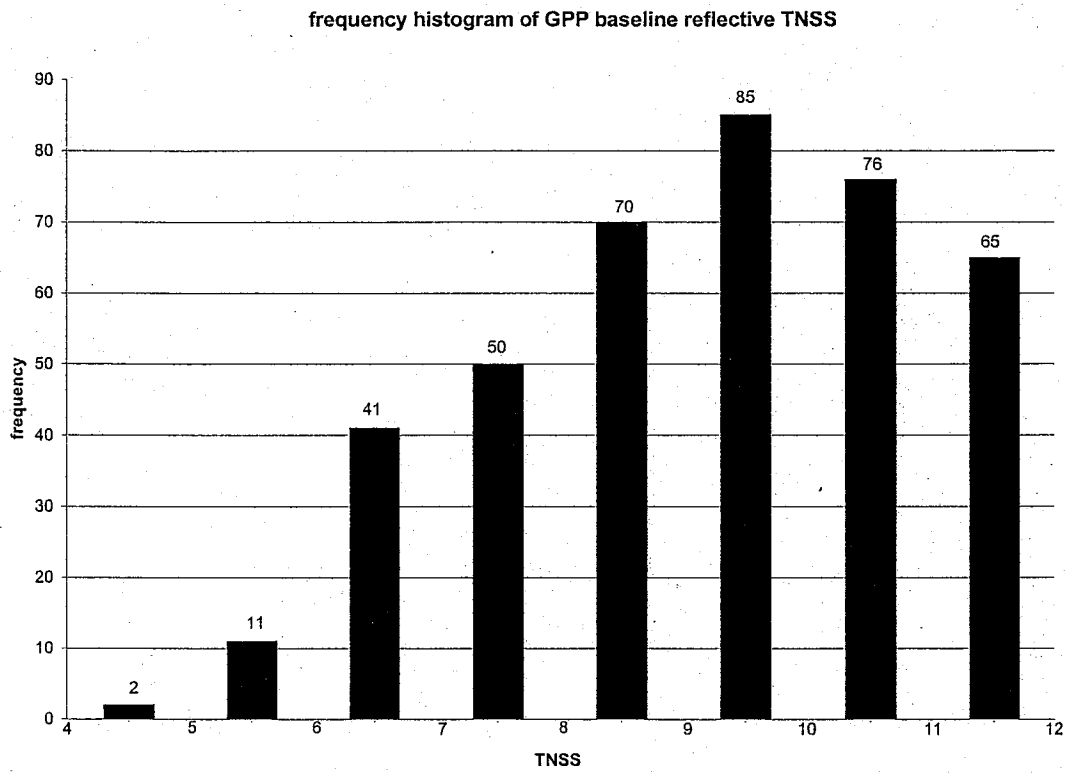
Please see the Office of Generic Drugs (OGD) Medical Reviewer's report.

Baseline

There are no statistically significant differences across the three treatment groups for any of the baseline variables (TNSS, runny nose, itchy nose, nasal congestion, and sneezing, both reflective and instantaneous) in any of the analysis data sets (GITT, GPP, SITT, or SPP; $p \geq 0.3651$ in all cases.) However, there are statistically significant baseline differences across the 33 study sites ($p \leq 0.0023$ in all cases.)

The distribution of the baseline endpoints tends to be skewed, with a "tail" of values on the low end. This is illustrated in Figure 1.

Figure 1. frequency histogram of baseline reflective TNSS from the GPP analysis data set



i.e. there are 65 baseline values > 11 and ≤ 12, 76 baseline values > 10 and ≤ 11, etc.

Because of the skewed distribution of baseline values, the sample mean baseline tends to be "pulled" in the direction of the tail. For skewed distributions the median (the value such that half the distribution is above it, half below it) is often regarded as a more meaningful measure of "central location" than the mean. For the four analysis data sets, the minimum, sample mean, sample median, and maximum values for reflective TNSS baseline are:

data set	minimum	sample mean	sample median	maximum
GITT	4.571	9.170	9.286	12
GPP	4.571	9.252	9.429	12
SITT	10.143	18.095	18.429	24
SPP	10.143	18.251	18.571	24

As noted before, because the Sponsor's analysis data sets are based on AM and PM *sums*, the possible range of values is doubled. In particular, a TNSS of 12 in the guidance-based data sets corresponds to a TNSS of 24 in the Sponsor's data sets.

Efficacy Analyses

Using the two ITT analysis data sets, the two-sided p-values from the analyses comparing active treatment to placebo are given in Table 1. In all analyses, data from two treatments were used. That is, in the analysis comparing Test to Placebo, no data from Reference were used, and in the analysis comparing Reference to Placebo, no data from Test were used.

Table 1 – Efficacy p-values ("overall" refers to scores averaged over both treatment weeks)

	GITT data set		SITT data set	
	T vs. P	R vs. P	T vs. P	R vs. P
reflective TNSS				
overall*	0.0002	0.0010	0.0001	0.0012
week 1	0.0076	**0.0817**	0.0062	**0.0889**
week 2	<.0001	<.0001	<.0001	<.0001
instantaneous TNSS				
overall	<.0001	0.0005	<.0001	0.0004
week 1	0.0043	0.0311	0.0055	0.0316
week 2	<.0001	<.0001	<.0001	<.0001
reflective Itchy Nose				
overall	0.0053	0.0094	0.0045	0.0083
week 1	**0.0661**	**0.2586**	0.0497	**0.1838**
week 2	0.0019	0.0006	0.0009	0.0006
instantaneous Itchy Nose				
overall	0.0038	0.0084	0.0025	0.0048
week 1	**0.0910**	**0.2018**	**0.0763**	**0.1374**
week 2	0.0009	0.0013	0.0002	0.0003
reflective Runny Nose				
overall	0.0002	0.0013	<.0001	0.0010
week 1	0.0060	**0.0687**	0.0033	**0.0618**
week 2	<.0001	<.0001	<.0001	<.0001
instantaneous Runny Nose				
overall	<.0001	0.0002	<.0001	0.0002
week 1	0.0010	0.0067	0.0013	0.0080
week 2	<.0001	<.0001	<.0001	<.0001

reflective Nasal Congestion				
overall	<.0001	0.0123	0.0003	0.0222
week 1	0.0059	**0.3068**	0.0115	**0.3981**
week 2	<.0001	0.0008	<.0001	0.0014
instantaneous Nasal Congestion				
overall	<.0001	0.0207	0.0002	0.0305
week 1	0.0056	**0.3628**	0.0147	**0.4953**
week 2	<.0001	0.0018	<.0001	0.0021
reflective Sneezing				
overall	0.0026	0.0010	0.0012	0.0013
week 1	0.0412	0.0432	0.0293	**0.0694**
week 2	0.0008	0.0001	0.0001	0.0001
instantaneous Sneezing				
overall	0.0009	0.0003	0.0004	0.0001
week 1	0.0258	0.0181	0.0182	0.0131
week 2	0.0002	<.0001	<.0001	<.0001

* primary endpoint

For overall average (i.e. averaged over both treatment weeks) assessments and week 2 average assessments, both Test and Reference were statistically significantly better than Placebo in all cases (two-sided $p \leq 0.0305$) for both ITT analysis data sets.

For week 1 average assessments, using the GITT, Test did not beat Placebo for reflective Itchy Nose and instantaneous Itchy Nose. Reference did not beat Placebo for reflective TNSS, reflective Itchy Nose, instantaneous Itchy Nose, reflective Runny Nose, reflective Nasal Congestion, and instantaneous Nasal Congestion.

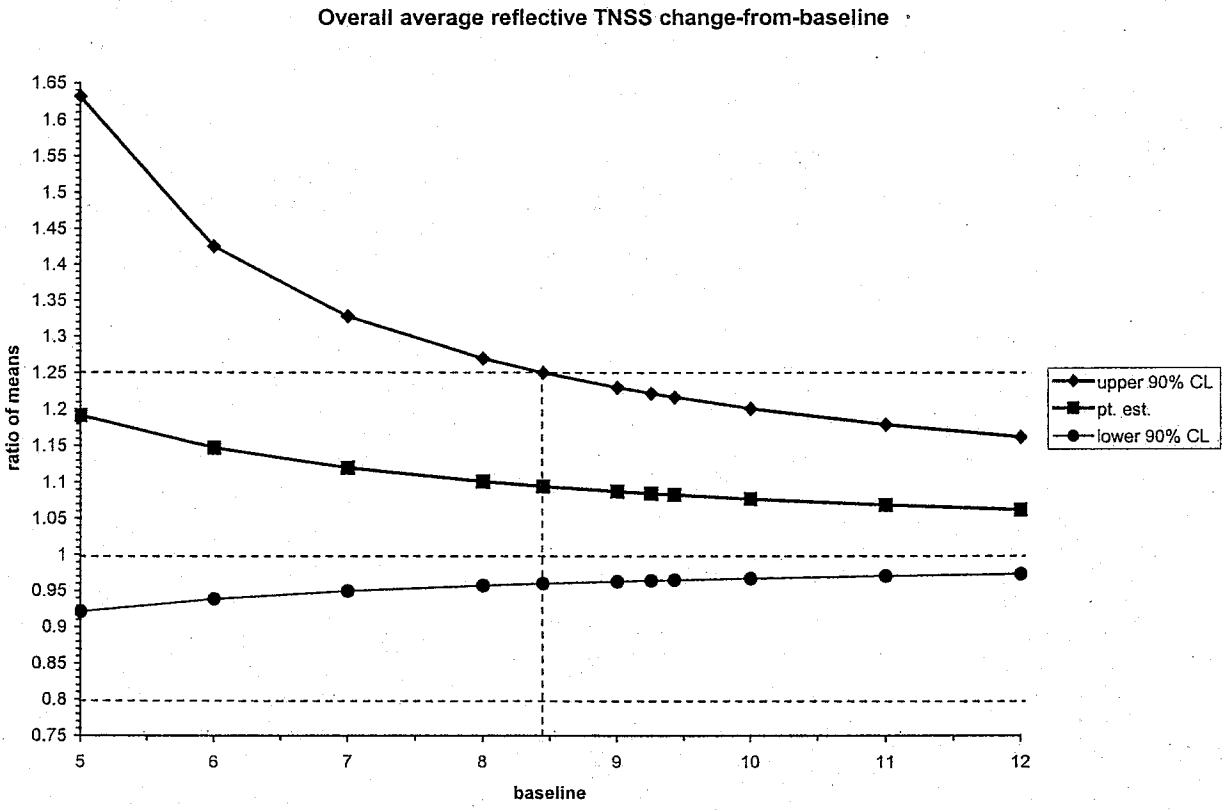
There were only two cases where conclusions (regarding statistical significance) differed between the GITT and the SITT. For average reflective Itchy Nose over week 1, Test did not beat Placebo ($p = 0.0661$) using the GITT but did beat Placebo ($p = 0.0497$) using the SITT. For average reflective Sneezing over week 1, Reference beat Placebo ($p = 0.0432$) using the GITT but did not beat Placebo ($p = 0.0694$) using the SITT.

Equivalence Results for the Primary Endpoint using the GPP

For the comparison of Test to Reference with respect to the primary endpoint, average reflective TNSS change from baseline, using the GPP, the 90% confidence interval for the ratio of the mean for Test over the mean for Reference fell within the standard equivalence limits of [0.80, 1.25] for all baseline values greater than or equal to 8.445. By comparison, the sample mean overall average baseline reflective TNSS for the GPP was 9.252 and the sample median overall average baseline reflective TNSS for the GPP was 9.429 (note that these mean and median

values were calculated from the data on all three treatments, but the confidence intervals were calculated using only data from Test and Reference.) So Test and Reference pass the usual equivalence test for all baseline values greater than or equal to the average baseline seen in the study regardless of how "average" is defined. The 90% confidence intervals are illustrated in Figure 2.

Figure 2 – 90% confidence limits and point estimates (as a function of baseline) for the ratio of the Test mean over the Reference mean – primary endpoint



Equivalence Results for Secondary Endpoints using the GPP

In the summaries that follow, I report the minimum baseline value for which the endpoint passes the usual equivalence test (i.e. the 90% confidence interval for the ratio of means falls within [0.80, 1.25]) using the GPP with data from Test and Reference (i.e. no Placebo data were used in calculating the confidence intervals.) I also report the sample mean and sample median (called "mean" and "median", respectively, in the summaries) from the GPP including all three treatments. In cases where the endpoint does not pass the test for any baseline value in the possible range (0-3 for individual symptoms), I report the point estimate and 90% confidence interval at the maximum value of baseline (3 for individual symptoms.)

reflective overall endpoints

Itchy Nose – passes for baseline ≥ 1.794. mean = 2.285 median = 2.429

Runny Nose – passes for baseline ≥ 2.485. mean = 2.431 median = 2.571

Nasal Congestion - does not pass for any baseline in the 0-3 range.
At baseline = 3: point estimate = 1.149, 90% confidence interval = (1.021, 1.299)

Sneezing - passes for baseline ≥ 1.401. mean = 1.956 median = 2

instantaneous overall endpoints

TNSS - passes for baseline ≥ 8.895 mean = 8.655 median = 8.857

Itchy Nose - passes for baseline ≥ 1.804 mean = 2.191 median = 2.286

Runny Nose - passes for baseline ≥ 2.609 mean = 2.323 median = 2.429

Nasal Congestion - does not pass for any baseline in the 0-3 range.
At baseline = 3: point estimate = 1.195, 90% confidence interval = (1.057, 1.361)

Sneezing - passes for baseline ≥ 1.299 mean = 1.628 median = 1.857

reflective week 1 endpoints

TNSS - passes for baseline ≥ 10.347 mean = 9.252 median = 9.429

Itchy Nose - passes for baseline ≥ 2.531 mean = 2.285 median = 2.429

Runny Nose - does not pass for any baseline in the 0-3 range.
At baseline = 3: point estimate = 1.113, 90% confidence interval = (0.990, 1.255)

Nasal Congestion - does not pass for any baseline in the 0-3 range.
At baseline = 3: point estimate = 1.179, 90% confidence interval = (1.032, 1.356)

Sneezing - passes for baseline ≥ 1.886 mean = 1.956 median = 2

instantaneous week 1 endpoints

TNSS - passes for baseline ≥ 10.148. mean = 8.648 median = 8.857

Itchy Nose - passes for baseline ≥ 2.187. mean = 2.186 median = 2.286

Runny Nose - passes for baseline ≥ 2.924. mean = 2.325 median = 2.429

Nasal Congestion - does not pass for any baseline in the 0-3 range.
At baseline = 3: point estimate = 1.207, 90% confidence interval = (1.052, 1.398)

Sneezing - passes for baseline ≥ 1.704. mean = 1.625 median = 1.857

reflective week 2 endpoints

TNSS -	passes for baseline ≥ 7.313	mean = 9.252	median = 9.429
Itchy Nose -	passes for baseline ≥ 1.425	mean = 2.285	median = 2.429
Runny Nose -	passes for baseline ≥ 2.173	mean = 2.431	median = 2.571

Nasal Congestion - does not pass for any baseline in the 0-3 range.
At baseline = 3: point estimate = 1.130, 90% confidence interval = (1.003, 1.278)

Sneezing -	passes for baseline ≥ 1.192	mean = 1.956	median = 2

instantaneous week 2 endpoints

TNSS -	passes for baseline ≥ 8.071.	mean = 8.666	median = 8.857
Itchy Nose -	passes for baseline ≥ 1.565.	mean = 2.194	median = 2.286
Runny Nose -	passes for baseline ≥ 2.470.	mean = 2.325	median = 2.429

Nasal Congestion - does not pass for any baseline in the 0-3 range.
At baseline = 3: point estimate = 1.175, 90% confidence interval = (1.041, 1.334)

Sneezing -	passes for baseline ≥ 1.140.	mean = 1.633	median = 1.857

Summary of GPP equivalence analyses

The following table summarizes the results of the equivalence analyses using the GPP. In the table, the following codes are used:

A passes at both the mean and the median
B passes at the median, but not at the mean
C passes at some baseline values in the possible range, but not at the mean or median
D does not pass for any baseline value in the possible range (0-12 for TNSS, 0-3 for individual symptoms)

where by "mean" and "median" I mean the sample mean and sample median baseline, respectively, calculated from the GPP using data from all three treatments.

endpoint	week	reflective assessments	instantaneous assessments
TNSS	overall	**A***	**C**
	1	**C**	**C**
	2	**A**	**A**
Itchy Nose	overall	**A**	**A**
	1	**C**	**B**
	2	**A**	**A**
Runny Nose	overall	**B**	**C**
	1	**D**	**C**
	2	**A**	**C**
Nasal Congestion	overall	**D**	**D**
	1	**D**	**D**
	2	**D**	**D**
Sneezing	overall	**A**	**A**
	1	**A**	**B**
	2	**A**	**A**

* primary endpoint

If we were to regard endpoints with codes of "A" or "B" as satisfying regulatory requirements (because they pass for all values of baseline ≥ the sample median), then the summary would be:

overall 6 endpoints pass (including the primary endpoint), 4 do not

week 1 3 endpoints pass, 7 do not

week 2 7 endpoints pass, 3 do not

As a further summary Tables 2 and 3 give the point estimates and 90% confidence intervals for the ratio of Test mean over Reference mean, in each case for baseline equal to the sample median baseline seen in the GPP. Table 2 is for reflective assessments and Table 3 is for instantaneous assessments.

Table 2: point estimates and 90% confidence intervals calculated for baseline = sample median baseline in the GPP – Reflective assessments

endpoint	week	sample median baseline	point estimate	90% confidence interval	falls within [0.80, 1.25]?
TNSS	overall*	9.429	1.082	0.965, 1.216	Yes
	1	9.429	1.123	0.984, 1.287	No
	2	9.429	1.057	0.944, 1.185	Yes
Itchy Nose	overall	2.429	1.049	0.930, 1.186	Yes
	1	2.429	1.091	0.947, 1.261	No
	2	2.429	1.023	0.908, 1.154	Yes
Runny Nose	overall	2.571	1.094	0.968, 1.239	Yes
	1	2.571	1.139	0.987, 1.319	No
	2	2.571	1.066	0.944, 1.206	Yes
Nasal Congestion	overall	2.714	1.169	1.024, 1.340	No
	1	2.714	1.207	1.037, 1.416	No
	2	2.714	1.144	1.004, 1.310	No
Sneezing	overall	2.000	1.021	0.903, 1.157	Yes
	1	2.000	1.059	0.913, 1.231	Yes
	2	2.000	0.998	0.884, 1.126	Yes

Table 3: point estimates and 90% confidence intervals calculated for baseline = sample median baseline in the GPP – Instantaneous assessments

endpoint	week	sample median baseline	point estimate	90% confidence interval	falls within [0.80, 1.25]?
TNSS	overall	8.857	1.101	0.971, 1.251	No
	1	8.857	1.123	0.971, 1.303	No
	2	8.857	1.081	0.959, 1.222	Yes
Itchy Nose	overall	2.286	1.046	0.919, 1.193	Yes
	1	2.286	1.062	0.913, 1.237	Yes
	2	2.286	1.032	0.910, 1.171	Yes
Runny Nose	overall	2.429	1.109	0.968, 1.275	No
	1	2.429	1.121	0.956, 1.320	No
	2	2.429	1.099	0.964, 1.256	No
Nasal Congestion	overall	2.571	1.239	1.069, 1.447	No
	1	2.571	1.263	1.065, 1.515	No
	2	2.571	1.208	1.048, 1.402	No
Sneezing	overall	1.857	1.016	0.889, 1.161	Yes
	1	1.857	1.045	0.893, 1.224	Yes
	2	1.857	0.995	0.876, 1.132	Yes

As may be seen in the tables, there are only 2 endpoints out of 30 for which the point estimate of the ratio of Test mean over Reference mean is less than 1.0. These 2 endpoints are reflective

sneezing for week 2 and instantaneous sneezing for week 2. Furthermore, there is no case where the lower limit of the 90% confidence interval falls below 0.80. Thus, in cases where the 90% confidence interval is not contained within [0.80, 1.25] it is because we cannot rule out the possibility that the Test product is *too much better* then the Reference product.

Equivalence Results using the SPP

Equivalence results using the SPP analysis data set are similar to results using the GPP. For the primary endpoint, the usual equivalence test was passed for all baseline values greater than or equal to 17.666. The sample mean baseline overall average TNSS was 18.251 and the sample median was 18.571 (as with the GPP analyses, confidence intervals were calculated using only data from Test and Reference, but the sample mean and median were calculated from the data set including all three treatments.) Since the SPP endpoints, based on AM and PM sums, have double the possible range of the GPP endpoints, the SPP baseline value 17.666 corresponds roughly to a baseline of 8.833 for the GPP.

The full results for the equivalence analyses using the SPP are given in Appendix A. In terms of the codes (A, B, C, and D, adjusted appropriately for the change in possible range of scores) described in the previous section, there are three cases where results using the SPP differ qualitatively from those using the GPP:

1. For overall reflective Runny Nose, the SPP result is C instead of B
2. For week 1 reflective Sneezing, the SPP result is B instead of A
3. For week 1 instantaneous Sneezing, the SPP result is C instead of B

If we once again classify codes of "A" and "B" as satisfying regulatory requirements, the summary for the SPP analyses would be:

overall	5 endpoints pass (including the primary endpoint), 5 do not
week 1	2 endpoints pass, 8 do not
week 2	7 endpoints pass, 3 do not

Influence of four subjects identified by the medical reviewer

The OGD medical reviewer made note of four subjects deleted from the evaluable (i.e. PP) analysis data set by the Sponsor. These were subject 19 at site 5 (in the Reference group), subject 6 at site 5 (Test group), subject 6 at site 18 (Placebo group), and subject 29 at site 34 (Test group.) In the cases of the first three of these, they discontinued the study because of increasing allergic symptoms or symptoms that were not controlled by the study drug. In the case of #29 at site 34, the subject took a prohibited drug product (Sudafed) to relieve allergy symptoms. If this had been a study with a dichotomous endpoint (i.e. cure/no cure, success/failure), these subjects would have been included in the evaluable analysis data set as treatment failures. For the present

study, the endpoints do not allow coding as "failure". However, we may evaluate the influence of these four subjects by repeating the equivalence analyses with their data included.

The results of equivalence analyses with these four subjects included are given in Appendix B (GPP) and Appendix C (SPP).

For analyses with the GPP, the results with these four subjects included agree qualitatively with results without the four subjects in every case.

For analyses with the SPP, there are two cases where results with these four subjects included differ qualitatively from results without the four subjects. For average week 1 instantaneous Itchy Nose, the results with these four subjects would be coded as C, compared to B without the four. For average week 2 instantaneous Runny Nose, the results with these four subjects would be coded as B, compared to C without the four. If results coded as "C" and "D" are regarded as not fulfilling regulatory requirements, the "pass/not pass" conclusion is changed in both of these cases – instantaneous week 1 Itchy Nose changes from "pass" to "not pass", and instantaneous week 2 Runny Nose changes from "not pass" to "pass".

Comments on the Sponsor's Analysis

As noted previously, the Sponsor used the same statistical model as I have used, including treatment and site as factors and baseline as a covariate. The Sponsor's method of equivalence analysis used SAS PROC MIXED and attempted to use Fieller's method to calculate 90% confidence intervals for the ratio of means based on the "least square means" produced by PROC MIXED. In the equivalence analyses the Sponsor used only data from Test and Reference, as I have done. Because of the nature of SAS "least square means", this method of analysis has the following properties:

1. The comparison is implicitly made at a baseline value equal to the sample mean of the baselines in the SPP for subjects who received Test or Reference.
2. The analysis implicitly puts equal weight on each of the sites.

Since it is the case for all of the endpoints examined in this review that the 90% confidence limits for the ratio of the Test mean over the Reference mean are closer to 1.0 for higher values of baseline, a favorable conclusion using the Sponsor's method would imply that the endpoint passed the usual equivalence test at least for all baseline values greater than or equal to the average baseline for Test and Reference subjects in the SPP. However, the Sponsor did not make this point, and ignored the question of baseline values other than the sample mean baseline for the active treatments.

For the primary endpoint (overall average reflective TNSS change from baseline), the sample mean baseline reflective TNSS for the Test and Reference subjects in the SPP is 18.262. This may be compared to 18.251 and 18.571, the sample mean and sample median respectively for all subjects (including Placebo subjects) in the SPP.

The Sponsor made an error in calculating the 90% confidence interval using Fieller's method. For the primary endpoint, the Sponsor reports a 90% confidence interval of (0.9906, 1.1995), but the correct 90% confidence interval is (0.9694, 1.2399). SAS code and output for carrying out the Fieller's method computations using PROC GLM (for the primary endpoint, using the SPP) are included in Appendix D.

Safety

Please see the details in the OGD medical reviewer's report.

Discussion and Conclusions

Efficacy: Both active treatments (Test and Reference) were statistically significantly better than Placebo for all endpoints (including the primary endpoint) based on overall assessments (averaged over both weeks of the treated period) and on week 2 assessments. For endpoints based on week 1 assessments, the active treatments beat Placebo for some endpoints but not for others (see details above.)

Equivalence: The linear relationship between the baseline covariate and the mean change from baseline endpoint was highly statistically significant in all cases (for example, using the GPP, $p < 0.0001$ for 29 of the 30 endpoints considered. For week 2 Nasal Congestion, $p = 0.0002$.) Thus, inclusion of the baseline covariate in the statistical model resulted in an important reduction in the residual variance. But in the model with a baseline covariate the ratio of the Test product mean over the Reference product mean *depends on baseline*, which leads to the question "For which values of baseline must equivalence be demonstrated?" One possible answer to this question is that equivalence should be demonstrated at the average value of baseline seen in the study. Because the distribution of baseline values seen in this study is skewed (with a "tail" of lower values), it is my belief that the median (the value such that half of the distribution is below it and half above it) is a more meaningful measure of "average value" or "central location" than is the mean, which tends to be "pulled" in the direction of the tail of the distribution.

If we decide that equivalence must be demonstrated for baseline values greater than or equal to the sample median baseline seen in the PP analysis data set, then equivalence between Test and Reference (under the usual criteria) is established in this study for the primary endpoint and for 15 out of 29 secondary endpoints, using the GPP. If we require that equivalence must be demonstrated for baseline values greater than or equal to the sample *mean* baseline seen in the PP analysis data set, then equivalence between Test and Reference (under the usual criteria) is established in this study for the primary endpoint and for 12 out of 29 secondary endpoints, using the GPP.

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Appendix A – Summary of equivalence analyses using the SPP

In the summaries of equivalence results using the SPP that follow, I report the minimum baseline value for which the endpoint passes the usual equivalence test (i.e. the 90% confidence interval for the ratio of means falls within [0.80, 1.25]) using the SPP with data from Test and Reference (i.e. no Placebo data were used in calculating the confidence intervals.) I also report the sample mean and sample median (called "mean" and "median", respectively, in the summaries) from the SPP including all three treatments. In cases where the endpoint does not pass the test for any baseline value in the possible range (0-6 for individual symptoms), I report the point estimate and 90% confidence interval at the maximum value of baseline (6 for individual symptoms.)

The codes – A, B, C, and D – are as described in the "Summary of GPP equivalence analyses" section of the review, with appropriate adjustment for the differing range of possible values.

reflective overall endpoints

TNSS -	passes for baseline ≥ 17.666.	mean = 18.251	median = 18.571	code = A
Itchy Nose –	passes for baseline ≥ 3.728.	mean = 4.516	median = 4.571	code = A
Runny Nose –	passes for baseline ≥ 5.260.	mean = 4.816	median = 5	code = C
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.149, 90% confidence interval = (1.017, 1.306)				code = D
Sneezing -	passes for baseline ≥ 3.056.	mean = 3.838	median = 4	code = A

instantaneous overall endpoints

TNSS -	passes for baseline ≥ 17.578.	mean = 17.036	median = 17.333	code = C
Itchy Nose -	passes for baseline ≥ 3.349.	mean = 4.320	median = 4.5	code = A
Runny Nose -	passes for baseline ≥ 5.272.	mean = 4.596	median = 4.857	code = C
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.189, 90% confidence interval = (1.045, 1.363)				code = D
Sneezing -	passes for baseline ≥ 2.549	mean = 3.194	median = 3.429	code = A

reflective week 1 endpoints

TNSS -	passes for baseline ≥ 21.425.	mean = 18.251	median = 18.571	code = C
Itchy Nose -	passes for baseline ≥ 5.248.	mean = 4.516	median = 4.571	code = C
Runny Nose - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.125, 90% confidence interval = (0.996, 1.277)				code = D
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.177, 90% confidence interval = (1.028, 1.359)				code = D
Sneezing -	passes for baseline ≥ 3.994	mean = 3.838	median = 4	code = B

instantaneous week 1 endpoints

TNSS -	passes for baseline ≥ 21.118.	mean = 17.036	median = 17.333	code = C
Itchy Nose -	passes for baseline ≥ 4.436.	mean = 4.320	median = 4.5	code = B
Runny Nose - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.105, 90% confidence interval = (0.972, 1.263)				code = D
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.203, 90% confidence interval = (1.041, 1.407)				code = D
Sneezing -	passes for baseline ≥ 3.503.	mean = 3.194	median = 3.429	code = C

reflective week 2 endpoints

TNSS -	passes for baseline ≥ 15.204.	mean = 18.251	median = 18.571	code = A
Itchy Nose -	passes for baseline ≥ 2.918.	mean = 4.516	median = 4.571	code = A
Runny Nose -	passes for baseline ≥ 4.583.	mean = 4.816	median = 5	code = A
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.128, 90% confidence interval = (0.996, 1.284)				code = D
Sneezing -	passes for baseline ≥ 2.575.	mean = 3.838	median = 4	code = A

instantaneous week 2 endpoints

TNSS -	passes for baseline ≥ 15.671.	mean = 17.036	median = 17.333	code = A
Itchy Nose -	passes for baseline ≥ 2.769.	mean = 4.320	median = 4.5	code = A
Runny Nose -	passes for baseline ≥ 4.884.	mean = 4.596	median = 4.857	code = C
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.179, 90% confidence interval = (1.036, 1.352)				code = D
Sneezing -	passes for baseline ≥ 2.263.	mean = 3.194	median = 3.429	code = A

At the sample median baseline there is one endpoint out of 30 for which the point estimate of the ratio of Test mean over Reference mean is less than 1.0. This endpoint is instantaneous sneezing for week 2. At the sample median baseline there is no case where the lower limit of the 90% confidence interval falls below 0.80. Thus, in cases where the 90% confidence interval is not contained within [0.80, 1.25] it is because we cannot rule out the possibility that the Test product is *too much better* then the Reference product.

Appendix B – Summary of equivalence analyses using the GPP, with the addition of four subjects

This appendix contains summaries of equivalence results using the GPP with the addition of four patients (subject 19 at site 5 (in the Reference group), subject 6 at site 5 (Test group), subject 6 at site 18 (Placebo group), and subject 29 at site 34 (Test group)) identified by the OGD medical reviewer. I report the minimum baseline value for which the endpoint passes the usual equivalence test (i.e. the 90% confidence interval for the ratio of means falls within [0.80, 1.25]) using data from Test and Reference (i.e. no Placebo data were used in calculating the confidence intervals.) I also report the sample mean and sample median (called "mean" and "median", respectively, in the summaries) from the augmented GPP including all three treatments. In cases where the endpoint does not pass the test for any baseline value in the possible range (0-3 for individual symptoms), I report the point estimate and 90% confidence interval at the maximum value of baseline (3 for individual symptoms.)

The codes – A, B, C, and D – are as described in the "Summary of GPP equivalence analyses" section of the review.

reflective overall endpoints

TNSS -	passes for baseline ≥ 8.426.	mean = 9.254	median = 9.429	code = A
Itchy Nose –	passes for baseline ≥ 1.759.	mean = 2.285	median = 2.429	code = A
Runny Nose –	passes for baseline ≥ 2.496.	mean = 2.434	median = 2.571	code = B
Nasal Congestion - does not pass for any baseline in the 0-3 range. At baseline = 3: point estimate = 1.149, 90% confidence interval = (1.020, 1.300)				code = D
Sneezing -	passes for baseline ≥ 1.389.	mean = 1.954	median = 2	code = A

instantaneous overall endpoints

TNSS -	passes for baseline ≥ 8.888.	mean = 8.653	median = 8.857	code = C
Itchy Nose -	passes for baseline ≥ 1.784.	mean = 2.190	median = 2.286	code = A
Runny Nose -	passes for baseline ≥ 2.618.	mean = 2.324	median = 2.429	code = C
Nasal Congestion - does not pass for any baseline in the 0-3 range. At baseline = 3: point estimate = 1.197, 90% confidence interval = (1.058, 1.364)				code = D
Sneezing -	passes for baseline ≥ 1.288.	mean = 1.625	median = 1.857	code = A

reflective week 1 endpoints

TNSS -	passes for baseline ≥ 10.445.	mean = 9.254	median = 9.429	code = C
Itchy Nose -	passes for baseline ≥ 2.531.	mean = 2.285	median = 2.429	code = C
Runny Nose - does not pass for any baseline in the 0-3 range. At baseline = 3: point estimate = 1.116, 90% confidence interval = (0.993, 1.259)				code = D
Nasal Congestion - does not pass for any baseline in the 0-3 range. At baseline = 3: point estimate = 1.183, 90% confidence interval = (1.036, 1.362)				code = D
Sneezing -	passes for baseline ≥ 1.873	mean = 1.954	median = 2	code = A

instantaneous week 1 endpoints

TNSS -	passes for baseline ≥ 10.277.	mean = 8.646	median = 8.857	code = C
Itchy Nose -	passes for baseline ≥ 2.191.	mean = 2.185	median = 2.286	code = B
Runny Nose –	passes for baseline ≥ 2.956.	mean = 2.325	median = 2.429	code = C
Nasal Congestion - does not pass for any baseline in the 0-3 range. At baseline = 3: point estimate = 1.214, 90% confidence interval = (1.058, 1.407)				code = D
Sneezing -	passes for baseline ≥ 1.711.	mean = 1.622	median = 1.845	code = B

reflective week 2 endpoints

TNSS -	passes for baseline ≥ 7.201.	mean = 9.254	median = 9.429	code = A
Itchy Nose -	passes for baseline ≥ 1.359.	mean = 2.285	median = 2.429	code = A
Runny Nose -	passes for baseline ≥ 2.147.	mean = 2.434	median = 2.571	code = A
Nasal Congestion - does not pass for any baseline in the 0-3 range. At baseline = 3: point estimate = 1.121, 90% confidence interval = (0.993, 1.270)				code = D
Sneezing -	passes for baseline ≥ 1.258.	mean = 1.954	median = 2	code = A

instantaneous week 2 endpoints

TNSS -	passes for baseline ≥ 7.881.	mean = 8.664	median = 8.857	code = A
Itchy Nose -	passes for baseline ≥ 1.508.	mean = 2.193	median = 2.286	code = A
Runny Nose -	passes for baseline ≥ 2.438.	mean = 2.326	median = 2.429	code = C
Nasal Congestion - does not pass for any baseline in the 0-3 range. At baseline = 3: point estimate = 1.168, 90% confidence interval = (1.032, 1.330)				code = D
Sneezing -	passes for baseline ≥ 1.210.	mean = 1.630	median = 1.857	code = A

At the sample median baseline there are 2 endpoints out of 30 for which the point estimate of the ratio of Test mean over Reference mean is less than 1.0. These endpoints are reflective sneezing for week 2 and instantaneous sneezing for week 2. At the sample median baseline there is no case where the lower limit of the 90% confidence interval falls below 0.80. Thus, in cases where

the 90% confidence interval is not contained within [0.80, 1.25] it is because we cannot rule out the possibility that the Test product is *too much better* then the Reference product.

Appendix C – Summary of equivalence analyses using the SPP, with the addition of four subjects

This appendix contains summaries of equivalence results using the SPP with the addition of four patients (subject 19 at site 5 (in the Reference group), subject 6 at site 5 (Test group), subject 6 at site 18 (Placebo group), and subject 29 at site 34 (Test group)) identified by the OGD medical reviewer. I report the minimum baseline value for which the endpoint passes the usual equivalence test (i.e. the 90% confidence interval for the ratio of means falls within [0.80, 1.25]) using data from Test and Reference (i.e. no Placebo data were used in calculating the confidence intervals.) I also report the sample mean and sample median (called "mean" and "median", respectively, in the summaries) from the augmented SPP including all three treatments. In cases where the endpoint does not pass the test for any baseline value in the possible range (0-6 for individual symptoms), I report the point estimate and 90% confidence interval at the maximum value of baseline (6 for individual symptoms.)

The codes – A, B, C, and D – are as described in the "Summary of GPP equivalence analyses" section of the review, with appropriate adjustment for the differing range of possible values.

reflective overall endpoints

TNSS -	passes for baseline ≥ 17.590.	mean = 18.270	median = 18.571	code = A
Itchy Nose –	passes for baseline ≥ 3.658.	mean = 4.515	median = 4.571	code = A
Runny Nose –	passes for baseline ≥ 5.254.	mean = 4.823	median = 5	code = C
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.150, 90% confidence interval = (1.016, 1.308)				code = D
Sneezing -	passes for baseline ≥ 3.007.	mean = 3.861	median = 4	code = A

instantaneous overall endpoints

TNSS -	passes for baseline ≥ 17.567.	mean = 17.001	median = 17.333	code = C
Itchy Nose -	passes for baseline ≥ 3.314.	mean = 4.299	median = 4.429	code = A
Runny Nose -	passes for baseline ≥ 5.266.	mean = 4.605	median = 4.857	code = C
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.191, 90% confidence interval = (1.047, 1.367)				code = D
Sneezing -	passes for baseline ≥ 2.520.	mean = 3.180	median = 3.429	code = A

reflective week 1 endpoints

TNSS -	passes for baseline ≥ 21.634.	mean = 18.270	median = 18.571	code = C
Itchy Nose -	passes for baseline ≥ 5.282.	mean = 4.515	median = 4.571	code = C
Runny Nose - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.126, 90% confidence interval = (0.997, 1.277)				code = D
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.182, 90% confidence interval = (1.032, 1.365)				code = D
Sneezing -	passes for baseline ≥ 3.948.	mean = 3.861	median = 4	code = B

instantaneous week 1 endpoints

TNSS -	passes for baseline ≥ 21.391.	mean = 17.001	median = 17.333	code = C
Itchy Nose -	passes for baseline ≥ 4.448.	mean = 4.299	median = 4.429	code = C
Runny Nose - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.107, 90% confidence interval = (0.974, 1.265)				code = D
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.210, 90% confidence interval = (1.046, 1.414)				code = D
Sneezing -	passes for baseline ≥ 3.534.	mean = 3.180	median = 3.429	code = C

reflective week 2 endpoints

TNSS -	passes for baseline ≥ 14.735.	mean = 18.270	median = 18.571	code = A
Itchy Nose -	passes for baseline ≥ 2.732.	mean = 4.515	median = 4.571	code = A
Runny Nose -	passes for baseline ≥ 4.495.	mean = 4.823	median = 5	code = A
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.120, 90% confidence interval = (0.987, 1.279)				code = D
Sneezing -	passes for baseline ≥ 2.486.	mean = 3.861	median = 4	code = A

instantaneous week 2 endpoints

TNSS -	passes for baseline ≥ 15.149.	mean = 17.001	median = 17.333	code = A
Itchy Nose -	passes for baseline ≥ 2.636.	mean = 4.299	median = 4.429	code = A
Runny Nose -	passes for baseline ≥ 4.795.	mean = 4.605	median = 4.857	code = B
Nasal Congestion - does not pass for any baseline in the 0-6 range. At baseline = 6: point estimate = 1.173, 90% confidence interval = (1.029, 1.349)				code = D
Sneezing -	passes for baseline ≥ 2.471.	mean = 3.180	median = 3.429	code = A

At the sample median baseline there are 2 endpoints out of 30 for which the point estimate of the ratio of Test mean over Reference mean is less than 1.0. These endpoints are reflective sneezing for week 2 and instantaneous sneezing for week 2. At the sample median baseline there is no case where the lower limit of the 90% confidence interval falls below 0.80. Thus, in cases where

the 90% confidence interval is not contained within [0.80, 1.25] it is because we cannot rule out the possibility that the Test product is *too much better* then the Reference product.

Appendix D – SAS code and output for computing the 90% confidence interval using the Sponsor's approach

The following SAS code may be used to calculate the 90% confidence interval, using Fieller's method, for the Test mean over the Reference mean (at baseline = the sample mean baseline for Test and Reference in the SPP) for the primary endpoint:

```
options nofmterr nocenter ps=65 ls=75;
libname rox 'c:\fluticasone\roxane';

proc sort data=rox.edrytnss;
by site subject;
run;
proc sort data=rox.treat;
by site subject;
run;

data withtrt; merge rox.edrytnss rox.treat;by site subject;
ctnssr=tnssr0-tnssravg;
if eval=1;
run;

data noplac; set withtrt; if trt ne 1;

proc glm data=noplac;
class site trt;
model ctnssr = site trt tnssr0;
lsmeans trt/e cov stderr out=getlsm;
estimate 'BASE=18.2624272 0.9694' intercept 0.0306 trt 1 -0.9694 tnssr0
      0.558830272;
estimate 'BASE=18.2624272 1.2399' intercept -0.2399 trt 1 -1.2399 tnssr0
      -4.381156285;
title1 'using EDRYTNSS';
run;

data tlsm; set getlsm; if trt=2;
drop _name_; x1=lsmean; se1=stderr; v1=cov1; cov=cov2;
run;

data rlsm; set getlsm; if trt=3;
drop _name_; x2=lsmean; se2=stderr; cov=cov1; v2=cov2;
t95=1.6502177127;
/*
NOTE: 1.6502177127 is the 95th percentile of Student's t-distribution
      with 285 degrees-of-freedom.
*/
run;

data lsm; merge tlsm rlsm;
a=(x2**2)-(t95**2)*v2;
c=(x1**2)-(t95**2)*v1;
b=2*(((t95**2)*cov)-(x1*x2));
low=((-b)-sqrt((b**2)-(4*a*c)))/(2*a);
high=((-b)+sqrt((b**2)-(4*a*c)))/(2*a);
drop trt lsmean stderr number cov1 cov2;
```

```
run;

proc print data=lsm;
title1 'lsmeans output';
title2 'low and high are the 90% confidence limits';
title3 'using Fieller method';
run;

quit;
```

The resulting output is:

```
using EDRYTNSS

The GLM Procedure

Dependent Variable: ctnssr

                                                 Standard
Parameter                        Estimate           Error    t Value    Pr > |t|

BASE=18.2624272 0.9694      0.83142294      0.50375959       1.65      0.1000
BASE=18.2624272 1.2399     -0.95800177      0.58059738      -1.65      0.1000

lsmeans output
low and high are the 90% confidence limits
using Fieller method

Obs       x1        se1         v1          cov         x2        se2         v2

 1     7.24424    0.40299    0.16240    0.036439    6.61525    0.41522    0.17241

Obs      t95          a           c           b          low         high

 1     1.65022     43.2920     52.0368     -95.6465     0.96942     1.23992
```

where "low" and "high" are the lower and upper confidence limits, respectively.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-504

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ANDA 76-504

NOV 13 2002

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
1809 Wilson Road
Columbus, OH 43228

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 Proprionate Nasal Spray, 0.05 mg/spray

DATE OF APPLICATION: October 3, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 4, 2002

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:

Peter Chen
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

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

ANDA 76-504
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB 12-NOV-2002 date
HFD-615/MShimer, CSO date 12 November 2002
Word File V:\Firmsnz\Roxane\Ltrs&rev\76504.ack
F/T EEH 11/12/02
ANDA Acknowledgment Letter!

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

XR

Attention: Jeen Min

Roxane Laboratories, Inc.

September 22, 2005

Elizabeth A. Ernst,
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

SECTION III – EXCLUSIVITY AMENDMENT

Dear Mr. Jeen Min:

Attached is the hard copy of the telephone amendment which was faxed to you today.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Matthew Annibaldi, Regulatory Affairs Associate, at (614) 241-4159.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Mike Smela

ORIG AMENDMENT

Roxane Laboratories, Inc.

August 5, 2005

Elizabeth A. Ernst,
Associate Director,
DRA-Multisource Products

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Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

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Telephone (614) 276-4000
Telefax (614) 274-0974

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

TELEPHONE AMENDMENT

Dear Mr. Smela:

Attached is the hard copy of the telephone amendment which was faxed to you today.

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4132.

Respectfully,

Virginia Z. Fojas for

Elizabeth Ernst
Associate Director, DRA-Multisource

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
M/RM

Attention: Peter Chen

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

TELEPHONE AMENDMENT
Chemistry Deficiencies

Roxane Laboratories, Inc.

July 22, 2005

Elizabeth A. Ernst,
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Mr. Chen:

We wish to amend ANDA 76-504 in response to the Telephone Amendment as discussed in our teleconference on July 11, 2005. Accordingly, we are submitting revised Product Specification No. 1521-05 for Fluticasone Propionate Nasal Spray, 50 mcg (provided as **Attachment A**) to provide the requested changes to Droplet Size Distribution (limits and method). We are also providing revised Drug Substance Specification No. 6112570-11 (see **Attachment B**) to include the requested changes to the Related Compounds limits.

Droplet Size Distribution

- Limits for D_{10} and D_{75} are revised as follows:

	Previous Limits	Revised Limits
D_{10}		
D_{75}		

b(4)

- The specification document includes the test method; as requested, the method has been revised to more clearly specify which sprays the test is performed on. It now includes the text "For each bottle, prime the bottle 6 times using the Innova Automated Actuator. Allow all of the priming sprays to go to waste. Wipe off the actuator tip. Analyze two beginning spray actuations (e.g. Sprays 7 and 8) from each of 5 separate bottles."
- As previously requested by FDA, Roxane Laboratories, Inc. (RLI) committed (in the May 25, 2005 Minor Amendment) to the post approval finalization of the Droplet Size Distribution (DSD) specifications based on significant manufacturing data. As requested, the post approval commitment included the following items:

  a. RLI acknowledges that the DSD limits provided in the ANDA at the time of approval are considered tentative.

b. RLI commits to file a Prior Approval Supplement to finalize the DSD limits within 60 days of manufacture of the twentieth commercial batch of product. The PAS will contain data from each of the 20 batches. RLI commits to propose final limits for DSD and SP based on the above data.

Drug Substance Related Compounds

- As requested, the limits for all impurities not named in the USP monograph have been tightened to N [redacted], and the limit for Single Largest Unknown has been tightened from N [redacted]
- In the July 11th teleconference, we discussed committing to using only drug substance produced by [redacted] This was clarified in a phone call on July 18th between Elizabeth Ernst and Peter Chen to mean that if Roxane updates our drug substance specification to be compliant with USP, then any API that meets the USP requirements will be acceptable to be used for commercial batches. Roxane Laboratories hereby makes that commitment; as discussed above, the USP specifications have been incorporated in the Drug Substance Specification No. 6112570-11.

b(4)

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc: I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4133.

Respectfully,

Virginia J. Fojo for

Elizabeth Ernst
Associate Director, DRA-Multisource

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N | Am

Roxane Laboratories, Inc.

May 25, 2005

Attention: Peter Chen

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

MINOR AMENDMENT
Chemistry Deficiencies

Elizabeth A. Ernst,
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Mr. Chen:

We wish to amend ANDA 76-504 in response to the Minor Amendment letter of March 24th, 2005 (copy enclosed). Enclosed please find a point-by-point response to the chemistry deficiencies and comment presented in that letter. We would also like to take this opportunity to provide the following revised documents:

- Section VIII – Raw Materials (to refer to [redacted] .S. Agent) b(4)
- Section XIII – Packaging Materials Controls section A (for the addition of an alternate clip).

These revisions are described in detail under the heading "Additional Information for the Reviewer", following the response to the Comments. Also included in this section is the additional information concerning the Active Ingredient manufacturing process change instituted by [redacted] nally explained in the Minor Amendment submitted November 11, 2003. b(4)

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

RECEIVED
MAY 26 2005
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Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

Roxane Laboratories, Inc.

February 18, 2005

Attention: Angela Payne

ANDA No. 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

LABELING AMENDMENT

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone 614-272-4785
Fax 614-276-2470
E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Ms. Payne:

We wish to amend ANDA 76-504. This is in response to the labeling revisions requested in the facsimile deficiency letter dated February 5, 2005. A copy of the letter is attached. Also included are the following:

- Twelve copies of the revised Package Insert/Patient Medication Guide
- Side-by-side comparison of the insert with the previously submitted version

We have also submitted a copy of this amendment to Ms. Kathleen D. Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4132.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

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Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

February 1, 2005

Attention: Peter Chen

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

MINOR AMENDMENT
Chemistry Deficiencies

Elizabeth A. Ernst,
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

Dear Mr. Chen:

We wish to amend ANDA 76-504 in response to the Minor Amendment letter of November 9, 2004 (copy enclosed). Enclosed please find a point-by-point response to the chemistry deficiencies and comment presented in that letter. We would also like to take this opportunity to provide the following revised documents:

- Section VIII – Raw Materials (to r [redacted] U.S. Agent)
- Section IX – Description of Manufacturing Facilities (to update description of manufacturing facility and to add description of Roxane's Western Region Distribution Facility [redacted]
- Revised blank batch records (manufacturing and packaging).

b(4)

These revisions are described in detail under the heading "Additional Information for the Reviewer", following the response to the Comment.

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

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Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/HF

Attention: Angela Payne

January 20, 2005

ANDA No. 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

MINOR AMENDMENT
(Labeling Deficiencies)

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone 614-272-4785
Fax 614-276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Ms. Payne:

We wish to amend ANDA 76-504. This is in response to the labeling revisions requested in the facsimile deficiency letter dated January 12, 2005. A copy of the letter is attached. Also included are the following:

- Twelve copies of the revised Package Insert/Patient Medication Guide
- Side-by-side comparison of the insert with the previously submitted version

We have also submitted a copy of this amendment to Ms. Kathleen D. Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4132.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

cc: Robert L. West, Deputy Director, OGD

RECEIVED
JAN 21 2005
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Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

Attention: John Grace

December 21, 2004

ANDA No. 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

MINOR AMENDMENT
(Labeling Deficiencies)

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone 614-272-4785
Fax 614-276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Mr. Grace:

We wish to amend ANDA 76-504. This is in response to the labeling revisions requested in the facsimile deficiency letter dated December 15, 2004. A copy of the letter is attached. Also included are the following:

- Twelve copies of the revised Package Insert/Patient Medication Guide
- Side-by-side comparison of the insert with the labeling presented in the December 15th fax
- Side-by-side comparison of the insert with the previously submitted version
- Twelve copies of the carton and bottle labels
- Side-by-side comparisons of the carton and bottle labels with the previously submitted versions

We have also submitted a copy of this amendment to Ms. Kathleen D. Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4132.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

RECEIVED
DEC 22 2004
OGD / CDER

cc: Robert L. West, Deputy Director, OGD

Boehringer Ingelheim
Roxane Laboratories

October 29, 2004

Steve Mazzella
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Metro Park North II
7500 Standish Place, HFD-650, Room E130
Rockville, Maryland 20855

N/MC

Elizabeth A. Ernst
Associate Director
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

Controlled Correspondence
ANDA 76-504 Fluticasone Propionate NS, 50mcg

Dear Steve,

Roxane Laboratories, Inc. received a deficiency letter from the Division of Bioequivalence (DBE) on October 19, 2004 regarding in-vitro testing that was conducted to support our ANDA for fluticasone propionate nasal spray.

After several internal discussions and a thorough review of all the in-vitro data for spray pattern and cascade impaction submitted to the Agency, Roxane feels strongly that a teleconference is needed to clarify the apparent deficiencies and to define the appropriate actions necessary for approval of our ANDA.

For Cascade Impaction, we need further clarification as to the specific criteria the Agency is using to determine bioequivalence. Bioequivalence with respect to Cascade Impaction was been established as outlined in the Draft Guidance for Industry "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action dated June 1999 which was in effect at the time Roxane completed the testing and submitted the ANDA. However, it appears that a mixture of the criteria in the 1999 and 2003 Guidance's are being applied to this test.

Bioequivalence was also demonstrated for Spray Pattern in the original submission. The "new" data that are apparently the subject of the deficiency letter are a consequence of the reanalysis of the images conducted after questions were raised by the Division of Scientific Investigation during the audit of [redacted] At the time the testing was done, automated methods for characterizing spray pattern were not available, and as there is some subjectivity in the manual methods, it is not unexpected that there will be some variation among those conducting the tests. We feel that the original analysis was appropriate and sufficient for approval and would like to discuss this issue with the Agency.

b(4)

Boehringer Ingelheim
Roxane Laboratories

A teleconference with DBE is crucial to Roxane Laboratories moving forward with this project. Consequently, we would like to set up a teleconference with the appropriate representatives of DBE as soon as possible to resolve these issues. We have worked closely with the DBE during the development of this product and throughout the review of our ANDA . Roxane feels it is critical to continue working closely to resolve all issues as quickly as possible.

Please contact me at your earliest convenience so that we can set up a time to discuss the issues in more detail. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470

Respectfully,

Elizabeth Ernst
Associate Director
DRA-Multisource Products

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

August 17, 2004

Attention: Steven Mazzella

ORIG AMENDMENT
N/AB

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

BIOEQUIVALENCY AMENDMENT

Dear Mr. Mazzella:

We wish to amend ANDA 76-504 for Fluticasone Propionate Nasal Spray, 50 mcg. This is in response to the facsimile bioequivalency deficiency letter dated August 3, 2004 (see copy attached). Enclosed please find the response to the bioequivalency deficiency. Also enclosed is an electronic version (SAS Transport File) for the Spray Pattern Data.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

cc: Dr. Dale P. Conner

7.1

ORIGINAL

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

Attention: Mujahid Shaikh

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

TELEPHONE AMENDMENT
Chemistry Deficiencies

Roxane Laboratories, Inc.

May 20, 2004

Elizabeth A. Ernst,
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Mr. Shaikh:

We wish to amend ANDA 76-504 in response to the telephone request by you and Mr. Mike Smela (Chemistry Team Leader, OGD) on May 19, 2004. You had two questions concerning the Assay/Related Substances test method contained in our drug substance specification, arising from the FDA laboratory's method validation testing:

- The assay method appears to be missing the actual calculation; please add it to the method to make it clear.
- The run time of 75 minutes is insufficient to allow detection of Fluticasone Dimer II (relative retention time 16.3). Please add a note to the method that ensures that the analyst runs the sample until the Fluticasone Dimer II is reported.

Regarding the first request, enclosed please find the newly revised Specification No. 6112570-08 which includes the appropriate assay calculation.

Regarding the second request, the specification/method document provided to the FDA laboratory in the Method Validation Amendment of February 17, 2004 was Specification No. 6112570-04. The run time was subsequently revised to 130 minutes to allow for detection of Dimer II, and the revised Specification No. 6112570-07 was provided to FDA in the Minor Amendment submitted on April 15, 2004. This correction has been retained in the current -08 revision, enclosed.

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

cc: Peter Chen, Project Manager, OGD

Telefax

Boehringer Ingelheim
Roxane Laboratories

Mr. Mujahid Shaikh
Office of Generic Drugs, CDER, FDA
301-827-5773
301-594-0180

Page: 1 of 18

Roxane Laboratories, Inc.

May 20, 2004

Elizabeth Ernst
Telephone 614-272-4785
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E-Mail eernst@col.boehringer-ingelheim.com

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

Telephone Amendment

Dear Mr. Shaikh

Per your request on May 19, 2004, please find the Telephone Amendment to the referenced ANDA attached; hard copy to follow.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

Am

Roxane Laboratories, Inc.

April 15, 2004

Attention: Peter Chen

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

MINOR AMENDMENT
Chemistry Deficiencies

Elizabeth A. Ernst,
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
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E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Mr. Chen:

We wish to amend ANDA 76-504 in response to the Minor Amendment letter of March 31, 2004 (copy enclosed). Enclosed please find a point-by-point response to the chemistry deficiencies and comments presented in that letter.

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

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APR 16 2004
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Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

Roxane Laboratories, Inc.

February 27, 2004

Attention: Peter Chen

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

MINOR AMENDMENT
Chemistry Deficiencies

Elizabeth A. Ernst,
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
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E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Mr. Chen:

We wish to amend ANDA 76-504 in response to the Minor Amendment letter of February 10, 2004 (copy enclosed). Enclosed please find a point-by-point response to the chemistry deficiencies and comments presented in that letter.

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

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MAR - 1 2004
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Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

Attention: Peter Chen

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

MINOR AMENDMENT
Chemistry Deficiencies

Roxane Laboratories, Inc.

November 11, 2003

Elizabeth A. Ernst,
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
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E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Mr. Chen:

We wish to amend ANDA 76-504 in response to the Minor Amendment letter of September 5, 2003 (copy enclosed). Enclosed please find a point-by-point response to the chemistry deficiencies and comments presented in that letter.

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

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OGD/CDER

11-25-03

Boehringer Ingelheim
Roxane Laboratories

Attn: Ruth Warzala
Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE
NC

August 28, 2003

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg
AMENDMENT - Electronic Submission (In-vitro data set for DBE)

Dear Ruth:

I am following up on the telephone conversations I had with Dr. Singh and Ms. Sanchez on 8/27/03 and 8/28/03 regarding clarification of the electronic files that are needed in order to facilitate and complete the in-vitro review for ANDA 76-504.

Based on our discussion, I have enclosed a diskette that contains the data used in the in vitro bioequivalence analyses of the bridging study (3 lots of test and 3 lots of reference product). The studies conducted and included on the diskette as a SAS transport file containing six (6) SAS datasets are as follows:

a. Cascade Impaction data = CI_DATA.SAS7BDAT[1]
b. Spray Content Uniformity data = SCU_PRP.SAS7BDAT
c. Droplet Size Distribution data = DSD_DATA.SAS7BDAT
d. Plume Geometry data = PG_DATA.SAS7BDAT
e. Spray Pattern data = SP_DATA.SAS7BDAT
f. Tail-off data = TO_DATA.SAS7BDAT
g. Readme.pdf file = Descriptions of the datasets, including output from SAS PROC CONTENTS, and instructions, with SAS code, for converting the transport file back to SAS datasets.

For your convenience, please see Attachment A that provides some background information regarding the differences between the first in-vitro study (primary study) and the second in-vitro study (bridging study).

[1] If the SAS transport file is converted back to SAS datasets using Version 6 of SAS, then the file extension will SD2 instead of SAS7BDAT.

RECEIVED
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OGD/CDER

If upon opening you have any questions or problems with the diskette or the files contained on it, please call me.

I apologize for any confusion regarding the data files and information sent previously. I hope the information will help expedite and finalize the review.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs, at (614) 241-4133.

Sincerely

Elizabeth Ernst
Associate Director
DRA-Multisource Products

cc; Dr. G. Singh
Lizzie Sanchez
Steve Mazzella

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Roxane Laboratories, Inc.

July 1, 2003

Attention: Peter Chen

ANDA 76-504
Fluticasone Propionate Nasal Spray, 50 mcg

ORIG AMENDMENT
N/AM

MINOR AMENDMENT
Chemistry and Labeling Deficiencies

Elizabeth A. Ernst,
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

Dear Mr. Chen:

We wish to amend ANDA 76-504 in response to the Minor Amendment letter of March 28, 2003 (copy enclosed). Enclosed please find a point-by-point response to the chemistry deficiencies and comments, and the labeling deficiencies presented in that letter.

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

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JUL 0 3 2003
COMPLIANCE

7/15/03

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

June 5, 2003

Bioequivalency Amendment
Fluticasone Propionate Nasal Spray, 50 mcg
ANDA 76-504

Elizabeth Ernst
Associate Director,
DRA-Multisource Products
Telephone: 614.272.4785
Telefax: 614.276.2470
E-Mail eernst@col.boehringer-ingelheim.com

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

Dear Mr. Buehler,

On March 7, 2003 Roxane Laboratories contacted Lizzie Sanchez informing her that we had received a call from [redacted] regarding our pivotal bioequivalence study, Study No. 451-05, submitted in on October 3, 2002 as part of the above referenced ANDA. During an internal audit [redacted] discovered an error in the reported fluticasone propionate concentrations for a small percentage of the plasma samples that were analyzed for study 451-05.

It appears that out of the 5956 samples assayed, there were 166 samples for which the concentration was incorrectly reported. The reason for the incorrect reporting was either a software problem on the Micromass instrument used to analyze the samples or an incorrect interpretation of the SOP for reporting concentration values following reassays. A 100% review of all data generated for study 451-05 was completed and appropriate corrections were made. [redacted] is confident that all of the data is now correct.

The corrected data was used to recalculate the pharmacokinetic parameters for study 451-05 and the associated statistical analyses were rerun. Upon completion of the analyses, the conclusions regarding bioequivalence have not significantly changed and are outlined below for your reference:

Parameter	90% Confidence Interval	
	Original	Revised
Cmax (pg/mL)	106.3 - 117.6	106.4 → 117.7
AUC_{0-t} (pg.h/mL)	109.4 – 126.7	109.5 → 127.0
AUC_{∞} (pg.h/mL)	104.8 – 124.1	105.2 → 125.4

Consistent with the original analysis using the full statistical model, the 90% confidence interval (CI) for the geometric ratio, test-to-reference, from the new analysis demonstrates that Cmax is within the bioequivalence window. In the original analysis, only the CI for AUC_{0-t} was outside the upper limits; however using the revised data, it appears that both AUC_{0-t} and AUC_{∞} are slightly outside the 80%→ 125% bioequivalence window.

It is important to note that in both original and revised analysis for study 451-05 there is a significant group* treatment effect ($p<0.10$) for log-transformed AUC_{0-t} which appears to be due to subjects in group 1.

As discussed in the original ANDA, a bootstrap analysis was completed in both the original and revised analyses to attempt to identify a subset of subjects within group I that appeared to be the source of the differences between groups and/or lack of bioequivalence for AUC_{0-t} and AUC_{∞} based on traditional bioeqivalence criteria. In the original analysis, based only on AUC_{0-t}, 5 subjects were found to contribute to the group effect and lack of bioequivalence. The same 5 subjects were still responsible in the revised data set and 2 additional subjects were identified based on AUC_{∞}. Below is a summary of the original versus the revised bootstrap analyses after removal of the 5 (original) or 7 (revised) subjects.

Parameter	90% Confidence Interval	
	Original	Revised
Cmax (pg/mL)	103.8 - 115.1	104.0 → 115.6
AUC_{0-t} (pg.h/mL)	104.0 – 120.6	104.2 → 121.0
AUC_{∞} (pg.h/mL)	101.5 – 118.6	100.4 → 117.7

Consistent with the original analysis, after exclusion of the identified outliers group effects were no longer significant and the CI for both the AUC0-t and AUC∞ are within the 80%→ 125% bioequivalence window.

At this time Roxane Laboratories would like to amend ANDA 76-504 for Fluticasone Propionate Nasal Spray, 50 mcg. Enclosed for review is a copy of the revised/amended Section VI of the ANDA, including a revised report for study 451-05 and the discussion of the bootstrap analysis. In addition, revised copies of the SAS transport data set are also included. A copy has also been submitted to archive.

We apologize for any inconvenience this has caused in regards to reviewing section VI of the ANDA. We appreciate your help and attention to this matter. Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470.

Respectfully,

~~Elizabeth~~ Ernst
Associate Director, DRA- Multisource Products

CC: Lizzie Sanchez
Peter Chen

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

505(j)(2)(A) OK
12-NOV-2002

October 3, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Abbreviated New Drug Application
Fluticasone Propionate Nasal Spray, 50 mcg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Madam/Sir:

In accordance with 21 CFR 314.94, Roxane Laboratories, Inc. is submitting an Abbreviated New Drug Application (ANDA) for Fluticasone Propionate Nasal Spray, 50 mcg. This ANDA consists of 64 volumes. This ANDA was formatted in accordance with the Guidance for Industry, Organization of an ANDA, February 1999.

The reference listed drug is FLONASE® (Fluticasone Propionate) Nasal Spray, 50 mcg, manufactured by Glaxo Wellcome. The active ingredient is fluticasone propionate.

Four complete copies of the draft labeling are contained in the Archival and CMC Review copies of this application. The drug product will be manufactured, tested, labeled, packaged and released by Roxane Laboratories, Inc. No contract manufacturers or packagers are used for the proposed drug product. *In vivo* and *in vitro* bioequivalence study reports are also included in this application. Furthermore, two copies of the ANDA Section XV, Analytical Methods, are enclosed separately along with this application.

Samples and the methods validation package will be submitted upon the request and direction of the Office of Generic Drugs. Roxane Laboratories, Inc. commits to provide full cooperation to resolve any problems that may arise during the methods validation testing as part of the "Post-Approval" for the above listed drug product.

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Mr. Steven Eastham, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4132.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

ANDA 76-504

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
Associate Director, DRA
1809 Wilson Road
Columbus, OH 43228

FEB 2 4 2006

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) for Fluticasone Propionate Nasal Spray, 0.05 mg (50 mcg) nasal spray, which was submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), and approved on February 22, 2006.

The Food and Drug Administration (FDA) is hereby notifying you that approval of this ANDA is suspended for 10 days pursuant to the temporary restraining order (Civil No. AMD 06-469) issued on February 23, 2006, by the United States District Court for the District of Maryland, Baltimore Division. This temporary restraining order expires on March 6, 2006, at 2:00 PM. Approval of this ANDA will not become effective until FDA issues a letter lifting the suspension of approval.

Please note that, pursuant to section 505(a) of the Act, no person "shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of the application filed pursuant to subsection 505(b) or (j) [of the Act] is effective with respect to such drug." Also, until the approval is no longer suspended, this drug product will not be listed in the "Orange Book".

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

Sincerely yours,

Gary Buehler 2/24/06
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Temporary Restraining Order

cc: ANDA 76-504
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff
HFD-617/P.Chen/

SUSPEND APPROVAL LETTER!

V:\FIRMSAM\ROXANE\LTRS&REV\76504SUSPEND.DOC
Drafted by: C.Parise 2/24/06
Edited by: D. Read, S. Vaid, L. Dickinson 2/24/06

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

GLAXO GROUP LTD.
d/b/a/ GLAXOSMITHKLINE *

Plaintiff, *

v. * CIVIL NO. AMD 06-469

MICHAEL O. LEAVITT., *
in his official capacity as
SECRETARY, DEPARTMENT OF *
HEALTH AND HUMAN SERVICES,
*
and
*
ANDREW C. VON ESCHENBACH, M.D.
in his official capacity as *
ACTING COMMISSIONER,
FOOD AND DRUG ADMINISTRATION, *

Defendants, *

and *

ROXANE LABORATORIES, *

Defendant-Intervenor. *

* *

TEMPORARY RESTRAINING ORDER

Upon consideration of the Complaint filed by the Plaintiff Glaxo Group Ltd. d/b/a/ GlaxoSmithKline ("GSK"), its Motion for a Temporary Restraining Order, the Memorandum in Support thereof, and having conducted a hearing on this date, and having heard opposition thereto from the Defendants and the Defendant Intervenor the Court finds that GSK has demonstrated some liklihood of success on the merits, that the balance of harms and the public interest clearly weigh in GSK's favor, and that GSK will suffer immediate and irreparable injury unless the Defendants and the

Defendant Intervenor are temporarily restrained as set forth in this Order.

Accordingly, IT IS HEREBY ORDERED pursuant to Rule 65(b) of the Federal Rules of Civil Procedure that:

(i) Plaintiff's Motion for a Temporary Restraining Order is GRANTED;

(ii) During the pendency of this Order, the approval and any future approval by the Food and Drug Administration of an abbreviated new drug application allowing the marketing and sale of a generic version of GSK's Flonase® Nasal Spray SHALL BE AND IS SUSPENDED; and

(iii) The Plaintiff and PAR Pharmaceuticals shall cease the distribution of such generic product and the Plaintiff will not contract with any other company to distribute such generic product during the pendency of this Order.

IT IS FURTHER HEREBY ORDERED, pursuant to Rule 65(c) that the Plaintiff shall post a surety bond with the Clerk of the Court in the amount of $3,000,000 by 5:00 pm February 24, 2006.

The Clerk of the Court shall provide a copy of this Order to counsel for each party on this date.

This Temporary Restraining Order shall expire at 2:00 pm on March 6, 2006.

The foregoing is Ordered this 23rd day of February 2006 at 6:47 pm.

/s/ Richard D. Bennett

Richard D. Bennett
United States District Judge