CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-025

***Name*:** Ipratropium Bromide Nasal Solution, 0.03%, (Nasal Spray), 0.021 mg/spray

***Sponsor*:** Bausch & Lomb Pharmaceuticals, Inc.

***Approval Date*:** March 31, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-025

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-025

APPROVAL LETTER

ANDA 76-025

MAR 31 2003

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated November 10, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ipratropium Bromide Nasal Solution, 0.03%, (Nasal Spray), 0.021 mg/spray, packaged in a 30 mL bottle fitted with a metered nasal spray pump.

Reference is also made to your amendments dated September 26, 2001; September 12, and October 3, 2002; and January 28, 2003.

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 Ipratropium Bromide Nasal Solution, 0.03%, (Nasal Spray), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Atrovent® Nasal Spray, 0.03%, of Boehringer Ingelheim Pharmaceuticals, Inc.).

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.

Post-marketing 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies that may be identified.

Sincerely yours,

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

3/31/03

cc: ANDA 76-025
Division File
Field Copy
HFD-610/R. West
HFD-610/Orange Book
HFD-330
HFD-205

Endorsements:
HFD-625/M.Shaikh/ 3/19/03
HFD-625/M.Smela/ 3/24/03
HFD-617/P.Chen/ for 3/24/03
HFD-613/A.Payne/ 3/24/03
HFD-613/J.Grace/ 3/24/2003

Robert West 3/26/2003

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F/T by:ard/3/19/03

APPROVAL / PMCT

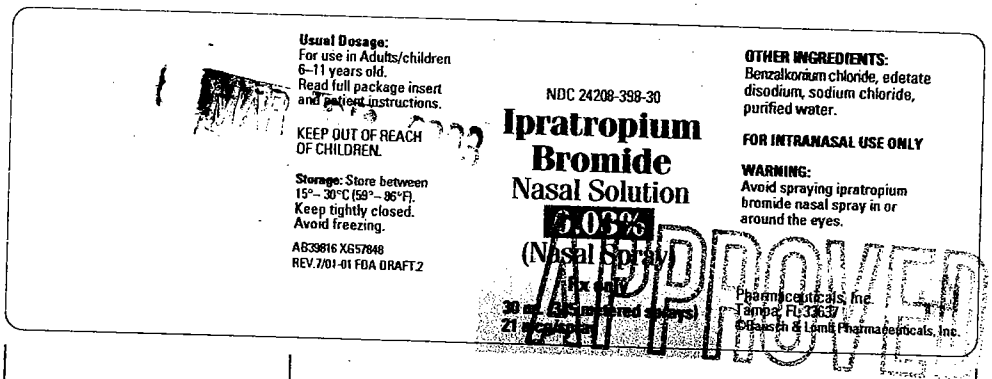
3/25/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-025

LABELING



3 3/8" x 1 1/8" 1" Non UV at left 1/16" Margins
CORE 39816
Art is at 100%
3 Color: Black, Process Blue, PMS 355
L-
PHARMACODE#

ENLARGED TO 150%
BY FOIA STAFF

CORE 39816
30 mL CARTON
Art is at 100%
Box Dimensions: 1 7/8" x 1 5/8" x 4 1/2"
3 Color: Black, Process Blue, PMS 355
L-2070
PHARMACODE#
SCANNER BAR LOCATION:

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)

BAUSCH & LOMB

NDC 24208-398-30

Ipratropium Bromide
Nasal Solution
0.03%
(Nasal Spray)

Rx only

30 mL (345 metered sprays)
21 mcg/spray

CONTAINS:
Ipratropium bromide 0.03% in a pH-adjusted to 4.7, isotonic aqueous solution which also contains benzalkonium chloride, edetate disodium, sodium chloride.

USUAL DOSAGE:
For use in Adults/ children 6–11 years old. Two sprays per nostril, two or three times daily. Read accompanying full package insert and patient instructions.

WARNING:
Avoid spraying ipratropium bromide nasal spray in or around the eyes.

BAUSCH & LOMB

NDC 24208-398-30

Ipratropium Bromide
Nasal Solution
0.03%
(Nasal Spray)

Rx only

30 mL (345 metered sprays)
21 mcg/spray

KEEP OUT OF REACH OF CHILDREN.

Storage:
Store between 15°– 30°C (59°– 86°F).
Keep tightly closed.
Avoid freezing.

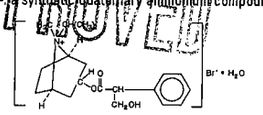
Bausch & Lomb
Pharmaceuticals, Inc.
Tampa, FL 33637

XQ91904
REV. 7/01-01
AB39816
FDA DRAFT.2

ATTENTION PHARMACIST: Detach "Patient's Instructions for Use" from package insert and dispense with product.

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)

DESCRIPTION: The active ingredient in Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is ipratropium bromide monohydrate. It is an anticholinergic agent chemically described as 8-azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate *(endo,syn)*-(±)- a synthetic quaternary ammonium compound, chemically related to atropine. Its structural formula is:



ipratropium bromide monohydrate

$C_{20}H_{30}BrNO_3 \cdot H_2O$

Mol. Wt. 430.4

Ipratropium bromide is a white to off-white, crystalline substance. It is freely soluble in lower alcohols and water, existing in an ionized state in aqueous solutions, and relatively insoluble in non-polar media.

Ipratropium bromide nasal solution 0.03% (Nasal Spray) is a metered-dose, manual pump unit which delivers 21 mcg (70 µL) ipratropium bromide per spray on an anhydrous basis in an isotonic aqueous solution with pH adjusted to 4.7. It also contains benzalkonium chloride, edetate disodium, sodium chloride, sodium hydroxide, hydrochloric acid, and purified water. Each bottle contains 345 sprays.

CLINICAL PHARMACOLOGY: Mechanism of Action: Ipratropium bromide is an anticholinergic agent that inhibits vagally-mediated reflexes by antagonizing the action of acetylcholine at the cholinergic receptor. In humans, ipratropium bromide has anti-secretory properties and, when applied locally, inhibits secretions from the serous and seromucous glands lining the nasal mucosa. Ipratropium bromide is a quaternary amine that minimally crosses the nasal and gastrointestinal membrane and the blood-brain barrier, resulting in a reduction of the systemic anticholinergic effects (e.g., neurologic, ophthalmic, cardiovascular, and gastrointestinal effects) that are seen with tertiary anticholinergic amines.

Pharmacokinetics:

Absorption: Ipratropium bromide is poorly absorbed into the systemic circulation following oral administration (2 - 3%). Less than 20% of an 84 mcg per nostril dose was absorbed from the nasal mucosa of normal volunteers, induced-cold patients, or perennial rhinitis patients.

Distribution: Ipratropium bromide is minimally bound (0 to 9% *in vitro*) to plasma albumin and a_1-acid glycoprotein. Its blood/plasma concentration ratio was estimated to be about 0.89. Studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier.

Metabolism: Ipratropium bromide is partially metabolized to ester hydrolysis products, tropic acid and tropane. These metabolites appear to be inactive based on *in vitro* receptor affinity studies using rat brain tissue homogenates.

Elimination: After intravenous administration of 2 mg ipratropium bromide to 10 healthy volunteers, the terminal half-life of ipratropium was approximately 1.6 hours. The total body clearance and renal clearance were estimated to be 2,505 and 1,019 ml/min, respectively. The amount of the total dose excreted unchanged in the urine (Ae) within 24 hours was approximately one-half of the administered dose.

Pediatrics: Following administration of 42 mcg of ipratropium bromide per nostril two or three times a day in perennial rhinitis patients 6-18 years old, the mean amounts of the total dose excreted unchanged in the urine (8.6 to 11.1%) were higher than those reported in adult volunteers or adult perennial rhinitis patients (3.7 to 5.6%). Plasma ipratropium concentrations were relatively low (ranging from undetectable up to 0.49 ng/ml). No correlation of the amount of the total dose excreted unchanged in the urine (Ae) with age or gender was observed in the pediatric population.

Special Populations: Gender does not appear to influence the absorption or excretion of nasally administered ipratropium bromide. The pharmacokinetics of ipratropium bromide have not been studied in patients with hepatic or renal insufficiency or in the elderly.

Drug-Drug Interaction: No specific pharmacokinetic studies were conducted to evaluate potential drug-drug interactions.

Pharmacodynamics: In two single-dose trials (n=17), doses up to 336 mcg of ipratropium bromide did not significantly affect pupillary diameter, heart rate or systolic/diastolic blood pressure. Similarly, in patients with induced-colds, ipratropium bromide nasal solution 0.06% (Nasal Spray) (84 mcg/nostril four times a day), had no significant effects on pupillary diameter, heart rate, or systolic/diastolic blood pressure.

Two nasal provocation trials in perennial rhinitis patients (n=44) using ipratropium bromide nasal spray showed a dose dependent increase in inhibition of methacholine induced nasal secretion with an onset of action within 15 minutes (time of first observation).

Controlled clinical trials demonstrated that intranasal fluorocarbon-propelled ipratropium bromide does not alter physiologic nasal functions (e.g., sense of smell, ciliary beat frequency, mucociliary clearance, or the air conditioning capacity of the nose).

Clinical Trials: The clinical trials for ipratropium bromide nasal solution 0.03% (Nasal Spray) were conducted in patients with nonallergic perennial rhinitis (NAPR) and in patients with allergic perennial rhinitis (APR). APR patients were those who experienced symptoms of nasal hypersecretion and nasal congestion or sneezing when exposed to specific perennial allergens (e.g., dust mites, molds) and were skin test positive to these allergens. NAPR patients were those who experienced symptoms of nasal hypersecretion and nasal congestion or sneezing throughout the year, but were skin test negative to common perennial allergens.

In four controlled, four- and eight-week comparisons of ipratropium bromide nasal solution 0.03% (Nasal Spray) (42 mcg per nostril, two or three times daily) with its vehicle, in patients with allergic or nonallergic perennial rhinitis, there was a statistically significant decrease in the severity and duration of rhinorrhea in the ipratropium bromide group throughout the entire study period. An effect was seen as early as the first day of therapy. There was no effect of ipratropium bromide nasal solution 0.03% (Nasal Spray) on degree of nasal congestion, sneezing, or postnasal drip. The response to ipratropium bromide nasal solution 0.03% (Nasal Spray) did not appear to be affected by the type of perennial rhinitis (NAPR or APR), age, or gender. No controlled clinical trials directly compared the efficacy of BID versus TID treatment.

INDICATIONS AND USAGE: Ipratropium bromide nasal solution 0.03% (Nasal Spray) is indicated for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older. Ipratropium bromide nasal solution 0.03% (Nasal Spray) does not relieve nasal congestion, sneezing, or postnasal drip associated with allergic or nonallergic perennial rhinitis.

CONTRAINDICATIONS: Ipratropium bromide nasal solution 0.03% (Nasal Spray) is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, or to any of the other ingredients.

WARNINGS: Immediate hypersensitivity reactions may occur after administration of ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

PRECAUTIONS: General: Ipratropium bromide nasal solution 0.03% (Nasal Spray) should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction, particularly if they are receiving an anticholinergic by another route. Cases of precipitation or worsening of narrow-angle glaucoma and acute eye pain have been reported with direct eye contact of ipratropium bromide administered by oral inhalation.

Information for Patients: Patients should be advised that temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma or eye pain may result if ipratropium bromide nasal solution 0.03% (Nasal Spray) comes into direct contact with the eyes. Patients should be instructed to avoid spraying ipratropium bromide nasal solution 0.03% (Nasal Spray) in or around their eyes. Patients who experience eye pain, blurred vision, excessive nasal dryness, or episodes of nasal bleeding should be instructed to contact their doctor. Patients should be reminded to carefully read and follow the accompanying Patient's Instructions for Use.

Drug Interactions: No controlled clinical trials were conducted to investigate drug-drug interactions. Ipratropium bromide nasal solution 0.03% (Nasal Spray) is minimally absorbed into the systemic circulation; nonetheless, there is some potential for an additive interaction with other concomitantly administered anticholinergic medications, including ipratropium bromide for oral inhalation.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In two-year carcinogenicity studies in rats and mice, ipratropium bromide at oral doses up to 6 mg/kg (approximately 190 and 95 times the maximum recommended daily intranasal dose in adults, respectively, and approximately 110 and 60 times the maximum recommended daily intranasal dose in children, respectively on a mg/m² basis) showed no carcinogenic activity. Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test, and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats was unaffected by ipratropium bromide at oral doses up to 50 mg/kg (approximately 1,600 times the maximum recommended daily intranasal dose in adults on a mg/m² basis). At an oral dose of 500 mg/kg (approximately 16,000 times the maximum recommended daily intranasal dose in adults on a mg/m² basis), ipratropium bromide produced a decrease in the conception rate.

Pregnancy: *TERATOGENIC EFFECTS Pregnancy Category B.* Oral reproduction studies were performed at doses of 10 mg/kg in mice, 1000 mg/kg in rats and 125 mg/kg in rabbits. These doses correspond, in each species respectively, to approximately 160, 32,000, and 8,000 times

PHARMACIST — DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT'S INSTRUCTIONS FOR USE

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)

Ipratropium bromide nasal solution 0.03% (Nasal Spray) is indicated for the symptomatic relief of rhinorrhea (runny nose) associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older. Ipratropium bromide nasal solution 0.03% (Nasal Spray) does not relieve nasal congestion, sneezing, or postnasal drip associated with allergic or nonallergic perennial rhinitis. Read complete instructions carefully and use only as directed.

To Use:

1. Remove the plastic dust cap and the safety clip from the nasal spray pump (Figure 1). The safety clip prevents the accidental discharge of the spray in your pocket or purse.

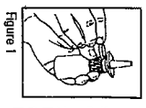


Figure 1

2. The nasal spray pump must be primed before ipratropium bromide nasal solution 0.03% (Nasal Spray) is used for the first time. To prime the pump, hold the bottle with your thumb at the base and your index and middle fingers on the white shoulder area. Make sure the bottle points upright and away from your eyes. Press your thumb firmly and quickly against the bottle seven times (Figure 2). The pump is now primed and can be used. Your pump should not have to be reprimed unless you have not used the medication for more than 24 hours; reprimming the pump will only require two sprays. If you have not used your nasal spray for more than seven days, reprimming the pump will require seven sprays.

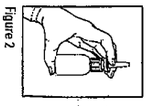


Figure 2

3. Before using ipratropium bromide nasal solution 0.03% (Nasal Spray), blow your nose gently to clear your nostrils if necessary.

4. Close one nostril by gently placing your finger against the side of your nose, tilt your head slightly forward and, keeping the bottle upright, insert the nasal tip into the other nostril (Figure 3). Point the tip toward the back and outer side of the nose.

5. Press firmly and quickly upwards with the thumb at the base while holding the white shoulder portion of the pump between your index and middle fingers. Following each spray, sniff deeply and breathe out through your mouth.

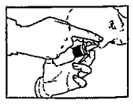


Figure 3

6. After spraying the nostril and removing the unit, tilt your head backwards for a few seconds to let the spray spread over the back of the nose.

7. Repeat steps 4 through 6 in the same nostril.

8. Repeat steps 4 through 7 in the other nostril (i.e., two sprays per nostril).

9. Replace the plastic dust cap and safety clip.

the maximum recommended daily intranasal dose in adults on a mg/m² basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg, respectively, (approximately 50 and 120 times, respectively, the maximum recommended daily intranasal dose in adults on a mg/m² basis). These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses above 90 mg/kg in rats (approximately 2,900 times the maximum recommended daily intranasal dose in adults on a mg/m² basis) embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration. However, no adequate or well controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, ipratropium bromide nasal solution 0.03% (Nasal Spray) should be used during pregnancy only if clearly needed.

Nursing Mothers: It is known that some ipratropium bromide is systemically absorbed following nasal administration; however the portion which may be excreted in human milk is unknown. Although lipid-insoluble quaternary bases pass into breast milk, the minimal systemic absorption makes it unlikely that ipratropium bromide would reach the infant in an amount sufficient to cause a clinical effect. However, because many drugs are excreted in human milk, caution should be exercised when ipratropium bromide nasal solution 0.03% (Nasal Spray) is administered to a nursing woman.

Pediatric Use: The safety of ipratropium bromide nasal solution 0.03% (Nasal Spray) at a dose of two sprays (42 mcg) per nostril two or three times daily (total dose 168 to 252 mcg/day) has been demonstrated in 77 pediatric patients 6-12 years of age in placebo-controlled, 4-week trials and in 55 pediatric patients in active-controlled, 6 month trials. The effectiveness of ipratropium bromide nasal solution 0.03% (Nasal Spray) for the treatment of rhinorrhea associated with allergic and nonallergic perennial rhinitis in this pediatric age group is based on extrapolation of the demonstrated efficacy of ipratropium bromide nasal solution 0.03% (Nasal Spray) in adults with these conditions and the likelihood that the disease course, pathophysiology, and the drug's effects are substantially similar to that of adults. The recommended dose for the pediatric population is based on within and cross-study comparisons of the efficacy of ipratropium bromide nasal solution 0.03% (Nasal Spray) in adults and pediatric patients and on its safety profile in both adults and pediatric patients. The safety and effectiveness of ipratropium bromide nasal solution 0.03% (Nasal Spray) in patients under 6 years of age have not been established.

ADVERSE REACTIONS: Adverse reaction information on ipratropium bromide nasal solution 0.03% (Nasal Spray) in patients with perennial rhinitis was derived from four multicenter, vehicle-controlled clinical trials involving 703 patients (356 patients on ipratropium bromide and 347 patients on vehicle), and a one-year, open-label, follow-up trial. In three of the trials, patients received ipratropium bromide nasal solution 0.03% (Nasal Spray) three times daily, for eight weeks. In the other trial, ipratropium bromide nasal solution 0.03% (Nasal Spray) was given to patients two times daily for four weeks. Of the 285 patients who entered the open-label, follow-up trial, 232 were treated for 3 months, 200 for 6 months, and 159 up to one year. The majority (>86%) of patients treated for one year were maintained on 42 mcg per nostril, two or three times daily, of ipratropium bromide nasal solution 0.03% (Nasal Spray).

The following table shows adverse events, and the frequency that these adverse events led to the discontinuation of treatment, reported for patients who received ipratropium bromide nasal solution 0.03% (Nasal Spray) at the recommended dose of 42 mcg per nostril, or vehicle two or three times daily for four or eight weeks. Only adverse events reported with an incidence of at least 2.0% in the ipratropium bromide group and higher in the ipratropium bromide group than in the vehicle group are shown.

	% of Patients Reporting Events*			
	Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) (n=356)		Vehicle Control (n=347)	
	Incidence%	Discontinued%	Incidence%	Discontinued%
Headache	9.8	0.6	9.2	0.0
Upper respiratory tract infection	9.8	1.4	7.2	1.4
Epistaxis[1]	9.0	0.3	4.6	0.3
Rhinitis*				
Nasal dryness	5.1	0.0	0.9	0.3
Nasal irritation[2]	2.0	0.0	1.7	0.6
Other nasal symptoms[3]	3.1	1.1	1.7	0.3
Pharyngitis	8.1	0.3	4.6	0.0
Nausea	2.2	0.3	0.9	0.0

* This table includes adverse events which occurred at an incidence rate of at least 2.0% in the ipratropium bromide group and more frequently in the ipratropium bromide group than in the vehicle group.

[1] Epistaxis reported by 7.0% of ipratropium bromide patients and 2.3% of vehicle patients, blood-tinged mucus by 2.0% of ipratropium bromide patients and 2.3% of vehicle patients.

[2] Nasal irritation includes reports of nasal itching, nasal burning, nasal irritation, and ulcerative rhinitis.

[3] Other nasal symptoms include reports of nasal congestion, increased rhinorrhea, increased rhinitis, posterior nasal drip, sneezing, nasal polyps, and nasal edema.

* All events are listed by their WHO term; rhinitis has been presented by descriptive terms for clarification.

Ipratropium bromide nasal solution 0.03% (Nasal Spray) was well tolerated by most patients. The most frequently reported nasal adverse events were transient episodes of nasal dryness or epistaxis. These adverse events were mild or moderate in nature, none was considered serious, none resulted in hospitalization and most resolved spontaneously or following a dose reduction. Treatment for nasal dryness and epistaxis was required infrequently (2% or less) and consisted of local application of pressure or a moisturizing agent (e.g., petroleum jelly or saline nasal spray). Patient discontinuation for epistaxis or nasal dryness was infrequent in both the controlled (0.3% or less) and one-year, open-label (2% or less) trials. There was no evidence of nasal rebound (i.e., a clinically significant increase in rhinorrhea, posterior nasal drip, sneezing or nasal congestion severity compared to baseline) upon discontinuation of double-blind therapy in these trials.

Adverse events reported by less than 2% of the patients receiving ipratropium bromide nasal solution 0.03% (Nasal Spray) during the controlled clinical trials or during the open-label follow-up trial, which are potentially related to ipratropium bromide's local effects or systemic anticholinergic effects include: dry mouth/throat, dizziness, ocular irritation, blurred vision, conjunctivitis, hoarseness, cough, and taste perversion. Additional anticholinergic effects noted with other ipratropium bromide dosage forms (ipratropium bromide inhalation solution, ipratropium bromide inhalation aerosol, and ipratropium bromide nasal solution 0.06% [Nasal Spray]) include: precipitation or worsening of narrow-angle glaucoma, urinary retention, prostatic disorders, tachycardia, constipation, and bowel obstruction.

There were infrequent reports of skin rash in both the controlled and uncontrolled clinical studies. Other allergic-type reactions such as angioedema of the throat, tongue, lips and face, urticaria, laryngospasm, and anaphylactic reactions have been reported with other ipratropium bromide products.

No controlled trial was conducted to address the relative incidence of adverse events of BID versus TID therapy.

OVERDOSAGE: Acute overdosage by intranasal administration is unlikely since ipratropium bromide is not well absorbed systemically after intranasal or oral administration. Following administration of a 20 mg oral dose (equivalent to ingesting more than four bottles of ipratropium bromide nasal solution 0.03% [Nasal Spray]) to 10 male volunteers, no change in heart rate or blood pressure was noted. Following a 2 mg intravenous infusion over 15 minutes to the same 10 male volunteers, plasma ipratropium concentrations of 22-45 ng/mL were observed (>100 times the concentrations observed following intranasal administration). Following intravenous infusion these 10 volunteers had a mean increase of heart rate of 50 bpm and less than 20 mmHg change in systolic or diastolic blood pressure at the time of peak ipratropium levels.

Oral median lethal doses of ipratropium bromide were greater than 1,000 mg/kg in mice (approximately 16,000 and 9,500 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m² basis), 1,700 mg/kg in rats (approximately 55,000 and 32,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m² basis), and 400 mg/kg in dogs (approximately 43,000 and 25,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m² basis).

DOSAGE AND ADMINISTRATION: The recommended dose of ipratropium bromide nasal solution 0.03% (Nasal Spray) is two sprays (42 mcg) per nostril two or three times daily (total dose 168 to 252 mcg/day) for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older. Optimum dosage varies with the response of the individual patient. Initial pump priming requires seven sprays of the pump. If used regularly as recommended, no further priming is required. If not used for more than 24 hours, the pump will require two sprays, or if not used for more than seven days, the pump will require seven sprays to reprime.

HOW SUPPLIED: Ipratropium bromide nasal solution 0.03% (Nasal Spray) is supplied as 30 ml of solution in a high density polyethylene (HDPE) bottle fitted with a metered nasal spray pump, a safety clip to prevent accidental discharge of the spray, and a plastic dust cap. It contains 31.1 g of product formulation, 345 sprays, each delivering 21 mcg (70 µL) of ipratropium per spray, or 28 days of therapy at the maximum recommended dose (two sprays per nostril three times a day).

STORAGE: Store between 15°-30°C (59°-86°F). Keep tightly closed. Avoid freezing. Keep out of reach of children. Avoid spraying in or around the eyes.

Patients should be reminded to read and follow the accompanying Patient's Instructions for Use, which should be dispensed with the product.

Rx only

AB39816

Bausch & Lomb Pharmaceuticals, Inc.
Tampa, FL 33637

XO51014 **(Folded)** REV. 7/01-01
FDA DRAFT.2

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10. At some time before the medication is completely used up, you should consult your physician or pharmacist to determine whether a refill is needed. You should not take extra doses or stop using ipratropium bromide nasal solution 0.03% (Nasal Spray) without consulting your physician.

CAUTION:
Ipratropium bromide nasal solution 0.03% (Nasal Spray) is intended to relieve your rhinorrhea (runny nose) with regular use. It is therefore important that you use ipratropium bromide nasal solution 0.03% (Nasal Spray) as prescribed by your physician. For most patients, some improvement in runny nose is usually apparent during the first full day of treatment with ipratropium bromide nasal solution 0.03% (Nasal Spray). Some patients may require up to two weeks of treatment to obtain maximum benefit.

Do not spray ipratropium bromide nasal solution 0.03% (Nasal Spray) in your eyes. Should this occur, immediately flush your eye with cool tap water for several minutes. If you accidentally spray ipratropium bromide nasal solution 0.03% (Nasal Spray) in your eyes, you may experience a temporary blurring of vision and increased sensitivity to light, which may last a few hours. Should eye pain or blurred vision occur contact your doctor.

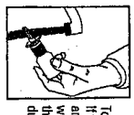
Should you experience excessive nasal dryness or episodes of nasal bleeding contact your doctor.

You should not use this drug if you have glaucoma or difficult urination due to an enlargement of the prostate, unless directed by a physician. Ipratropium bromide nasal solution 0.03% (Nasal Spray) should not be used during pregnancy or breastfeeding unless directed by a physician. It is not known whether ipratropium bromide is excreted in human milk; however, many drugs are excreted in human milk.

STORAGE: Store between 15°-30°C (59°-86°F). Keep tightly closed. Avoid freezing. Keep out of reach of children.

Rx only

Figure 4



To clean:
If the nasal tip becomes clogged, remove the plastic dust cap and safety clip. Hold the nasal tip under running, warm tap water (Figure 4) for about a minute. Dry the nasal tip, reprime the nasal spray pump (step 2 above), and replace the plastic dust cap and safety clip.

Bausch & Lomb
Pharmaceuticals, Inc.
Tampa, FL 33637

XO51014 **(Folded)** REV. 7/01-01 AB39816 FDA DRAFT.2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-025

LABELING REVIEWS

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

ANDA Number: 76-025 Date of Submission: Nov. 10, 2000
Applicant's Name: Bausch & Lomb
Established Name: Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) (0.021mg/spray)

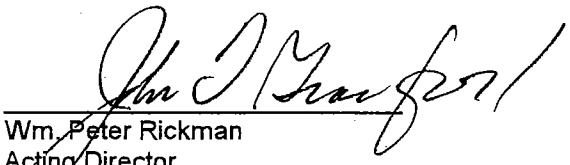
Labeling Deficiencies:

1. CONTAINER 21 mcg/spray (345 meter sprays)
   a. Revise the established name to read as follows : Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray).
   b. We encourage you to include "for use in Adults/children 6-11 years old."
2. CARTON (1 x 21 mcg/spray) – See comments under CONTAINER.
3. PROFESSIONAL PACKAGE INSERT – Please revise your insert labeling to be in accord with latest approved labeling for Atrovent Nasal Spray 0,03% (Beohringer Ingelheim Pharmaceutical, Inc. NDA 20-393/S-001 approved April 1, 1998; revised 4/98. We have enclosed a copy for your convenience. Please note comment 1a. under CONTAINER above regard the generic product name.
4. PATIENT LEAFTLET- See comment under Professional package insert.

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling or draft insert labeling if you prefer

Prior 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 the enclosed innovators labeling with all differences annotated and explained.



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

Enclosure (Atrovent Nasal Spray 0.03%)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels:
Carton Labeling:
Unit Dose Blister Label:
Unit Dose Carton Label:
Professional Package Insert Labeling:
Patient Package Insert Labeling:
Auxiliary Labeling:
Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: atrovent
NDA Number: 20-393
NDA Drug Name: Ipratropium bromide Nasal spray).03%
NDA Firm: Boehringer Ingel
Date of Approval of NDA Insert and supplement #: s-001 approved in FPL Oct. 8, 98.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Labels submitted with application
Basis of Approval for the Carton Labeling: Labels submitted with application
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		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			
Is this a new packaging configuration, never been approved by an ANDA or NDA? 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.		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	
Labeling(continued)	Yes	No	N.A.
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		X	

Manufactured by...", statement needed?			
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 (page #) 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 page # 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?			X
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of Atrovent (Boehring Ingelhemin, NDA 20-303, revised 4/98; approved april 1, 90 draft and oct 8, 98 FPL).
2. Patent/ Exclusivities: applicant filed a Paragraph I patent certification and there are no unexpired exclusivities

Patent data - NDA

No	Expiration	Use Code	Use	File

Exclusivity Data– NDA

Code	Reference	Expiration

3. Storage Conditions:
   NDA - Store tightly closed betwe 15-30C. Avoid Freezing, keep out of reach of children
   ANDA - same
   USP – not applicable
4. Dispensing Recommendations:
   NDA – Dispense with Patient instruction sheet.

ANDA - same
USP –

6. Product Line:
The innovator markets their product in in a white HDPE bottle fitted with a white and clear metered nasal spray pump, a green safety clip and a clear plastic dust cap. It contains 31.1g of product, 345 sprays, at 21 mcg/spray or 28 days of therapy at the maxium dose of 2 sprays per nostril 3 x daily.
The applicant proposes to market their product in same as RLD except color of saftey clip.

8. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 261 (Volume 1.1).

Date of Review: April 8, 2001 **Date of Submission: Nov. 10, 2000**

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cc: ANDA: 76-025
DUP/DIVISION FILE
HFD-613/APayne/ JGrace (no cc)
V:firmsam/bausch/let&rev/76025na1.l
Review

John Glynn 5/17/2001

APPEARS THIS WAY
ON ORIGINAL

Copy of Reference Listed Drug labeling removed.
(2 pages)

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

ANDA Number	76-025
Date of Submission	Dec. 07, 2001
Applicant	Bausch & Lomb
Drug Name	Ipratropium Bromide Nasal Solution (Nasal Spray)
Strength(s)	0.03% (21 mcg/spray)

FPL Approval Summary		
Container Labels		
21 mcg/spray	30 mL	Submitted Dec. 07, 2001 vol. 2.1 attachment 26.
Carton labeling		
21 mcg/spray	1x 30 mL	Submitted Dec. 07, 2001 vol. 2.1 attachment 26.
Package Insert Labeling	#AB39816 Rev. Date 7/01-01	Submitted Dec. 07, 2001 vol. 2.1 attachment 26.
Patient Information sheet	#AB39816 Rev. Date 7/01-01	Submitted Dec. 07, 2001 vol. 2.1 attachment 26.

BASIS OF APPROVAL:

No Patent Data for NDA 20-393. Applicant filed a Paragraph I.

Exclusivity Data For NDA 20-393			
Code/sup	**Expiration**	**Description**	**Labeling impact**
I-233	Apr. 01, 2001	Symptomatic relieaf of rhinorrheas associated with alergic and nonallergic perennial rhinitis in children age 6 years to 11.	Same As

Reference Listed Drug

RLD on the 356(h) form	Atrovent
NDA Number	20-393
RLD established name	Ipratropium bromide Nasal spray 0.03%
Firm	Boehringer Ingel
Currently apprvoved PI	S-001
AP Date	4/01/98 (AR Oct. 8, 1998)

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		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			
Is this a new packaging configuration, never been approved by an ANDA or NDA? 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.		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	
Labeling(continued)	Yes	No	N.A.
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 (page #) 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 page # 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?			X

Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of Atrovent (Boehring Ingelhemin, NDA 20-393/S-001, revised 4/98; approved april 1, 98 draft and oct 8, 98 FPL).
2. Patent/ Exclusivities: applicant filed a Paragraph I patent certification and there are no unexpired exclusivities
3. Storage Conditions:
   NDA - Store tightly closed betwe 15-30C. Avoid Freezing, keep out of reach of children
   ANDA - same
   USP – not applicable
4. Dispensing Recommendations:
   NDA – Dispense with Patient instruction sheet.
   ANDA - same
   USP –
6. Product Line:
   The innovator markets their product in in a white HDPE bottle fitted with a white and clear metered nasal spray pump, a green safety clip and a clear plastic dust cap. It contains 31.1g of product, 345 sprays, at 21 mcg/spray or 28 days of therapy at the maxium dose of 2 sprays per nostril 3 x daily.
   The applicant proposes to market their product in same as RLD except color of saftey clip.
8. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 261 (Volume 1.1).

Date of Review: **February 19, 2002**

Date of Submission: **December 7, 2001**

cc: ANDA: 76-025
DUP/DIVISION FILE
HFD-613/APayne/ JGrace (no cc)
V:firmsam/bausch/let&rev/76025ap.L
Review

APayne 02/20/02

JGrace 2/21/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-025

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 76-025

3. NAME AND ADDRESS OF APPLICANT

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Ipratropium Bromide

13. DOSAGE FORM
Nasal Spray

14. STRENGTH(s)
0.03%

10. PHARMACOLOGICAL CATEGORY
Anticholinergic agent for perennial rhinitis

11. Rx or OTC Rx

4. LEGAL BASIS FOR SUBMISSION
NDA 20393, Atrovent®, Boehringer Ingelheim

5. SUPPLEMENT(s)
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 to 1.16: (A1.4 to A1.16 are Bio only.)

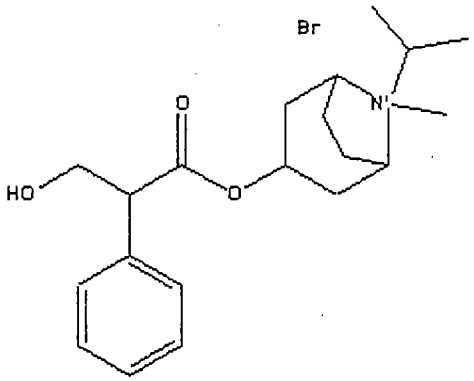
11/10/00 Original ANDA
12/15/00 Revised patent certification
12/19/00 Acknowledgement - acceptable for filing 11/13/00

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

15. CHEMICAL NAME AND STRUCTURE

Ipratropium bromide monohydrate [*66985-17-9*]
CAS number for anhydrous form is *22254-24-6*.

$C_{20}H_{30}BrNO_3-H_2O$
412.3659 anhydrous, 430.38 monohydrate



16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points: 23.A, 23.B, 25, 26, 28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)
A nasal spray is not required to be sterile.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS
We will schedule the study after the test method issues are resolved.

32. LABELING
The labeling information is pending review.

33. ESTABLISHMENT INSPECTION
The facilities were found **acceptable** 3/14/01.

34. BIOEQUIVALENCE STATUS
The bioequivalence information is pending review.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 76-025 is **NOT APPROVED - MAJOR AMENDMENT requested.**

19. REVIEWER:	DATE COMPLETED:	REVISED:
Eugene L. Schaefer, Ph.D.	4/11/01	4/26/01

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

cc: ANDA 76-025
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/ELSchaefer, Chemist/ ES 5/1/01

HFD-625/MSmela, Team Leader/4/27/01 M Smela 5/2/01

HFD-617/MDillahunt, Project Manager/4/27/01 MDillahunt 5/1/01

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F/T by gp/4/30/01

CHEMISTRY REVIEW - NOT APPROVABLE - MAJOR

1. CHEMISTRY REVIEW NO. **2**

2. ANDA # **76-025**

3. NAME AND ADDRESS OF APPLICANT
Bausch & Lomb Pharmaceuticals, Inc.(B&L)
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

4. LEGAL BASIS FOR SUBMISSION
NDA 20393, Atrovent®, Boehringer Ingelheim

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Ipratropium Bromide

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 11-10-00
NC: 12-15-00
* Amendment: 5-7-01 (To add new testing facility of B&L).
* Major Amendment: 12-7-01 (Response to NA letter dated 5-5-01)
* Gratuitous Amendment: 1-24-02

FDA:
Accepted for filing: 11-13-00 (Acknowledgement letter: 12-19-00).
NA letter: 5-7-01
Bio deficiency letter: 6-8-01
Bio Information letter: 12-20-01

10. PHARMACOLOGICAL CATEGORY
Anticholinergic agent for perennial rhinitis

11. Rx or OTC:
Rx

12. RELATED IND/NDA/DMF(s):
See DMF Checklist

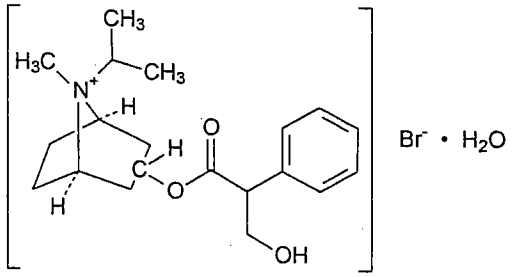
13. DOSAGE FORM
Nasal Spray

14. STRENGTH(s)
0.03%

15. CHEMICAL NAME AND STRUCTURE

Ipratropium bromide monohydrate [*66985-17-9*]
CAS number for anhydrous form is *22254-24-6*.

$C_{20}H_{30}BrNO_3-H_2O$
412.3659 anhydrous, 430.38 monohydrate



16. RECORDS AND REPORTS
N/A

17. A. GENERAL COMMENTS:

1. DMF ——— for ——————— is adequate per review completed on 6-21-01. No new information is submitted since this review.
2. Acceptance specifications for Ipratropium Bromide drug substance are satisfactory.
3. Manufacturing process for the drug product is acceptable.
4. Information regarding container/closure became acceptable.
5. B&L has submitted adequate stability data to grant an expiration dating period of 24 months for the drug product.

6. EER: Acceptable as of 3-14-01. However, a new facility is being added.
7. B&L has not submitted a response to bio deficiency letter dated 6-8-01 yet. Based on this letter, Bioequivalency for the drug has not been demonstrated. B&L is being asked to submit response to deficiencies cited June 8, 2001.
8. FPL: Acceptable per review of 2-21-02 completed by A. Payne.
9. Methods Validation is being requested concurrent to this review.

18. CONCLUSIONS AND RECOMMENDATIONS
NOT APPROVED. NA (Minor) Letter

19. REVIEWER: Mujahid L. Shaikh

DATE COMPLETED: 6-25-02
Revised on 7-2-02

Redacted 41 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

8. Your have provided an equation in response to deficiency # 9.d which can give percentage RSD from the recovery values. You failed to give a definition of each parameter used in the equation.

9. Please submit revised acceptance specifications for Ipratropium Bromide drug substance, and revised release and stability specifications for the drug product incorporating the revisions suggested above.

10. Bioequivalence for the drug product has not been demonstrated. Please reply to the deficiencies dated June 8, 2001.

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

1. Please provide any additional long term stability data that may be available.

2. We require an acceptable Methods Validation to support the ANDA. We have scheduled the validation with the laboratory. Please provide samples promptly when contacted.

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

Sincerely yours,

Paul Schwartz 7/9/02

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

cc: ANDA 76-025
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/MShaikh/7/2/02 Mujaid Shaikh 7/5/02
HFD-625/Msmela/7/3/02 M Smela 7/9/02
HFD-617/PChen, Project Manager/ Pat Chen 7/9/02

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F/T by: DJ 7/9/02

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 3

2. ANDA # **76-025**

3. NAME AND ADDRESS OF APPLICANT
Bausch & Lomb Pharmaceuticals, Inc.(B&L)
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

4. LEGAL BASIS FOR SUBMISSION
NDA 20393, Atrovent®, Boehringer Ingelheim

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Ipratropium Bromide

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 11-10-00
NC: 12-15-00
Amendment: 5-7-01 (To add new testing facility of B&L).
Major Amendment: 12-7-01 (Response to NA letter dated 5-5-01)
Gratuitous Amendment: 1-24-02
* Minor Amendment: 8-13-02 (Response to July 11, 2002 ltr.)

FDA:
Accepted for filing: 11-13-00 (Acknowledgement letter: 12-19-00).
NA letter: 5-7-01
Bio deficiency letter: 6-8-01
Bio Information letter: 12-20-01
NA letter: 7-11-02

10. PHARMACOLOGICAL CATEGORY
Anticholinergic agent for perennial rhinitis

11. Rx or OTC:
Rx

12. RELATED IND/NDA/DMF(s):
See DMF Checklist

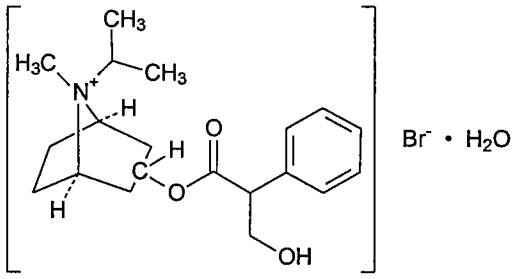
13. DOSAGE FORM
Nasal Spray

14. STRENGTH(s)
0.03%

15. CHEMICAL NAME AND STRUCTURE

Ipratropium bromide monohydrate [*66985-17-9*]
CAS number for anhydrous form is *22254-24-6*.

$C_{20}H_{30}BrNO_3-H_2O$
412.3659 anhydrous, 430.38 monohydrate



16. RECORDS AND REPORTS
N/A

17. A. GENERAL COMMENTS:

1. DMF —— for ———— is adequate per review completed on 8-27-02. No new information is submitted since this review.
2. Acceptance specifications for Ipratropium Bromide drug substance are satisfactory per CR # 2.
3. Information regarding container/closure became acceptable (CR # 2).
4. B&L has submitted adequate stability data to grant an expiration dating period of 24 months for the drug product. Additional stability data is submitted in this amendment.
5. EER: Pending

6. B&L has not submitted a response to bio deficiency letter dated 6-8-01 yet. Based on this letter, Bioequivalency for the drug has not been demonstrated. B&L stated in this amendment that they will likely respond in September 2002.
7. FPL: Acceptable per review of 2-21-02 completed by A. Payne.
8. Methods Validation has been requested on 7-3-02 concurrent to CR # 2.

18. CONCLUSIONS AND RECOMMENDATIONS
NA (minor) letter

19. REVIEWER: Mujahid L. Shaikh

DATE COMPLETED: 9-9-02

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information from

CHEMISTRY REVIEW #3

38. Chemistry Comments to be Provided to the Applicant

ANDA: 76-025

APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Solution, 0.03%

The deficiencies presented below represent MINOR deficiencies.

1. Bioequivalence for the drug product has not been demonstrated. Please reply to this communication no earlier than your reply to the bioequivalence deficiencies dated June 8, 2001.

2. [redacted]

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

1. An acceptable compliance evaluation is needed for approval and the evaluation is pending.

2. An acceptable Methods Validation is needed to support the ANDA and the study is in process.

Sincerely yours,

Paul Schuttenberg 9/17/02

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

cc: ANDA 76-025
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/MShaikh/9/10/02 Mugabed Shaikh 9/16/02
HFD-625/Msmela/9/10/02 M Smela 9/16/02
HFD-617/PChen, Project Manager/9/11/02 Peter Chen 9/16/02

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APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 76-025

3. NAME AND ADDRESS OF APPLICANT
Bausch & Lomb Pharmaceuticals, Inc.(B&L)
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

4. LEGAL BASIS FOR SUBMISSION
NDA 20393, Atrovent®, Boehringer Ingelheim

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Ipratropium Bromide

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 11-10-00
NC: 12-15-00
Amendment: 5-7-01 (To add new testing facility of B&L).
Major Amendment: 12-7-01 (Response to NA letter dated 5-5-01)
Gratuitous Amendment: 1-24-02
Minor Amendment: 8-13-02 (Response to July 11, 2002 ltr.)

- Amendment (Bio): 9-12-02 (Response to June 8, 2001 bio deficiency letter)
- Minor Amendment: 10-3-02 (Response to 9-18-02 NA letter)

FDA:
Accepted for filing: 11-13-00 (Acknowledgement letter: 12-19-00).
NA letter: 5-7-01
Bio deficiency letter: 6-8-01
Bio Information letter: 12-20-01
NA letter: 7-11-02
NA letter: 9-18-02

10. PHARMACOLOGICAL CATEGORY
Anticholinergic agent for perennial rhinitis

11. Rx or OTC:
Rx

12. RELATED IND/NDA/DMF(s):
See DMF Checklist

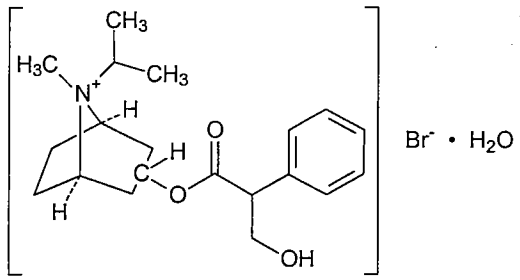
13. DOSAGE FORM
Nasal Spray

14. STRENGTH(s)
0.03%

15. CHEMICAL NAME AND STRUCTURE

Ipratropium bromide monohydrate [*66985-17-9*]
CAS number for anhydrous form is *22254-24-6*.

$C_{20}H_{30}BrNO_3$-H_2O
412.3659 anhydrous, 430.38 monohydrate



16. RECORDS AND REPORTS
N/A

17. A. GENERAL COMMENTS:

1. DMF —— for ———— is adequate per review completed on 8-27-02. No new information is submitted since this review.
2. Acceptance specifications for Ipratropium Bromide drug substance are satisfactory per CR # 2.
3. Information regarding container/closure became acceptable (CR # 2).
4. B&L has submitted adequate stability data to grant an expiration dating period of 24 months for the drug

product. Additional stability data is submitted in this amendment.

5. EER: Pending inspection of B&L.
6. B&L has submitted a response to bio deficiency letter dated 6-8-01 on September 12, 2002 which is pending review..
7. FPL: Acceptable per review of 2-21-02 completed by A. Payne.
8. Methods Validation has been requested on 7-3-02 concurrent to CR # 2. No results yet.
9. Release and stability specifications became acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Chemistry Closed.

Bio and EER Pending

19. REVIEWER: Mujahid L. Shaikh — DATE COMPLETED: 10-8-02

cc: ANDA 76-025
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/MShaikh/ Mujahid Shaikh 10/9/02
HFD-625/Msmela/ M Smela 10/9/02

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F/T by:

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confidential commercial

information from

CHEMISTRY REVIEW #4

Addendum to Chemist Review # 4 for:

ANDA 76-025

Ipratropium Bromide Nasal Spray, 0.03%

Bausch & Lomb Pharmaceuticals, Inc., FL

This addendum is being written to cover the following outstanding issues and CMC information in bioequivalence telephone amendment submitted on January 28, 2003:

Status of Methods Validation: The request has been received on July 8, 2002 and the report is still pending based on the available information.

Status of DMF ____ : Adequate per review completed by this reviewer on August 27, 2002. No new information is submitted.

EER Status: Acceptable on March 3, 2003 by J. D. Ambrogio.

Bio Status: Acceptable as of March 14, 2003.

Telephone Amendment (January 28, 2003): In this amendment, B&L submitted the requested information of the Division of Bioequivalence (DBE). B&L submitted date of manufacture and test data for lot # 286162 and 286163, assay values for reference drug lot # 156737A and 156799A, the lot size and number of the drug product units from each lot of test product and a copy of HPLC test method C-1573. All lots meet the requirements. The bulk lot ———— is packaged into three sub-lots, each using a different lot of spray pumps. Lot # 286161 consisted of ——— filled units, lot # 286162 consisted of ——— filled units, and lot # 286163 consisted of ——— filled units. The batch reconciliation for bulk solution, lot # 28616 is provided. B&L submitted complete certificate of analysis for lot # 286162 and # 286163. B&L also submitted complete CoAs for the RLD lot # 156737A and # 156799. B&L submitted in-process test results for lot # 286161. All the results meet the in-process control cited in section # 28 of CR # 4. Finally, B&L provided a copy of HPLC test method C-1573. Above information is not really new. These lots were submitted in the original submission.

Conclusion: Recommended for approval.

cc: ANDA 76-025
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-625/MShaikh/3/18/03 Mujahid Shaikh 3/19/03
HFD-625/Msmela/3/18/03

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F/T by:ard/3/19/03 M Smela 3/24/03

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 76-025

FIRM: Bausch & Lomb Pharmaceuticals, Inc. (B&L)
8500 Hidden River Parkway
Tampa, FL 33637

DOSAGE FORM: Metered Nasal Spray

STRENGTH: 0.03%

DRUG: Ipratropium Bromide

CGMP STATEMENT/EIR UPDATED STATUS:
EER is acceptable on 3-3-03.

BIO STUDY:
Bio status: Acceptable as of 3-14-03.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Being Conducted. No report available

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
CCS used in the stability studies is identical to that listed in container section.

LABELING:
Acceptable for approval per A. Payne's review completed on 5-21-02.

STERILIZATION VALIDATION (IF APPLICABLE):
No micro review is required.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Bio batches are 286161/2/3 and they are split filled from a bulk lot of [redacted].

Source of NDS:
DMF # [redacted]: Adequate per review completed on 8-27-02.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
The stability batch is lot 286161, which is one of the bio-

batches.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
Intended production batch size: ———————

Manufacturing process for the intended production size batch is identical to that used for the exhibit/bio/stability batch.

cc: ANDA 76-025
Endorsements:
HFD-625/M.Shaikh/3/17/03
HFD-625/M.Smela/3/18/03
F/t by:ard/3/19/03

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M Shaikh 3/19/03

M Smela 3/24/03

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-025

BIOEQUIVALENCE REVIEWS

Ipratropium Bromide Solution
0.03% Nasal Spray, 21 mcg/spray
ANDA #76-025
Reviewer: Chandra S. Chaurasia

Bausch & Lomb Pharmaceuticals, Inc.
8500 Hidden River Parkway
Tampa, FL 33637
Submission Date:
November 10, 2000

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Review of Formulation and In Vitro Performance Data

BACKGROUND

1. The firm has submitted this ANDA pursuant to 21 CFR 314.94(a) and Section 505(j) of Federal Food, Drug and Cosmetic Act for its drug product, Ipratropium Bromide Nasal Spray, 0.03%. The reference-listed drug (RLD) is Atrovent® Nasal Spray, 0.03% (21 mcg/spray, NDA #20-393) manufactured by Boehringer Ingelheim.

2. ATROVENT® (ipratropium bromide) Nasal Spray 0.03% is indicated for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older (Electronic PDR, 2001).

3. The RLD is supplied as 30 mL of solution in a high density polyethylene bottle fitted with a metered nasal spray pump, a safety clip to prevent accidental discharge of the spray and a clear plastic dust cap. The 30-mL bottle is designed to deliver 345 sprays of 0.07 mL each (21-mcg ipratropium bromide).

4. The recommended dose of Atrovent® Nasal Spray 0.03% is 2 sprays (42 mcg) per nostril two or three times daily for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older.

Agency's Recommendations:

The demonstration of equivalence of aqueous nasal sprays may be based on: a) Q1 and Q2 sameness of the generic and innovator formulations, and b) equivalent in vitro performance of the test and reference product devices.

The comparative performance of the drug delivery devices of the test and reference products may be based on the following tests:

1. Unit Dose/Content Uniformity
2. Priming, loss of prime, and tail off
3. Droplet size distribution by at least 2 methods
4. Spray pattern
5. Plume geometry

Review of application:

Formulation: (not to be released under FOI)

Comparative compositions of the test and the reference products are as follows:

Ingredient	Test Product			Reference Listed Drug[§]		
	mg/mL	% w/v	mg/spray	mg/mL	% w/v	mg/spray
Ipratropium bromide monohydrate, EP	0.314*	0.03	0.021	0.313*		0.021
Benzalkonium Chloride, NF						
Edetate Disodium Dihydrate, NF						**
Sodium Chloride, NF						
Purified Water, USP	q.s. to 1.0 mL	-	-	q.s. to 1.0 mL	-	q.s.
Sodium Hydroxide, NF	pH adjuster	-	-	pH adjuster	-	-
Hydrochloric acid, NF	pH adjuster	-	-	pH adjuster	-	-

[§] Formulation of the reference-listed drug was obtained from the NDA 20-393 submission (Vol. 28.1, June 18, 1999) – Valve size of 70 uL.

*The ingredient is added as ipratropium bromide, monohydrate, to achieve a final concentration of 0.3 mg/mL of ipratropium bromide on an anhydrous basis.

**Edetate Disodium, USP was used in the reference product. *Please note Edetate Disodium, USP is referred as Edetate Disodium Dihydrate in the USP (Electronic 2001)*

Note: There is an error in the formulation provided in COMIS Drug Product Reference File, in that the RLD formulation is listed as mg/spray instead of mg/mL.

Comment on Formulation:

The concentrations of the inactive ingredients for the test product are within the acceptable range (±5%) of the approved RLD. The formulation of the test product is Q1 and Q2 same as that of the RLD. The test product formulation is acceptable.

Comparability of Spray Devices:

———, the manufacturer of the pump used for the RLD, has supplied Bausch and Lomb with a pump, which is essentially the same as that used for the innovator's product. The pump used for Bausch and Lomb's ipratropium bromide Nasal Spray, 0.03%, is identical to the RLD pump with the exception of the closure thread finish and the amount of blue colorant in the closure gasket. The firm states that these differences have no potential to affect the pump's performance. The firm has provided a comparison of the component parts for the pumps used in the test and reference products (page 71, Vol. 1.1, Attachment I). Based on this information, all components of the pump used for the test product are identical to those used for the RLD pump with the exception of the closure thread finish and the amount of blue colorant in the closure gasket.

Drug Products:

The in vitro performance data are based on **only one lot** of the test and reference products.

Test: Ipratropium Bromide Nasal Spray 0.03%, 21 mcg/spray, Lot #286161; Manufacturing date: 04/00, Assay: 101.1%

Reference: Atrovent® Nasal Spray, 0.03%; Lot #819013B, manufactured by Boehringer Ingelheim; Expiry Date: 8/2001, Assay: 100.7%

Procedures and Information Applicable to All Tests:

All actuations of the nasal spray products were done using an automated actuator to actuate the nasal sprays in a reproducible manner. The automated actuator was a proprietary unit designed by ——————— for nasal spray actuation. The actuation parameters for this system were setup as follow:

Dose Time: 20 ± 2 msec.
Return Time: 50 ± 1.5 msec.
Hold Time: 0.5 sec.
Spray Force: 5.50 ± 0.05 kg

UNIT DOSE AND UNIFORMITY OF UNIT DOSE:

SOP C-1580-04, Vol. 3, pp. 869

Testing was performed for 10 units each of reference and test product for all sprays including beginning (actuations #8-17), middle (actuations #176-185), and end (actuations #343-352) of the use life. The amount actuated per spray was measured by a validated HPLC analysis (Method C-1573-02, Volume 3, Section 15/Validation Report) with measurement by weight recorded as supportive data. A summary of the HPLC method validation is as follows: The peak area was linear over a range of ——— ——. to ———.. The limit of detection was ———————. The LOQ was ———————. The method exhibited acceptable specificity, accuracy and precision.

The firm notes that the test was not blinded because automated actuation of the bottle, automated weighing of the bottle, and the scintillation vial were also weighed.

The firm applied the criteria for content uniformity for the test and reference products as set forth in the May 1999 draft "Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation." The draft Guidance recommends a mean of 85-115% of the label claim, NMT one outside 80-120% at the first tier (10 canisters), and none outside 75-125% of the label claim.

Statistical Analysis:

The firm has analyzed data for the test and reference drug products by calculation of mean values and the variability of data. The 90% confidence intervals for the ratio of

true means (true mean of Test over true mean of Reference product) were constructed using Fieller's theorem. In addition, the firm has also calculated the f2 similarity factor for the percent label claim delivered for test and reference to provide another measure of the comparability of the data.

Results:

The firm has provided a summary containing the mean data for the beginning, middle and end actuations for the 10 bottles of test and reference products tested.

Based on the sponsor's calculations, mean delivery of the test product is 3.1% higher than the reference product at Actuations #8-17; 4.0% higher at Actuations #176-185; and 3.4% higher at Actuations #343-352. For the test and reference products no spray was outside the 75-125% label claim range for the 10 bottles tested in this study.

PRIMING AND TAIL OFF CHARACTERISTICS:

The labeling of the test and reference products states: "Initial pump priming requires seven sprays of the pump. If used regularly as recommended, no further priming is required. If not used for more than 24 hours, the pump will require two sprays, or if not used for more than seven days, the pump will require seven sprays to reprime."

The firm has submitted data for sprays #1-7 for 10 bottles of test product and 10 bottles of reference product using HPLC assay. The firm has also submitted a graphic depiction of priming data demonstrating that by the 7^{th} actuation of all products an acceptable dose is delivered for the 10 bottles tested for test and reference products.

Prime Retention: The firm has conducted a study to test the ability of the test and reference pump system to maintain its prime after a given time period from last use. The pumps were tested for 1, 3, 5, 7, 10 and 16 days after priming. Based on the study results the firm concludes that all test and reference products tested delivered doses within 85-115% (17.85 –24.15 ug/spray) of the label claim with consideration to the RLD instructions which allow two actuations to reprime after 24 hours of non-use, and a full 7 sprays to reprime after 7 days of non-use (Report 1f, Vol. 1.1, pp. 126).

Tail Off:

The firm has provided data for actuations #343 and beyond demonstrating that for the test and reference products the labeled amount of "345 metered sprays" is delivered.

Comments On the Unit Dose Data , Priming and Tail Off Characteristics:

The firm determined comparative unit dose data based on **single lots** of the test and reference products. The in vitro studies were conducted approximately a year after the

issuance of the draft guidance "*Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*" issued in June 1999.

The draft Nasal BA/BE guidance recommends in vitro equivalence based on three lots of the test and reference products, because the proposed method of evaluation takes into consideration the relative within-lot and lot-to-lot variations of the test and reference products. The reviews of all applications submitted after the issuance of guidance, which also contain in vitro studies conducted after the issuance of the guidance, are being evaluated based on three lots' data.

The statistical method given in the guidance is still under development. However the Division of Bioequivalence is currently evaluating generic nasal sprays based on relative variability of test and reference products. Therefore, data submitted by Bausch and Lomb do not lend themselves to the DBE's current approach as well as the statistical methodology given in the guidance.

DROPLET SIZE DISTRIBUTION

SOP C-1581-00, Archival Vol. 3, pp. 886
SOP 73-109-02, Archival Vol. 3, pp. 987

Testing was performed on the [redacted] with one spray per test per distance (duplicate testing per interval). Testing was performed on 10 units each of the reference and test products at the beginning (sprays #8-13), middle (sprays #176-181), and end (sprays #343-348) of the use life. Distances from the laser beam were 3, 5 and 7 cm.

Two instruments were used in conjunction with each other to make the analysis completely automated. The [redacted] is the device that mechanically actuates the nasal spray into the [redacted]; the laser diffractor that reads the droplet size.

The firm states that this test was not blinded because the actuation of spray pumps for both the test and reference products was automated, and all analyses were performed by the instrument. There was no human intervention. Automated actuation by definition involves the same dose time, return time, hold time and force for the test and reference products as defined in the Methods C-1581-00, 73-109-00 and 73-088-06 (Section 15, Vol. 3).

Data for the test and reference products were analyzed by calculation of the mean values and the variability of the data. The 90% confidence intervals for the ratio of means (mean of Test over mean of Reference product) were constructed using Fieller's theorem. In addition, the firm has also calculated the f2 similarity factor for the percentage of droplets between 10 and 500 um and percentage greater than 500 um to provide another measure of the comparability of the data.

Comments on the Droplet Size Distribution:

1. As mentioned above the in vitro testing was performed on **single lots** of test and reference products. Therefore, the comment given for the Unit dose data is applicable to the Droplet Size Distribution data.

2. With regard to the testing procedure, the firm does not state the stage of plume formation for which the D50 and SPAN data were collected. In the absence of this information, it is difficult to determine if these data represent fully formed sprays.

3. Based on the above comments, the droplet size distribution data are unacceptable. The firm should repeat this test using three lots of the test and reference products. The test should be performed at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, the firm should provide D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam:

    (1) Plume formation characterized by increase in %obscuration.

    (2) Fully formed plume characterized by a period of relatively stable obscuration.

    (3) Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.

The revised droplet size distribution data should be accompanied by representative (≥ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible data regarding the duration of the "fully formed" plume as well as the entire spray of test and reference products should also be submitted.

CASCADE IMPACTION:

Nasal Instrument Procedure NIP-2000-001 Archival Vol. 3, pp 1012

The ——— cascade impactor selectively segregates particles less than about 10 microns in diameter. Cascade impaction is performed to determine that there is not an excess mass of fines in the test product relative to the RLD.

Testing was performed on 10 units each of the test and reference drug products at beginning (sprays #8-17) and end (sprays #343-352) of the product use life. There were 10 actuations per test. Setup of the ——— cascade impactor instrument included

method (Method C-1573-02, Section 15, Vol. 3/Validation Report). For the HPLC method, the limit of detection was —— % and the limit of quantification was ——%. Testing was conducted according to Nasal Instrument Procedure NIP-200-001.

Testing was performed in a blinded manner to hide the identity of test and RLD products from the analyst. For this test, the units were manually actuated (10 actuations per test) for all testing for the test and reference products.

The procedure used for blinding test and RLD products from the analyst is fully described in the blinding procedure description (Section 15, Vol. 3, see Attachment II).

Comments on Cascade Impaction Data

As mentioned above the in vitro testing was performed on **single lots** of test and reference products. Therefore, the comment given for the Unit Dose data is applicable to the Cascade Impaction data.

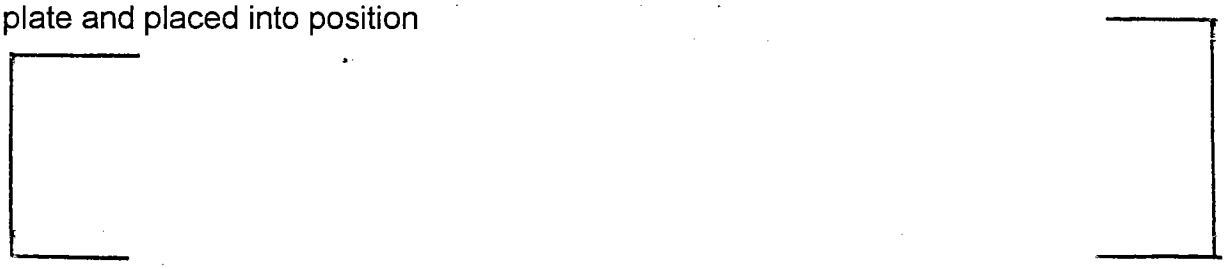
SPRAY PATTERN:

SOP 73-108-02, Archival Vol. 3, pp. 977,
SOP 73-147, Archival Vol. 3, pp. 1004

Spray pattern testing was done on 10 units each of test and reference products at 3, 4, and 5 cm distances from nozzle to plate, and tested at beginning (8th actuation) and end (343rd actuation) of the use life. Duplicate testing was conducted for each of the three distances — 1 spray at 3 cm, 1 spray at 4 cm, 1 spray at 5 cm. For visualization of the spray pattern on the plate, the TLC plate (——————————————— ———————) was evenly sprayed with ——————————— solution (a pH sensitive indicator), turning the plate a pale orange color. The image was read using an UV light at 254 nm, leaving a green pattern wherever the drug formulation rests on the black background of the plate. Color images were then digitized and analyzed by the ——— ——————————. This system automatically determines the longest and shortest radii and calculates the corresponding spray angles, the elliptical ratio (longest/ shortest angle), and the ovality ratio (longest/shortest diameter).

The test was not blinded as all units were mechanically actuated with no analyst mechanical intervention on the results. The results are measured by computer.

Operation of ——————————: Once the pattern is detected on a TLC plate and placed into position



Statistical Analysis: Same as above.

Comments on Spray Pattern Data

As mentioned above, the in vitro testing was performed on **single lots** of test and reference products. Therefore, the comment given for the Unit dose data is applicable to the Spray Pattern data.

PLUME GEOMETRY by FREEZE-FRAME PHOTOGRAPHY:

SOP for Blinding Archival Vol. 3, pp. 1011
Nasal Instrument Procedure NIP-2000-006 Archival Vol. 3, pp 1023

The firm has conducted this test as per the May 1999 draft CMC guidance for Nasal Spray Drug Products

The freeze-frame photography for 10 units each of the test and reference products was captured photographically at the beginning of the product use life. At least, six time delays (0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds) were used.

Testing was performed in a blinded manner so as to hide the identity of test and reference products from the analyst. The units were manually actuated 7 times to assure prime with the 8th spray being the test. Testing was conducted according to Nasal Instrument Procedure NIP-2000-006 (Section 15, Vol. 3).

Each plume was sprayed in an upright, stationary position. As it is being filmed, the spray evolved and dissipated in front of a grid graduated in inches. The room in which testing was performed was ventilation free and sound proof to eliminate any currents or vibration of droplets. There was no exhaust hood above the plume.

The plume angle was measured using [redacted]. The program has a function built into it that allows an analyst to [redacted]

Individual photographs per bottle are provided in volume 15 and 16.

Comments on Plume Geometry Data

As mentioned above the in vitro testing was performed on single lots of test and reference products. Therefore, the comment given for the Unit dose data is applicable to the Plume Geometry data.

Additionally, the firm should be advised that plume measurements at 3 time-delays 0.033, 0.066 and 0.100 seconds may be sufficient, instead of the 6 time-delays 0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds used in the above study.

Deficiencies:

1. **On comparability of spray devices:**

   The firm is requested to provide technical/engineering drawings of the test and reference pumps.

2. **On all In vitro tests:**

   The firm has used **single lots** of the test and reference products to determine comparative data for all in vitro testing. The in vitro studies were conducted approximately a year after the issuance of the draft guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" issued in June 1999.

   The draft guidance recommends in vitro equivalence based on **three lots** of the test and reference products, because the proposed method of in vitro evaluation takes into consideration the relative within lot and lot-to-lot variations of the test and reference products.

The firm's in vitro performance testing is therefore unacceptable. The firm should be advised to submit data from **three batches** of the test and reference products for all in vitro tests.

3. **On the Droplet Size Distribution:**

With regard to the testing procedure, the firm has not stated the stage of plume formation for which the D50 and SPAN data were collected. Thus, it is difficult to determine if these data represent fully formed sprays.

The firm should repeat this test using three lots of the test and reference products. The test should be performed at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, the firm should submit D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or transmission) of the laser beam:

(1) Plume formation characterized by increase in %obscuration.
(2) Fully formed plume characterized by a period of relatively stable obscuration.
(3) Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.
(4) The above data should be accompanied by representative ($\geq$ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible data regarding the duration of the "fully formed" plume as well as the entire spray of test and reference products should also be submitted.

Recommendations:

The in vitro performance testing conducted by Bausch and Lomb on its Ipratropium Bromide Nasal Spray, 0.03%, Lot # 286161 comparing it with the reference product, Atrovent Nasal Spray, 0.03%, Lot #819013B has been found incomplete due to the deficiencies mentioned above.

Additionally, it is noted that the firm has submitted separate applications on ipratropium bromide 0.06% and 0.03% nasal sprays. The firm should note that based on the *Draft Nasal BA/BE Guidance*, full in vitro testing on the lower strength product (0.03%) is not required if the lower and higher strength products use the same pump and actuator. In that case abbreviated in vitro testing on the lower strength product may be sufficient. The recommended abbreviated testing includes:

In vitro test	Low strength
Dose content uniformity	Yes, Beginning and End Only
Priming and repriming	Yes
Tail off	Yes
Droplet size distribution	
By laser diffraction	Yes, Beginning only
By cascade impactor	**Not requested**
Spray Pattern	Beginning Only
Plume Geometry	**Not requested**

The firm should be informed of the deficiencies and recommendations.

Chandra S. Chaurasia
Review Branch I
Division of Bioequivalence

Date: 5/24/2001

RD INITIALED YHUANG
FT INITIALED YHUANG

Date: 5/24/2001

Concur:

Date: 5/24/2001

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

ANDA:76-025 APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.
DRUG PRODUCT: Ipratropium Bromide Nasal Spray 0.03%
V:\firmsam\Bausch\ltrs&rev\76025wai.n00
CC: DIVISION FILE, HFD-652/Bio Secretary-Bio Drug File, HFD-650/C.Chaurasia

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:76-025 APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Spray 0.03%

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

1. All In vitro tests:

You have used *single lots* of the test and reference products to determine comparative data for all in vitro testing. The in vitro studies were conducted approximately a year after the issuance of the draft guidance "*Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*" issued in June 1999. The draft guidance recommends in vitro equivalence based on three lots of the test and reference products, because the proposed method of evaluation takes into consideration the relative within-lot and lot-to-lot variations of the test and reference products.

Your in vitro performance testing is therefore unacceptable. You are advised to submit data using three lots of the test and reference products for the following in vitro tests:

1. Unit Dose/Content Uniformity
2. Priming, loss of prime, and tail off
3. Droplet size distribution by at least two methods
4. Spray pattern
5. Plume geometry

2. On the Droplet Size Distribution:

With regard to the testing procedure, you have not stated the stage of plume formation for which the D50 and SPAN data were collected. When you repeat this test using three lots of the test and reference products, data should be collected at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, please submit D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam:

(1) Plume formation characterized by increase in obscuration.
(2) Fully formed plume characterized by a period of relatively stable obscuration.
(3 Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.

The above data should be accompanied by representative (≥ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible, please submit data regarding the duration of the "fully formed" plume as well as the entire spray of test and reference products.

Additionally, the Agency recommends the following:

1. **On comparability of spray devices:**
   Please submit technical/engineering drawings of the test and reference pumps, if possible.

2. **On Plume Geometry data:**
   The Agency considers that using only 3 time-delays - e.g., 0.033, 0.066 and 0.100 seconds may be sufficient, instead of the 6 time-delays - 0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds used in your Plume Geometry study.

3. **Data Submission:**
   Please submit data for the three lots of the test and reference products in Excel spread sheets format attached herewith. Test/Reference ratios based on geometric means are also requested.

It is also noted that you have submitted separate applications on ipratropium bromide 0.06% and 0.03% nasal sprays. Please note that based on the *Draft Nasal BA/BE Guidance*, full in vitro testing on the lower strength product (0.03%) is not required if the lower and higher strength products use the same pump and actuator. In that case abbreviated in vitro testing on the lower strength product may be sufficient. The recommended abbreviated testing includes:

In vitro test	Low strength
Dose content uniformity	Yes, Beginning and End only
Priming and repriming	Yes

Tail off	Yes
Droplet size distribution	
By laser diffraction	Yes, Beginning only
By cascade impactor	**Not requested**
Spray Pattern	Beginning only
Plume Geometry	**Not requested**

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 76-025
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-650/C.Chaurasia

Endorsements: (Draft and Final with Dates)
HFD-652/CS Chaurasia 5/23/2001
HFD-655/Gur J.P. Singh 5/23/01
HFD-652/YC Huang
HFD-617/K Scardina
HFD-650/Dale Conner 5/24/2001

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Printed in Final on 05/23/2001

BIOEQUIVALENCY – **Incomplete**

Submission Date: 11/10/2000

~~Other (OTH): In Vitro Performance Data~~
(STD) Study Dissolution
(15)

Strength: 0.03%
Outcome: IC

Outcome Decisions:

IC - Incomplete

WinBio Comments:

- The in vitro performance data are incomplete.

Ipratropium Bromide Solution
0.06% and 0.03% Nasal Spray
ANDA #76-103 (0.06%) and 76-025 (0.03%)
Reviewer: Gur J.P. Singh
File #76103A.901 and 76025A.901

Bausch & Lomb
8500 Hidden River Parkway
Tampa, FL 33637
Submission Date: Sept. 26, 2001

Review of an ANDA Amendment

On January 18, 2001, the firm submitted comparative in vitro performance data on its ipratropium bromide nasal spray (0.06% and 0.03%) and the innovator product, Atrovent® Nasal Spray 0.06%. The Division of Bioequivalence completed its review of the in vitro data on May 11, 2001. Based on that review the firm was informed of the following deficiencies:

1. All in vitro tests:

You have used single lots of the test and reference products to determine comparative data for all in vitro testing. The in vitro studies were conducted approximately a year after the issuance of the draft guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" issued in June 1999. The draft guidance recommends in vitro equivalence based on three lots of the test and reference products, because the proposed method of evaluation takes into consideration the relative within-lot and lot-to-lot variations of the test and reference products.

Your in vitro performance testing is therefore unacceptable. You are advised to submit data using three lots of the test and reference products for the following in vitro tests:

1. *Unit Dose/Content Uniformity*
2. *Priming, loss of prime, and tail off*
3. *Droplet size distribution by at least two methods*
4. *Spray pattern*
5. *Plume geometry*

2. Droplet size distribution:

With regard to the testing procedure, you have not stated the stage of plume formation for which the D50 and SPAN data were collected. When you repeat this test using three lots of the test and reference products, it should be performed at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, please submit D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam:

(1) *Plume formation characterized by increase in obscuration.*
(2) *Fully formed plume characterized by a period of relatively stable obscuration.*
(3) *Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.*

The above data should be accompanied by representative (≥ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible, please submit data regarding the duration of the "fully formed" plume of test and reference products.

Additionally, the Agency recommends the following:

1. ***Comparability of spray devices:*** *Please submit technical/engineering drawings of the test and reference pumps.*

2. ***Plume geometry data:*** *The Agency recommends using only 3 time-delays - e.g. 0.033, 0.066 and 0.100 seconds, instead of the 6 time-delays - 0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds used in your Plume Geometry study.*

3. ***Data submission:*** *Please submit data electronically for the lots of the test and reference products in spread-sheet format as attached herewith. Test/Reference ratios based on geometric means are also requested. Please note that the minimum ANDA batch size should be 5000 bottle. Please indicate the number of bottles in each lot of the test product.*

On August 10, 2001, the firm held a tele-conference with the Division representative to clarify some of the above deficiencies. In the current amendment, the firm has submitted (1) its proposal for determination of droplet size distribution of the test product, and (2) requested a copy of the spreadsheet-format template for submission of in vitro data.

Comments

1. ***Analysis of Droplet Size Distribution:*** Droplet size distribution will be determined by laser diffraction at 3, 5 and 7 cm distances from the orifice and at beginning, middle and end sectors of product use. At each of the distance/sector combination, the firms will determine droplet size distribution for three regions of the spray plume. These regions will be determined based on % obscuration of the laser light. Of the three regions, Plume Formation is characterized by a rise in % obscuration, the Fully Formed Plume by stable obscuration, and Plume Dissipation by decline in % obscuration. In each of the three regions, samples will be taken every two msec over a period of 120 msec. The values reported for a given stage of plume life will represent average of the 2-msec samples taken over the entire region.

   The firm's proposal is acceptable. The firm does not need to submit standard deviation and % RSD for parameter values representing single sprays. Instead, the single D10, D50, D90 and SPAN values for the stable region of each spray should be submitted in the attached spreadsheet format. The criteria for identifying the initiation and termination of the stable region should be specified in the protocol/SOP. Parametric data for the initial (plume formation) and end (plume dissipation) sections of the plume need not to be submitted. The requested ≥ 20% time-history plots over the entire life of the spray

(instrument onset to offset) should contain the % obscuration, D10, D50 and D90 data for a given spray on the same plot. Each plot should be labeled to identify the stable region of the plume, distance, product life stage, and the product, batch number and bottle number. Plots of SPAN data are not essential.

2. The spreadsheet format template requested by the firm is attached herewith.

Recommendation

The firm's proposal for droplet size distribution testing is acceptable. It should be informed of the comments #1. In addition, the firm should be provided with a copy of the attached spreadsheet format.

Gur Jai Pal Singh, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR Date 11/20/2001

Concur: Date 12/11/2001

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA: 76-103 and 76-025 APPLICANT: Bausch & Lomb

DRUG PRODUCT: Ipratropium Bromide Nasal Sprays 0.06% and 0.03%

The Division of Bioequivalence has completed its review of your application acknowledged on the cover sheet. It has the following comments:

Analysis of Droplet Size Distribution: Your proposal indicated that you will determine droplet size distribution by laser diffraction at 3, 5 and 7 cm distances from the orifice and at the beginning, middle and end sectors of product use. At each of the distance/sector combination, you will determine droplet size distribution for three regions of the spray plume. These regions will be determined based on % obscuration of the laser light. Of the three regions, Plume Formation is characterized by a rise in % obscuration, the Fully Formed Plume by stable obscuration, and Plume Dissipation by decline in % obscuration. In each of the three regions, samples will be taken every two msec over a period of approximately 120 msec. The parameter (i.e., D50, D90..) values reported for a given stage of plume life will represent average of the 2-mec samples taken over the entire region.

Your proposal is acceptable. However please note that you do not need to submit standard deviation and % RSD for parameter values representing single sprays. Instead, the single D10, D50, D90 and SPAN values for the stable region of each spray should be submitted in the attached spreadsheet format. The criteria for identifying the initiation and termination of the stable region should be specified in the protocol/SOP. Parametric data for the initial (plume formation) and end (plume dissipation) sections of the plume need not to be submitted. The requested ≥ 20% time-history plots over the entire life of the spray (instrument onset to offset) should contain the % obscuration, D10, D50 and D90 data for a given spray on the same plot. Each plot should be labeled to identify the stable region of the plume, distance, product life stage, and the product, batch number and bottle number. Plots of SPAN data are not essential.

Spreadsheet Format. The spreadsheet template requested in your correspondence is attached herewith.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA # 76-103 and 76-025
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Reviewer
HFD-655/ Team Leader

\\CDS008\WP51F99\FIRMSAM\BAUSCH\LTRS&REV\76103A.901.doc
and 76025A.901.doc

Endorsements: (Final with Dates)
HFD-655/ Gur J.P. Singh GPS 10-31-01 11/20/01
HFD-655/ S. Nerurkar
HFD-650/ D. Conner for 12/11/2001

BIOEQUIVALENCY - Acceptable Submission Date: Sept. 26, 2001

Study Amendment (STA)

Strength: 0.06%
Outcome: ~~AC~~ IC

Study Amendment (~~STA~~ NC)

Strength: 0.03%
Outcome: AC

APPEARS THIS WAY ON ORIGINAL

Draft Format Tables
for
Comparative In Vitro Performance Data
for
Oral Inhalation Aerosols, Nasal Aerosols and Nasals Sprays

Table 1: Unit Dose Data*....(ANDA # .....)

Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
TEST	1	Beg														
		Mid														
		End														
	2	Beg														
		Mid														
		End														
	3	Beg														
		Mid														
		End														
REF	1	Beg														
		Mid														
		End														
	2	Beg														
		Mid														
		End														
	3	Beg														
		Mid														
		End														

** For Nasal sprays, Beginning (Beg) and End only.*

*** Based on combined data of three lots, separately at Beg, Middle (Mid) and End*

Table 2: Priming Data....(ANDA # .....)

(Similar table for Repriming Data, where applicable per REF labeling)

Product	Lot #	Actuation #	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
TEST	1	1														
		2														
		3														
		⋎														
		To the first full medication dose														
	2	1														
		2														
		3														
		⋎														
		To the first full medication dose														
	3	1														
		2														
		3														
		⋎														
		To the first full medication dose														
REF	1	1														
		2														
		3														
		⋎														
		To the first full medication dose														
	2	1														
		2														
		3														
		⋎														
		To the first full medication dose														
	3	1														
		2														
		3														
		⋎														
		To the first full medication dose														

*** Based on combined data of three lots.*

2

Table 3: Tail Off Data....(ANDA # .....)

Product	Lot #	Actuation #	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
TEST	1	Last labeled (LL) LL + 1 LL + 2 ⋎ Depletion														
	2	Last labeled (LL) LL + 1 LL + 2 ⋎ Depletion														
	3	Last labeled (LL) LL + 1 LL + 2 ⋎ Depletion														
REF	1	Last labeled (LL) LL + 1 LL + 2 ⋎ Depletion														
	2	Last labeled (LL) LL + 1 LL + 2 ⋎ Depletion														
	3	Last labeled (LL) LL + 1 LL + 2 ⋎ Depletion														

*** Based on combined data of three lots.*

3

Table 4: Cascade Impaction Data....(ANDA # .....)

(For nasal aerosols & nasal sprays, data may be combined into three groups per the draft Nasal BA/BE Guidance)
(Table format is based on the Andersen Cascade Impactor. It should be modified appropriately for other devices)

PROD	SECTOR	Lot #	Can #	Drug Deposition on (Mass Units)										
				Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
TES	BEG		5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

4

PROD	SECTOR	Lot #	Can #	Drug Deposition on (Mass Units) Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
TES	END		4												
			5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

TeS/REF (Grand Mean)	BEG	
	END	
*p (Tvs.R)***	BEG	
	END	

*** Based on combined data of three lots, separately at Beg & End*

5

Table 4: Cascade Impaction Data....(ANDA # .....)

For nasal aerosols & nasal sprays, data may be combined into three groups per the draft Nasal BA/BE Guidance)
(Table format is based on the Andersen Cascade Impactor. It should be modified appropriately for other devices)

PROD	SECTOR	Lot #	Can #	Drug Deposition on (Mass Units)										
				Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
REF	BEG		5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

6

PROD	SECTOR	Lot #	Can #	Drug Deposition on (Mass Units) Valve Stem	Act.	Throat	S-0	S-1	S-2	S-3	S-4	S-5	S-6	S-7	Filter
			1												
			2												
			3												
			4												
			5												
		1	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
REF	END		4												
			5												
		2	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
			1												
			2												
			3												
			4												
			5												
		3	6												
			7												
			8												
			9												
			10												
			Mean												
			%CV												
		Grand	Mean												
		Grand	%CV												

7

Table 5: Particle Sizing by Laser Diffraction....(ANDA # .....)

Note: Laser diffraction data for each of the three phases (Initial, Full and Dissipation) of plume should be reported at Beginning, Middle and End of product use life.

D50 *(Comparable tables for D10 and D90 are also requested)*

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
(3, 5 and 7 cm are provided as examples. Other distances may be appropriate for specific products)		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
3 cm		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

8

D50 *(Comparable tables for D10 and D90 are also requested)*

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
5 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

9

D50 *(Comparable tables for D10 and D90 are also requested)*

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
			Beg														
		1	Mid														
			End														
			Beg														
	TEST	2	Mid														
			End														
			Beg														
		3	Mid														
			End														
7 cm																	
			Beg														
		1	Mid														
			End														
			Beg														
	REF	2	Mid														
			End														
			Beg														
		3	Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

10

Table 5: Particle Sizing by Laser Diffraction....(ANDA # .....)

SPAN [(D90-D10)/D50]

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
3 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

11

SPAN [(D90-D10)/D50]

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
5 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

12

SPAN [(D90-D10)/D50]

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	Beg														
			Mid														
			End														
	TEST	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														
7 cm																	
		1	Beg														
			Mid														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			Mid														
			End														

*** Based on combined data of three lots, separately at Beg, Mid & End*

13

Table 6: Spray Pattern Data....(ANDA # .....)

Dmin

Distance	Product	Lot #	Lot #	Stage	Bottle/Can # 1 2 3 4 5 6 7 8 9 10	Mean	%CV	Test/Ref	p (Tvs.R)**
(3, 5 and 7 cm are provided as examples. Other distances may be appropriate for specific products)		1	1	Beg					
				End					
	TEST	2	2	Beg					
				End					
		3							
			3	Beg					
				End					
3 CM		1	1	Beg					
				End					
	REF	2	2	Beg					
				End					
		3	3	Beg					
				End					

*** Based on combined data of three lots, separately at Beg & End*

14

Dmin

Distance (Example)	Product	Lot #	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		1	1	Beg														
				End														
	TEST	2	2	Beg														
				End														
		3																
			3	Beg														
				End														
5 CM																		
		1	1	Beg														
				End														
	REF	2	2	Beg														
				End														
		3																
			3	Beg														
				End														

*** Based on combined data of three lots, separately at Beg & End*

15

Dmin

Distance (Example)	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
10 Cm																	
		1	Beg														
			End														
	REF	2	Beg														
			End														
		3	Beg														
			End														

*** Based on combined data of three lots, separately at Beg & End*

16

Table 6: Spray Pattern Data....(ANDA # .....)

Dmax

Distance (Example)	Product	Lot #	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		1	1	Beg														
				End														
	TEST	2	2	Beg														
				End														
		3																
			3	Beg														
				End														
3 CM																		
		1	1	Beg														
				End														
	REF	2	2	Beg														
				End														
		3	3	Beg														
				End														

*** Based on combined data of three lots, separately at Beg & End*

17

Dmax

Distance (Example)	Product	Lot #	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		1	1	Beg														
				End														
	TEST	2	2	Beg														
				End														
		3	3	Beg														
				End														
5 CM																		
		1	1	Beg														
				End														
	REF	2	2	Beg														
				End														
		3																
			3	Beg														
				End														

*** Based on combined data of three lots, separately at Beg & End*

18

Dmax

Distance	Product	Lot #	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref
(Example)																	
		1	1	Beg													
				End													
	TEST	2	2	Beg													
				End													
		3	3	Beg													
				End													
10 Cm																	
		1	1	Beg													
				End													
	REF	2	2	Beg													
				End													
		3	3	Beg													
				End													

*** Based on combined data of three lots, separately at Beg & End*

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Table 6: Spray Pattern Data....(ANDA # .....)

Ovality Ratio (Dmax/Dmin)

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
3 CM																	
		1	Beg														
			End														
	REF	2	Beg														
			Mid														
			End														
		3	Beg														
			End														

*** Based on combined data of three lots, separately at Beg & End*

20

Ovality Ratio

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
5 CM																	
		1	Beg														
			End														
	REF	2	Beg														
			End														
		3	Beg														
			End														

** *Based on combined data of three lots, separately at Beg & End*

21

Ovality Ratio

Distance	Product	Lot #	Stage	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	** Based on combined data of three lots, separately at Beg & End
		1	Beg														
			End														
	TEST	2	Beg														
			End														
		3	Beg														
			End														
10 Cm																	
		1	Beg														
			End														
	REF	2	Beg														
			End														
		3	Beg														
			End														

22

Table 7: Plume Geometry Data....(ANDA # .....)

Plume Width

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		0.015															0.015													
		0.030															0.030													
		0.045															0.045													
	1	0.060														1	0.060													
		0.090															0.090													
		0.120															0.120													
TEST	2	0.015													REF	2	0.015													
		0.030															0.030													
		0.045															0.045													
		0.060															0.060													
		0.090															0.090													
		0.120															0.120													
		0.015															0.015													
		0.030															0.030													
	3	0.045														3	0.045													
		0.060															0.060													
		0.090															0.090													
		0.120															0.120													

** Postactuation delay times noted here may need optimization based on nasal spray plume characteristics. Different delay times may be appropriate for pressurized aerosol products. For additional information, see Nasal BA/BE Guidance*

*** Based on combined data of three lots*

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Table 7: Plume Geometry Data....(ANDA # .....)

Plume Length

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	p (Tvs.R)**
		0.015															0.015														
		0.030															0.030														
		0.045															0.045														
	1	0.060														1	0.060														
		0.090															0.090														
		0.120															0.120														
		.															.														
		0.015															0.015														
		0.030															0.030														
TEST	2	0.045													REF	2	0.045														
		0.060															0.060														
		0.090															0.090														
		0.120															0.120														
		.															.														
		0.015															0.015														
		0.030															0.030														
	3	0.045														3	0.045														
		0.060															0.060														
		0.090															0.090														
		0.120															0.120														
		.															.														

** Postactuation delay times noted here may need optimization based on nasal spray plume characteristics. Different delay times may be appropriate for pressurized aerosol products. For additional information, see Nasal BA/BE Guidance*

*** Based on combined data of three lots*

Table 7: Plume Geometry Data....(ANDA # .....)

Plume Angle

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV
		0.015												
		0.030												
		0.045												
	1	0.060												
		0.090												
		0.120												
		0.015												
		0.030												
TEST	2	0.045												
		0.060												
		0.090												
		0.120												
		0.015												
		0.030												
	3	0.045												
		0.060												
		0.090												
		0.120												

PROD	LOT	Time* (Sec)	Bottle/Can # 1	2	3	4	5	6	7	8	9	10	Mean	%CV	Test/Ref	*p* (Tvs.R)**
		0.015														
		0.030														
		0.045														
	1	0.060														
		0.090														
		0.120														
		0.015														
		0.030														
REF	2	0.045														
		0.060														
		0.090														
		0.120														
		0.015														
		0.030														
	3	0.045														
		0.060														
		0.090														
		0.120														

** Postactuation delay times noted here may need optimization based on nasal spray plume characteristics. Different delay times may be appropriate for pressurized aerosol products. For additional information, see Nasal BA/BE Guidance*

*** Based on combined data of three lots*

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Ipratropium Bromide Solution
0.03% Nasal Spray, 21 mcg/spray
ANDA #76-025
Reviewer: Kuldeep R. Dhariwal
V:\firmsam\Bausch\ltrs&rev\76025A0902.doc

Bausch & Lomb Pharmaceuticals, Inc.
8500 Hidden River Parkway
Tampa, FL 33637
Submission Dates:
9/12/2002, 1/28/2003

Review of an Amendment Containing *In Vitro* Performance Data

Drug information:

The reference-listed drug (RLD) is Atrovent® (ipratropium bromide) nasal spray, 0.03% (21 mcg/spray, NDA #20-393) manufactured by Boehringer Ingelheim. Atrovent® nasal spray 0.03% is indicated for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older. The RLD is supplied as 30 mL of solution in a high density polyethylene bottle fitted with a metered nasal spray pump, a safety clip to prevent accidental discharge of the spray and a clear plastic dust cap. The 30-mL bottle is designed to deliver 345 sprays of 0.07 mL each (21-mcg ipratropium bromide). The recommended dose of Atrovent® nasal spray 0.03% is 2 sprays (42 mcg) per nostril two or three times daily for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older.

Background

The firm submitted this ANDA for its drug product, ipratropium bromide nasal spray, 0.03% on November 10, 2000. The firm used *single lots* of the test and reference products to determine comparative data for all *in vitro* testing. The *in vitro* studies were conducted approximately a year after the issuance of the draft guidance "*Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*" issued in June 1999. The draft guidance recommends *in vitro* equivalence based on three lots of the test and reference products, because the proposed method of evaluation takes into consideration the relative within-lot and lot-to-lot variations of the test and reference products. The firm was therefore advised to submit data using three lots of the test and reference products.

It was also noted that the firm submitted separate applications on ipratropium bromide 0.06% and 0.03% nasal sprays. Based on the *Draft Nasal BA/BE Guidance*, full *in vitro* testing on the lower strength product (0.03%) is not requested if the lower and higher strength products use the same pump and actuator. In that case abbreviated *in vitro* testing on the lower strength product may be sufficient. The recommended abbreviated testing includes:

In vitro test	Low strength
Dose content uniformity	Yes, Beginning and End only
Priming and repriming	Yes
Tail off	Yes
Droplet size distribution	
By laser diffraction	Yes, Beginning only
By cascade impactor	**Not requested**
Spray Pattern	Beginning only
Plume Geometry	**Not requested**

In this amendment, the firm has submitted the data as requested by the Division of Bioequivalence. Reviewer, Chandra Chaurasia, reviewed the original submission.

Firm's response to the deficiencies communicated to them on 6/8/2001:

Deficiency 1. All *In vitro* tests:

You have used *single lots* of the test and reference products to determine comparative data for all *in vitro* testing. The *in vitro* studies were conducted approximately a year after the issuance of the draft guidance "*Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*" issued in June 1999. The draft guidance recommends *in vitro* equivalence based on three lots of the test and reference products, because the proposed method of evaluation takes into consideration the relative within-lot and lot-to-lot variations of the test and reference products.

Your in vitro performance testing is therefore unacceptable. You are advised to submit data using three lots of the test and reference products for the following *in vitro* tests:

1. Unit Dose/Content Uniformity
2. Priming, loss of prime, and tail off
3. Droplet size distribution by at least two methods
4. Spray pattern
5. Plume geometry

Firm's response: Bausch and Lomb has performed the requested testing on two additional sub-lots of the test drug product, each manufactured with a different lot of pumps and on two additional lots of the reference drug product.

Deficiency 2. Droplet Size Distribution: With regard to the testing procedure, you have not stated the stage of plume formation for which the D50 and SPAN data were collected. When you repeat this test using three lots of the test and reference products,

data should be collected at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, please submit D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam:

(1) Plume formation characterized by increase in obscuration.
(2) Fully formed plume characterized by a period of relatively stable obscuration.
(3 Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.

The above data should be accompanied by representative ($\geq$ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible, please submit data regarding the duration of the "fully formed" plume as well as the entire spray of test and reference products.

Firm's response: As discussed in a telephone conference conducted with the Agency on August 10, 2001 and further described in a protocol submitted to the Agency on September 26, 2001, Bausch and Lomb has repeated the droplet size test using three lots of the test and reference products. Testing was performed at the beginning of product life and at three distances between the orifice and the laser beam. For each spray, D10, D50, D90 and SPAN data for three stages of plume formation based on obscuration of the laser beam are provided. Representative 20% graphs of obscurations vs. time for the above data are provided.

Deficiency 3. Additionally, the Agency recommends the following:

1. **On comparability of spray devices:** Please submit technical/engineering drawings of the test and reference pumps, if possible.

2. **On Plume Geometry data:** The Agency considers that using only 3 time-delays – e.g., 0.033, 0.066 and 0.100 seconds may be sufficient, instead of the 6 time-delays - 0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds used in your Plume Geometry study.

3. **Data Submission:** Please submit data for the three lots of the test and reference products in Excel spread sheet format attached herewith. Test/Reference ratios based on geometric means are also requested.

Firm's response: Information regarding the comparability of the spray devices is enclosed. Drawings of the spray device assembly, along with detail drawings of the actuator and pump are enclosed. Bausch and Lomb acknowledges the Agency's comments regarding the plume geometry time delays. No plume geometry data are included (as discussed in the Following Agency comment). Data for the test and

reference products are submitted in the Excel spread sheet format provided by the Agency.

Agency comment: It is also noted that you have submitted separate applications on ipratropium bromide 0.06% and 0.03% nasal sprays. Please note that based on the *Draft Nasal BA/BE Guidance*, full *in vitro* testing on the lower strength product (0.03%) is not required if the lower and higher strength products use the same pump and actuator. In that case abbreviated *in vitro* testing on the lower strength product may be sufficient. The recommended abbreviated testing includes:

In vitro test	Low strength
Dose content uniformity	Yes, Beginning and End only
Priming and repriming	Yes
Tail off	Yes
Droplet size distribution	
By laser diffraction	Yes, Beginning only
By cascade impactor	**Not requested**
Spray Pattern	Beginning only
Plume Geometry	**Not requested**

Firm's response: Bausch and Lomb acknowledges comments regarding abbreviated testing.

Review of application:

Formulation: (not to be released under FOI)

Comparative compositions of the test and the reference products are as follows:

Ingredient	Test Product			Reference Listed Drug[§]		
	mg/mL	% w/v	mg/spray	mg/mL	% w/v	mg/spray
Ipratropium bromide monohydrate, EP	0.314*	0.03	0.021	0.313*		0.021
Benzalkonium Chloride, NF						
Edetate Disodium Dihydrate, NF						**
Sodium Chloride, NF						
Purified Water, USP	q.s. to 1.0 mL	-	-	q.s. to 1.0 mL	-	q.s.
Sodium Hydroxide, NF	pH adjuster	-	-	pH adjuster	-	-
Hydrochloric acid, NF	pH adjuster	-	-	pH adjuster	-	-

[§] Formulation of the reference-listed drug was obtained from the NDA 20-393 submission (Vol. 28.1, June 18, 1999) – Valve size of 70 uL.

*The ingredient is added as ipratropium bromide, monohydrate, to achieve a final concentration of 0.3 mg/mL of ipratropium bromide on an anhydrous basis.

**Edetate Disodium, USP was used in the reference product. *Please note Edetate Disodium, USP is referred as Edetate Disodium Dihydrate in the USP (Electronic 2001)*

Note: This formulation table was taken from earlier review by Dr. Chaurasia. He pointed out that there is an error in the formulation provided in COMIS Drug Product Reference File, in that the RLD formulation is listed as mg/spray instead of mg/mL.

Comments on Formulation:

The concentrations of the inactive ingredients for the test product are within the acceptable range (±5%) of the approved RLD. The formulation of the test product is Q1 and Q2 same as that of the RLD. The test product formulation is acceptable.

Comparability of Spray Devices:

——— the manufacturer of the pump used for the RLD, has supplied Bausch and Lomb with a pump, which is essentially the same as that used for the innovator's product. The pump used for Bausch and Lomb's ipratropium bromide Nasal Spray, 0.03%, is identical to the RLD pump with the exception of the amount of blue colorant in the closure gasket. The firm has provided on page 28, vol. 4.1 a comparison of the component parts for the pumps used in the test and reference products (attachment). The firm has submitted the drawing of the spray device assembly, along with detail drawings of the actuator and pump. Only one set of drawings is provided since the same drawings describe the spray devices used for both the test and reference products (attachment).

Drug Products:

Test: Ipratropium Bromide Nasal Spray 0.03%, 21 mcg/spray,
Lot #286161, manufacturing date: 04/00, assay: 101.1%
Lot #286162, manufacturing date: 04/00, assay: 101.1%
Lot #286163, manufacturing date: 04/00, assay: 101.1%
The ——— bulk lot (#28616) was compounded on April 18, 2000 and subsequently packaged into three sub-lots, each using a different lot of spray pumps. Lot #286161 consisted of ———filled units, lot #286162 consisted of ——— filled units, and run #286163 consisted of ———filled units.

Reference: Atrovent® Nasal Spray, 0.03%; manufactured by Boehringer Ingelheim;
Lot #819013B, expiration 8/01, assay: 100.7%
Lot #156737A, expiration 6/03, assay: 99.1%
Lot #157699A, expiration 8/03, assay: 99.1%

Procedures and Information Applicable to All Tests:

All actuations of the nasal spray products were done using an automated actuator to actuate the nasal sprays in a reproducible manner. The automated actuator was a proprietary unit designed by ———., for nasal spray actuation. The actuation parameters for this system were setup as follows:

Dose Time: 20 ± 2 msec.
Return Time: 50 ± 1.5 msec.
Hold Time: 0.5 sec.
Spray Force: 5.50 ± 0.05 kg

UNIT DOSE AND UNIFORMITY OF UNIT DOSE:

The amount actuated per spray was measured by a validated HPLC analysis (method C-1573) with measurement by weight recorded as supportive data. The HPLC method exhibited acceptable specificity, accuracy, and precision.

The firm states that the test was not blinded because of mechanical (automated) actuation of the bottle, mechanical weighing of the bottle, and the fact that scintillation vials were also weighed. Mechanical actuation by definition involves the same dose time, return time, hold time and force for the test and reference products. The assay result (determined from the chromatogram) is checked against the 2 spray weights (bottle weight before and after actuation and weight of sample collected in the scintillation vial), so the chances for bias are essentially eliminated.

The DBE has previously accepted such justification for lack of blinding in another solution nasal sprays (ANDA #74830, 75702).

Based on the product stated delivery of 345 sprays, the firm established the following intervals as actuations to be collected and analyzed by HPLC:

Priming actuations	1-7
Beginning actuations	8-17
End actuations	343-352
Tail-off actuations	353-450

For beginning and end of unit life, the firm took mean of 10 actuations (#8-17 for beginning and #343-352 for end) from each bottle. The reviewer took spray #8 for beginning and spray #352 for end. For each test, 10 units from each of the three lots of the test product and each of the three lots of the reference product were used. Therefore, for each test a total of 30 units of the test product and 30 units of the reference product were used. The following table provides a summary based on the reviewer's calculation:

Product	Sector	Mean		Variability			T/R		p value
		Arith (N=30)	Geo	Within-lot (N=10)	Between-lot (N=3)	Total (N=30)	Arith	Geo	
Test	BEG	20.43	20.42	2.23-3.82	2.55	3.60	1.00	1.00	0.697
	END	20.71	20.70	1.61-3.38	1.66	3.08	1.01	1.01	0.270
Ref	BEG	20.35	20.33	1.56-5.96	0.27	4.01			
	END	20.47	20.45	3.23-6.83	1.80	4.82			

PRIMING, PRIME RETENTION, AND TAIL OFF CHARACTERISTICS:

The labeling of the test and reference products states: "Initial pump priming requires 7 sprays of the pump. If used regularly as recommended, no further priming is required. If not used for more than 24 hours, the pump will require 2 sprays, or if not used for more than seven days, the pump will require 7 sprays to reprime."

Priming studies were evaluated by collecting individual sprays #1-7 for 10 bottles from each of the three lots of the test and reference product.

Prime Retention: The firm has conducted a study to test the ability of the test and reference pump system to maintain its prime after a given time period from last use. All units were analyzed for initial (day 0) testing. For each unit tested on day 0, prime actuations 1-7 were delivered mechanically by the ——————→ instrument, and spray weights were recorded. The priming actuations were not collected into scintillation vials. Collection and HPLC analysis for day 0 was only performed for actuations 8-10 of each unit. After initial testing was completed, all units were stored in the laboratory at room temperature, upright orientation until pulled for testing. Three periods of non-use (1 day, 7 days, and 10 days) were analyzed. The study days and actuations were as follows:
Day 0, actuations 8,9,10
Day 1, actuations 11-15
Day 7, actuations 11-20
Day 10, actuations 11-20

Tail Off: The firm has provided data for actuations #343 and beyond demonstrating that for the test and reference products the labeled amount of "345 metered sprays" is delivered.

Unit Dose Data:

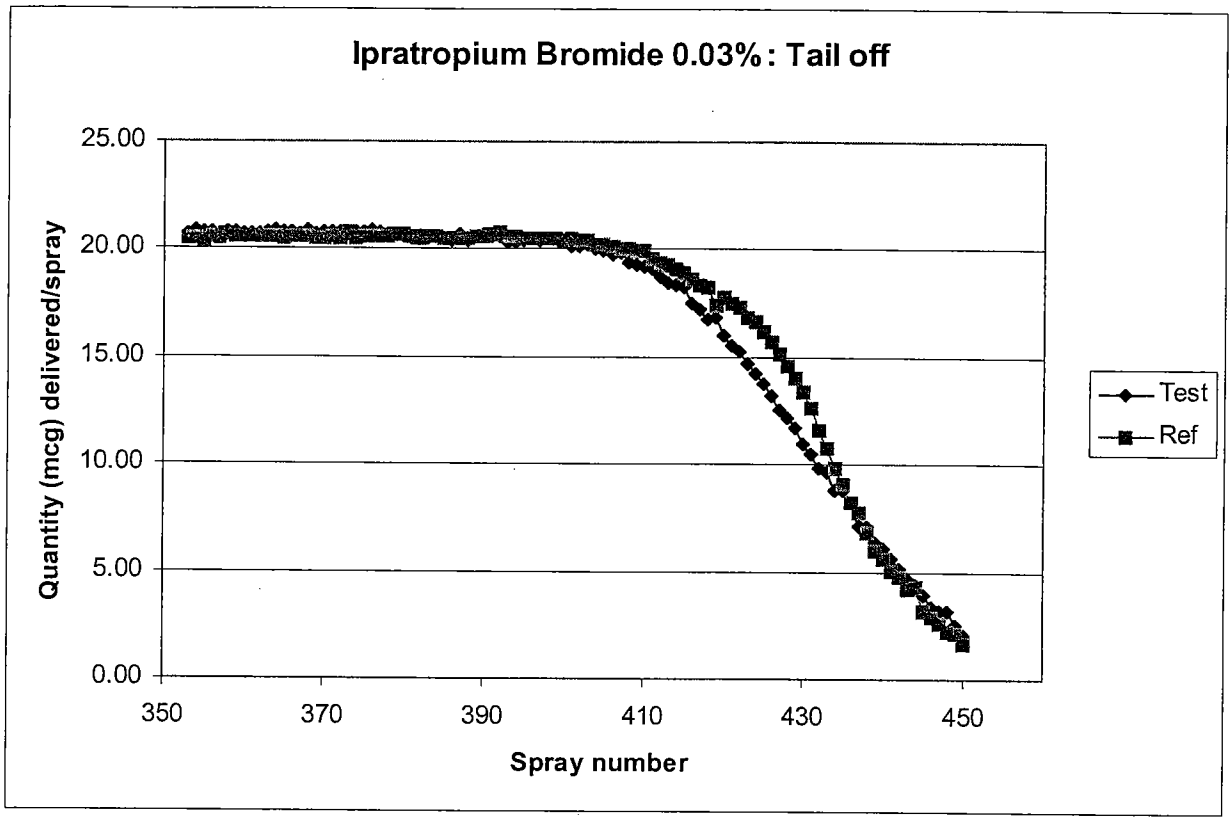
1. The firm determined comparative unit dose data based on mean of 10 sprays at beginning and mean of 10 sprays at end of unit life of the test and reference products. Unit spray content through life studies should have been evaluated on spray #8, the first label claim spray and spray #352, the last label claim spray #345, following seven priming sprays. The reviewer recalculated the data using spray #8 as beginning and spray #352 as end of unit life.
2. Based on reviewer's calculations, the mean delivery of the test and reference products is identical at both beginning and end stage of unit life.
3. The criteria for content uniformity for the test and reference products as set forth in the May 1999 draft "Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation" were applied. The draft guidance recommends that based on the 'first tier' of testing (10 units), not more than one unit should be outside 80-120% of the label claim, none should be outside 75-125%, and mean values should not be outside 85-115%. The test and reference products meet these criteria.

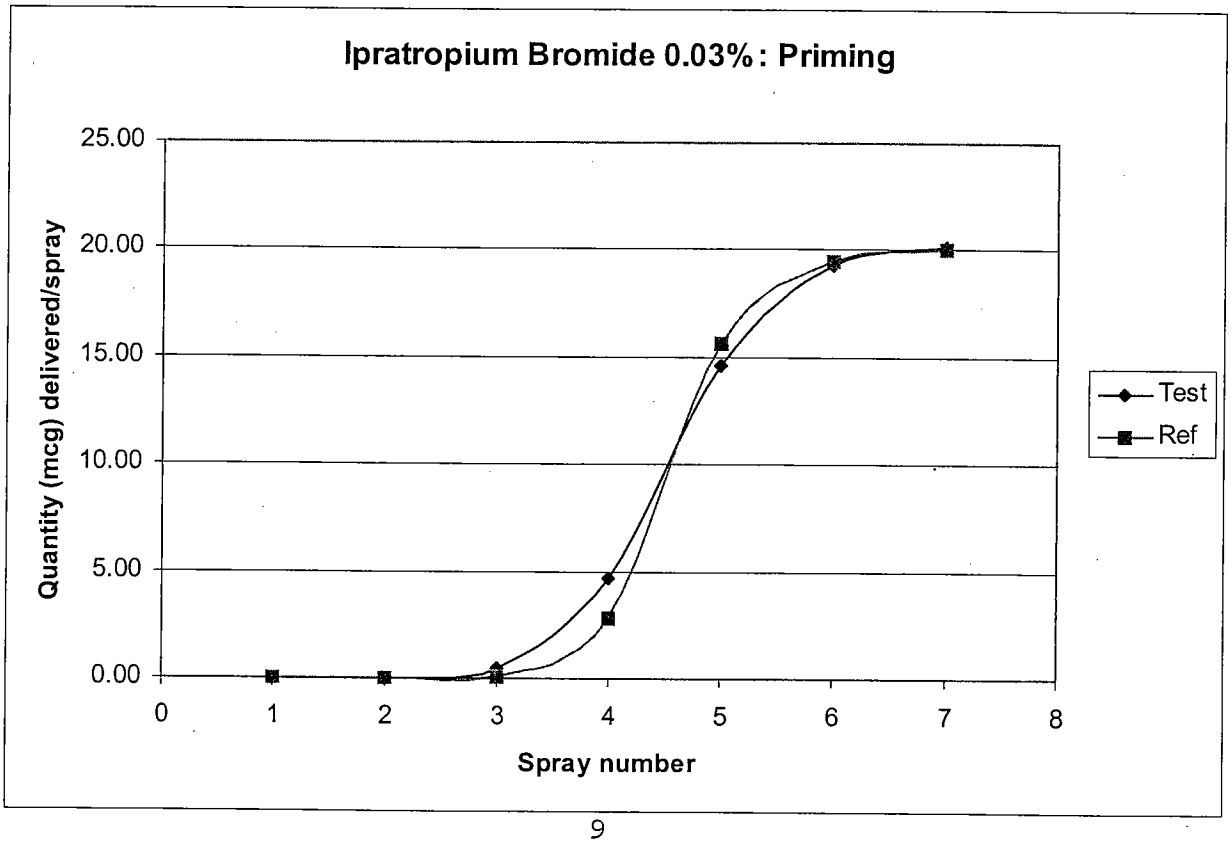
Priming and Prime Retention:

1. Based on the data obtained, the test product is fully primed at the 7^{th} spray.
2. Prime retention: On day 1, spray #11 and 12 were considered as priming and spray #13 was compared. Similarly on day 7, sprays #11-17 were considered as priming and spray #18 from the test and reference were compared for prime retention. This comparison showed that the test and reference products have the same prime retention characteristics following storage for a period of up to 10 days (page 162, vol. 4.1).
3. There is a good correlation between the quantity of the drug delivered per spray obtained by weight and that obtained by an assay using HPLC.

Tail-off:

1. The tail off profile characterizes the decrease in emitted dose following delivery of the labeled number of actuations. The tail off is documented by tabulating the spray quantity from spray #353 (corresponding to full spray #345) to product exhaustion. Data given in figures below indicate that the test product delivers the labeled numbers of doses and its tail off is no more erratic than that of the reference product.


Ipratropium Bromide 0.03%: Tail off
Quantity (mcg) delivered/spray
25.00
20.00
15.00
10.00
5.00
0.00
350
370
390
410
430
450
Spray number
Test
Ref


Ipratropium Bromide 0.03%: Priming
Quantity (mcg) delivered/spray
25.00
20.00
15.00
10.00
5.00
0.00
0
1
2
3
4
5
6
7
8
Spray number
Test
Ref

Comments:

1. The HPLC method used for calculating the amount of ipratropium bromide was validated for accuracy, precision, and specificity. The linearity of peak area response for ipratropium bromide was shown to be directly proportional to the concentration of the analyte in solution. The peak area was linear over a range of ———— to ———— (page 670, A1.2). However, only one concentration of the standard was run during sample analyses. The standard curve has only one value and a fit type of linear through zero was used for the calibration curve. A calibration curve should consist of six to eight non-zero concentrations covering the expected range of analyte in the samples. The firm should explain that why only one standard concentration was used for the calibration curve during sample analysis.

DROPLET SIZE DISTRIBUTION

SOP C-1581-01, Vol. A1.3, pp. 886
SOP 73-109-00, Vol. A1.3, pp. 987

Two instruments were used in conjunction with each other to make the analysis completely automated. The ———— is the device that mechanically actuates the nasal spray into the ———— the laser diffractor that reads the droplet size.

The firm states that this test was not blinded because the actuation of spray pumps for both the test and reference products was automated, and all analyses were performed by the instrument. There was no human intervention. Automated actuation by definition involves the same dose time, return time, hold time and force for the test and reference products as defined in the Methods C-1581-00, 73-109-00 and 73-088-06 (Section 15, Vol. A1.3).

Testing was performed on the ———— Prior to dosing, each bottle was mechanically primed 7 times using the ———— automated spray pump actuation station. The following table outlines the actuations that were analyzed at each distance:

Beginning of bottle life

Actuation #	Distance from Laser
8 & 9	3 cm
10 & 11	5 cm
12 & 13	7 cm

The DBE did not request the data for the middle and end stages of bottle life for this strength.

Individual sprays were dissected into multiple experiments, referred to as slices, to represent the development of the plume over time. For each spray a sixty slice analysis was performed. Each experiment or slice is a snapshot of the droplet size distribution at a 0.002 second interval. Therefore, a total of 0.12 seconds are needed to define the plume formation, full plume, and plume dissipation based on %obscuration. Plume formation is characterized by an increase in obscuration (beginning of plume formation), full plume by a relatively stable obscuration (middle of plume formation), and plume dissipation by a decrease in obscuration (end of plume formation). Full plume is first determined by identifying the maximum % obscuration within an analyzed spray. A spray's full plume is initiated at the time point when the % obscuration first reaches $\geq$ 80% of the maximum % obscuration. Full plume is thereby terminated at the first time point after the maximum % obscuration has been reached and when the % obscuration falls below 80% of the maximum.

Based on the DBE recommendation, the firm has provided the D10, D50, D90, % obscuration and SPAN data at 3, 5, and 7 cm distances and for the middle of plume formation stage (full plume). The data are the mean of 2 sprays: mean of actuation #8 and 9 for 3 cm, mean of actuation #10 and 11 for 5 cm, and mean of actuation #12 and 13 for 7 cm. The firm did not summarize the data for beginning and end of plume formation stage.

Droplet Size Distribution-D50 Data and Test/Ref Ratios

Product	Distance	Plume Formation	Mean		Variability (%CV)			TEST/REF		p
			Arith (N=30)	Geo (N=30)	Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	Arith	Geo	
	3	Full	30.64	30.55	2.42-9.97	5.354	7.93	0.948	0.958	0.4278
TEST	5	Full	35.77	35.74	3.95-4.76	1.339	4.364	1.001	1.001	0.9291
	7	Full	43.76	43.69	4.29-5.87	4.171	5.919	0.998	0.999	0.961
	3	Full	32.32	31.89	6.05-23.11	8.838	17.912			
REF	5	Full	35.74	35.7	3.42-6.52	0.713	5.143			
	7	Full	43.86	43.73	5.74-7.38	5.907	7.857			

Droplet Size Distribution- SPAN Data and Test/Ref Ratios

Product	Distance	Plume Formation	Mean Arith (N=30)	Mean Geo (N=30)	Variability (%CV) Within-Lot (N=10)	Variability (%CV) Between-lot (N=3)	Variability (%CV) Total (N=30)	TEST/REF Arith	TEST/REF Geo	p
	3	Full	1.39	1.383	8.56-14.48	7.049	12.665	0.88	0.94	0.3873
TEST	5	Full	1.07	1.071	5.68-7.91	1.84	6.597	0.942	0.952	0.1635
	7	Full	1.04	1.029	9.25-19.82	3.534	14.114	0.99	0.997	0.8737
	3	Full	1.58	1.471	9.44-88.03	20.486	62.511			
REF	5	Full	1.14	1.125	8.38-21.85	5.653	18.244			
	7	Full	1.05	1.032	9.57-23.06	9.094	19.415			

Comments on the Droplet Size Distribution:

1. The evaluation of droplet size distribution by laser diffraction is based on the D50 and SPAN data. Furthermore, consistent with the Division of Bioequivalence's review of other solution nasal sprays (ANDA #75-499, 75-824, ——— 75-427, 75-759, ———, 76-155 and ———), evaluation of equivalence of the test and reference products' droplet size distribution is based on the fully formed plume.
2. The ratios of the test geometric means to the reference geometric means for D50 and SPAN are within the acceptable 0.90-1.11 range.
3. The overall variability of the test product was less than that of the reference product.
4. Based on these data, distribution of droplets in the test product spray is similar to that of the reference product spray.

SPRAY PATTERN:

SOP 73-108-02, Vol. A1.3, pp. 977
SOP 73-147-00, Vol. A1.3, pp. 1004

Spray pattern testing was done on 10 bottles from each of the three lots of the test and reference products at 3, 4, and 5 cm distances from nozzle to the plate. The data were obtained at the beginning (8^{th} actuation) of product life after pumps were mechanically primed seven times. Spray pattern was determined for each bottle by evaluating two TLC plates at each of three distances (3 cm, 4 cm and 5 cm) from the spray nozzle. Each TLC plate was exposed to a single spray. For visualization of the spray pattern on the plate, the TLC plate was evenly sprayed with ——— solution (a pH sensitive indicator), turning the plate a pale orange color. The image was read using an UV light at 254 nm, leaving a green pattern wherever the drug formulation rests on the

black background of the plate. Color images were then digitized and analyzed by the [redacted]. This system automatically determines the longest and shortest radii and calculates the corresponding spray angles, the elliptical ratio (longest/ shortest angle), and the ovality ratio (longest/shortest diameter).

The test was not blinded as all units were mechanically actuated with no analyst mechanical intervention on the results. The results are measured by computer.

Operation of [redacted] is the same as detailed in the DBE review of the higher strength of this product (ANDA #76-103).

The following data were obtained based on the reviewer's calculations:

Spray Pattern Data and Test/Ref Ratios

PROD.	Distance	Plume Formation	Mean Arith (N=30)	Mean Geo (N=30)	Variability (%CV) Within-Lot (N=10)	Variability (%CV) Between-lot (N=3)	Variability (%CV) Total (N=30)	TEST/REF Arith	TEST/REF Geo	p
	3	Dmin	5.53	5.506	4.91-9.59	6.463	8.821	1.055	1.058	0.477
	3	Dmax	6.36	6.338	4.93-7.61	5.136	7.3	1.001	1.005	0.987
	3	Oval. Ratio	1.15	1.15	3.56-5.17	2.107	4.417	0.94	0.946	0.074
	4	Dmin	6.26	6.239	4.81-8.75	5.415	8.19	1.03	1.036	0.707
TEST	4	Dmax	7.31	7.289	4.68-7.99	6.357	8.242	0.966	0.969	0.609
	4	Oval. Ratio	1.17	1.168	1.45-5.16	2.355	4.261	0.923	0.934	0.102
	5	Dmin	6.6	6.567	8.33-9.69	4.881	9.759	1.055	1.064	0.547
	5	Dmax	7.99	7.967	6.35-7.36	4.535	7.591	0.97	0.975	0.625
	5	Oval. Ratio	1.22	1.215	3.36-6.63	0.689	5.319	0.906	0.915	0.055
	3	Dmin	5.24	5.205	6.25-10.42	10.02	11.513			
	3	Dmax	6.35	6.309	6.84-10.65	9.203	11.34			
	3	Oval. Ratio	1.23	1.216	3.39-23.15	3.812	14.059			
	4	Dmin	6.08	6.025	3.54-13.14	11.405	13.277			
REF	4	Dmax	7.57	7.519	4.86-13.17	8.583	11.665			
	4	Oval. Ratio	1.27	1.251	4.55-27.88	5.896	17.747			
	5	Dmin	6.26	6.17	7.85-17.12	13.498	16.123			
	5	Dmax	8.24	8.173	9.37-13.01	8.958	12.977			
	5	Oval. Ratio	1.34	1.328	7.49-23.46	6.069	16.338			

Comments on Spray Pattern Data

1. The ratios of the test geometric means to the reference geometric means for Dmin, Dmax, and ovality are within the acceptable 0.90-1.11 range.
2. The overall variability of the test product was less than that of the reference product.

Deficiencies:

To calculate the amount of ipratropium bromide actuated per spray by HPLC, a calibration curve containing one concentration of standard and a fit type of linear through zero was used. A calibration curve should usually consist of six to eight non-zero concentrations covering the expected range of analyte in the samples. The firm should explain and justify the use of only one concentration of standard.

Recommendations:

1) The formulation of Bausch and Lomb's Ipratropium Bromide Nasal Spray, 0.03% is qualitatively and quantitatively (Q1 and Q2) same as the RLD, Atrovent® Nasal Spray, 0.03%, manufactured by Boehringer Ingelheim Pharmaceuticals Ltd.

2) The in vitro performance testing conducted by Bausch and Lomb on its Ipratropium Bromide Nasal Spray, 0.03%, Lots #286161, 286162 and 286163 comparing them with the reference product, Atrovent® Nasal Spray, 0.03%, Lots #819013B, 156737A and 157699A is incomplete due to above deficiency.

D Mohariwal 2/5/03
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

DO NOT CUNCUR: SEE THE ADDENDUM. 3/17/2003

RD INITIALED S. Nerurkar
FT INITIALED S. Nerurkar _____ Date: 2/25/2003

DO NOT CONCUR. PLEASE SEE ADDENDUM 0/ 3/14/03

~~Concur:~~ _____ Date: 3/14/03
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

CC: ANDA 76-025
ANDA DUPLICATE
DIVISION FILE
HFD-652/Bio Secretary-Bio Drug File
HFD-655/Dhariwal

Endorsements: (Draft and Final with Dates)
HFD-655/Dhariwal 2/25/03
HFD-658/Gur J.P. Singh 2-26-03 2/25/03
HFD-655/Nerurkar
HFD-617/Nwaba
for HFD-650/Dale Conner 3/11/03

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BIOEQUIVALENCY - DEFICIENCIES

Submission Dates: 09/12/2002
01/28/2003

1. **STUDY AMENDMENT** (STA)
9/12/02
Strengths: 0.03%
Outcome: IC

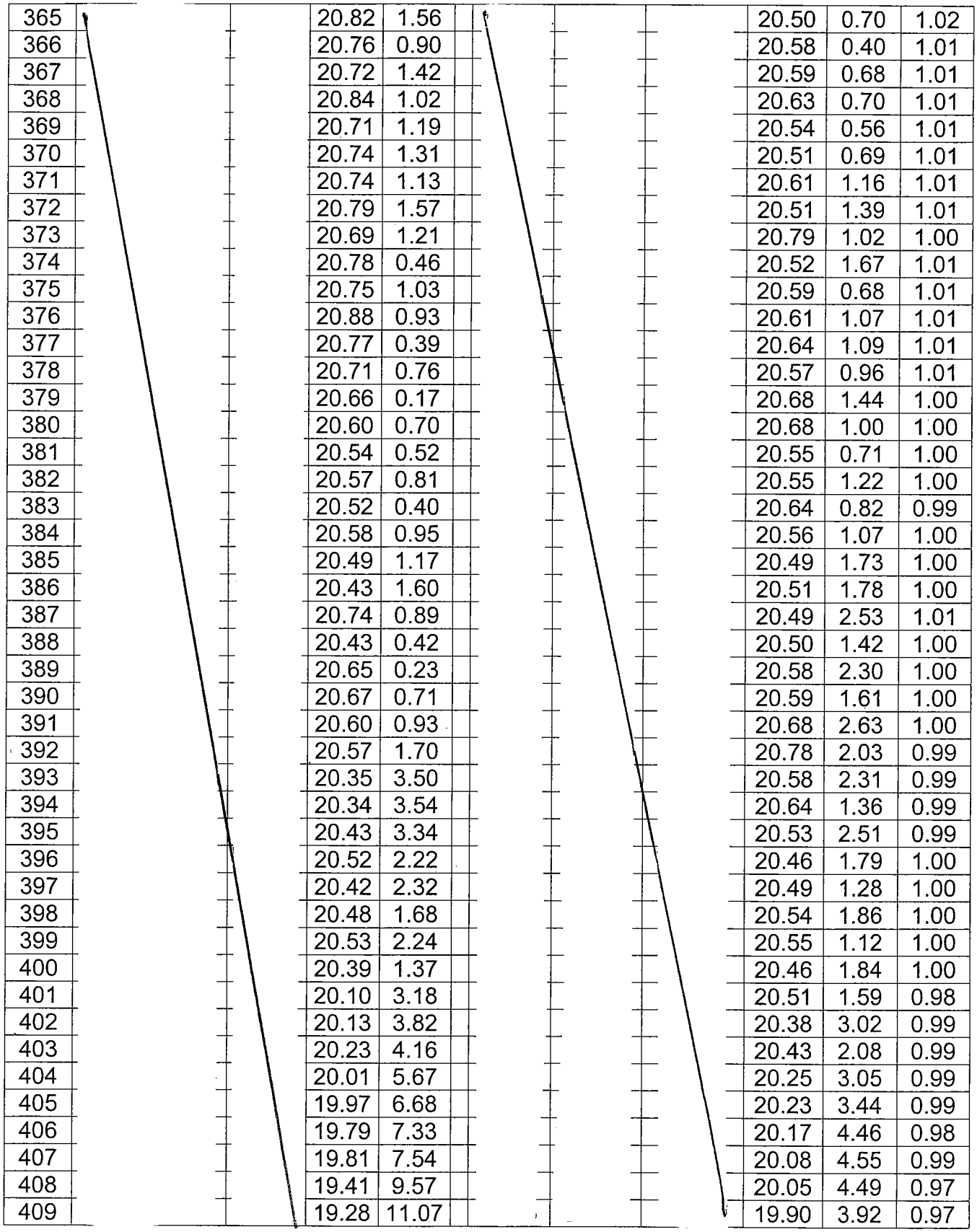
2. **NEW CORRESPONDENCE**
1/28/03
Strengths: 0.03%
Outcome: IC

Outcome Decisions:

IC - Incomplete

Priming and Tail-off Data: Quantity (mcg) delivered/spray

	Test					Ref					
Spray #	Lot 1	Lot 2	Lot 3	Mean	%CV	Lot 1	Lot 2	Lot 3	Mean	%CV	T/R
	*	*	*			*	*	*			
1				0.02	91.65				0.03	92.97	0.65
2				0.02	95.73				0.04	100.9	0.41
3				0.50	163.3				0.12	113.8	4.22
4				4.73	75.70				2.83	59.15	1.67
5				14.60	23.20				15.64	6.63	0.93
6				19.30	5.99				19.52	0.90	0.99
7				20.17	1.86				20.08	0.66	1.00
8				20.43	2.60				20.35	0.27	1.00
9				20.41	2.59				20.31	0.42	1.01
10				20.45	2.80				20.36	0.17	1.00
11				20.44	2.85				20.49	0.95	1.00
12				20.46	3.40				20.41	0.20	1.00
13				20.56	2.81				20.60	0.24	1.00
14				20.44	2.92				20.53	0.29	1.00
15				20.54	3.31				20.39	0.72	1.01
16				20.48	2.89				20.33	0.38	1.01
17				20.44	2.97				20.50	0.36	1.00
343				20.62	0.76				20.26	1.38	1.02
344				20.77	1.58				20.46	1.17	1.02
345				20.72	1.81				20.44	0.80	1.01
346				20.66	1.70				20.64	0.78	1.00
347				20.72	1.24				20.48	0.85	1.01
348				20.84	1.32				20.59	0.20	1.01
349				20.67	1.65				20.49	1.27	1.01
350				20.84	0.78				20.41	1.08	1.02
351				20.78	1.32				20.52	1.61	1.01
352				20.71	1.67				20.47	1.76	1.01
353				20.74	1.43				20.46	2.08	1.01
354				20.84	1.20				20.54	1.24	1.01
355				20.76	1.31				20.40	1.65	1.02
356				20.81	1.45				20.60	1.26	1.01
357				20.73	1.10				20.54	1.02	1.01
358				20.82	1.63				20.65	1.02	1.01
359				20.79	1.67				20.56	0.48	1.01
360				20.69	0.98				20.56	0.65	1.01
361				20.73	1.43				20.56	0.63	1.01
362				20.69	1.17				20.58	0.82	1.01
363				20.76	1.26				20.63	0.58	1.01
364				20.84	1.20				20.63	0.84	1.01



365	20.82	1.56		20.50	0.70	1.02		
366	20.76	0.90		20.58	0.40	1.01		
367	20.72	1.42		20.59	0.68	1.01		
368	20.84	1.02		20.63	0.70	1.01		
369	20.71	1.19		20.54	0.56	1.01		
370	20.74	1.31		20.51	0.69	1.01		
371	20.74	1.13		20.61	1.16	1.01		
372	20.79	1.57		20.51	1.39	1.01		
373	20.69	1.21		20.79	1.02	1.00		
374	20.78	0.46		20.52	1.67	1.01		
375	20.75	1.03		20.59	0.68	1.01		
376	20.88	0.93		20.61	1.07	1.01		
377	20.77	0.39		20.64	1.09	1.01		
378	20.71	0.76		20.57	0.96	1.01		
379	20.66	0.17		20.68	1.44	1.00		
380	20.60	0.70		20.68	1.00	1.00		
381	20.54	0.52		20.55	0.71	1.00		
382	20.57	0.81		20.55	1.22	1.00		
383	20.52	0.40		20.64	0.82	0.99		
384	20.58	0.95		20.56	1.07	1.00		
385	20.49	1.17		20.49	1.73	1.00		
386	20.43	1.60		20.51	1.78	1.00		
387	20.74	0.89		20.49	2.53	1.01		
388	20.43	0.42		20.50	1.42	1.00		
389	20.65	0.23		20.58	2.30	1.00		
390	20.67	0.71		20.59	1.61	1.00		
391	20.60	0.93		20.68	2.63	1.00		
392	20.57	1.70		20.78	2.03	0.99		
393	20.35	3.50		20.58	2.31	0.99		
394	20.34	3.54		20.64	1.36	0.99		
395	20.43	3.34		20.53	2.51	0.99		
396	20.52	2.22		20.46	1.79	1.00		
397	20.42	2.32		20.49	1.28	1.00		
398	20.48	1.68		20.54	1.86	1.00		
399	20.53	2.24		20.55	1.12	1.00		
400	20.39	1.37		20.46	1.84	1.00		
401	20.10	3.18		20.51	1.59	0.98		
402	20.13	3.82		20.38	3.02	0.99		
403	20.23	4.16		20.43	2.08	0.99		
404	20.01	5.67		20.25	3.05	0.99		
405	19.97	6.68		20.23	3.44	0.99		
406	19.79	7.33		20.17	4.46	0.98		
407	19.81	7.54		20.08	4.55	0.99		
408	19.41	9.57		20.05	4.49	0.97		
409	19.28	11.07		19.90	3.92	0.97		

410			19.16	12.00				19.95	4.44	0.96
411			19.09	12.95				19.53	4.94	0.98
412			18.71	14.86				19.39	5.65	0.97
413			18.46	16.40				19.30	6.97	0.96
414			18.31	16.77				19.12	8.19	0.96
415			18.29	15.29				18.94	9.20	0.97
416			17.50	21.35				18.67	10.52	0.94
417			17.24	21.57				18.36	11.94	0.94
418			16.77	21.74				18.28	11.32	0.92
419			16.85	20.53				17.46	18.31	0.97
420			16.03	23.47				17.77	16.07	0.90
421			15.55	25.26				17.49	16.76	0.89
422			15.22	26.43				17.33	17.07	0.88
423			14.74	30.08				16.86	20.11	0.87
424			14.24	30.82				16.71	18.82	0.85
425			13.75	33.47				16.18	21.06	0.85
426			13.17	36.81				15.74	24.96	0.84
427			12.52	39.69				15.12	22.38	0.83
428			12.17	42.95				14.63	24.08	0.83
429			11.73	41.40				14.06	23.64	0.83
430			10.96	48.59				13.37	24.26	0.82
431			10.51	52.96				12.60	23.21	0.83
432			9.84	56.23				11.58	22.00	0.85
433			9.65	55.87				10.77	22.29	0.90
434			8.80	65.47				9.79	21.29	0.90
435			8.84	63.40				9.07	21.25	0.98
436			8.24	64.14				8.25	16.99	1.00
437			7.15	74.95				7.75	11.35	0.92
438			7.08	74.41				6.82	17.65	1.04
439			6.35	80.44				6.00	23.13	1.06
440			6.12	79.22				5.65	20.30	1.08
441			5.59	79.33				5.07	21.27	1.10
442			5.17	79.82				4.75	25.69	1.09
443			4.64	76.29				4.21	19.09	1.10
444			4.37	78.89				4.30	53.42	1.02
445			3.93	79.53				3.15	37.19	1.25
446			3.37	86.34				2.95	47.70	1.14
447			3.17	73.88				2.60	55.47	1.22
448			3.23	85.12				2.24	52.61	1.44
449			2.53	84.13				2.13	68.42	1.19
450			2.10	73.31				1.67	79.03	1.25
Test Lot 1= 286161										
Test Lot 2= 286162										
Test Lot 3= 286163										

Ref Lot 1= 819013B												
Ref Lot 2= 156737A												
Ref Lot 3= 157699A												

* Average of ten units

APPEARS THIS WAY
ON ORIGINAL

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW OF 9/12/2002 SUBMISSION
[ATTACHMENT]

MAR 19 2003

Ipratropium Bromide Solution Nasal Spray
0.03% (21 mcg/mL)
ANDA #76-025
File # V:\FIRMSAM\BAUSCH\LTRS&REV\76025AD314.doc

Bausch & Lomb Pharmaceuticals, Inc.
8500 Hidden River Parkway
Tampa
Florida 33637
Submission Dates: September 12, 2002 and January 28, 2003

An Addendum to the Bioequivalency Review

The review of the Bausch and Lomb's ipratropium bromide nasal spray (76-025 for the 0.03% solution) has identified the following deficiency:

To calculate the amount of ipratropium bromide actuated per spray by HPLC, a calibration curve containing only one concentration of standard and a fit type of linear through zero was used. A calibration curve should usually consist of six to eight non-zero concentrations covering the expected range of analyte in the samples. Please explain and justify the use of only one concentration of standard.

A review of the relevant information revealed that the firm used a validated method with documented linearity in the range of [redacted]. The signal to noise ratio at the lowest concentration (0.05 mcg/mL) was 10. Therefore the assay used by the firm was validated for a wide range of concentration below and above the drug concentration per spray. The assay was used for determination of the Unit spray content.

Based on discussion with the chemistry team leader (Mike Smela) the single calibration standards are routinely used in such chemical analyses based on documented linearity over the range of assayed concentrations. The DBE therefore finds the method acceptable.

3/14/2003
Shriniwas Nerurkar
Team Leader
Division of Bioequivalence

Concur: Mike Smela _____ Date: 3/14/03
Team Leader
Division of Chemistry I

Concur: Dale Conner _____ Date: 3/14/03
for Director
Division of Bioequivalence

BIOEQUIVALENCY DEFICIENCIES

ANDA:76-025 APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Spray 0.03%

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

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,

Barbara M. Davit

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # :	**76-025**
SPONSOR :	**Bausch & Lomb Pharmaceuticals Inc.**
DRUG AND DOSAGE FORM :	**Ipratropium Bromide Solution, Nasal Spray**
STRENGTH(S) :	**0.03% (21 mcg/ml)**
TYPES OF STUDIES :	**In Vitro studies**
CLINICAL STUDY SITE(S) :	**Not applicable**
ANALYTICAL SITE(S) :	**In House**
STUDY SUMMARY :	**Dose content uniformity, Priming and Repriming, Tail off, Droplet size distribution (laser diffraction), Spray Pattern**
DISSOLUTION :	**Not applicable**

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _No____	Inspection requested: (date)	
New facility _No____	Inspection completed: (date)	
For cause _____		
Other _____		

TEAM LEADER : Shriniwas Nerurkar BRANCH : 2

INITIAL : _____ DATE : 3/17/2003

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

INITIAL : Barbara M Davit DATE : 3/19/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-025

CORRESPONDENCE

Pharmaceuticals,Inc. | 8500 Hidden River Parkway Tampa, FL 33637 | 813 975 7700 Fax 813 975 7757

November 10, 2000

BAUSCH & LOMB

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

505(b)(2)(A) OK
19-Dec-2000
Gregory S. Davis

see 75-552 a

Based on previous labeling reviews of other applicant the established name for this product is

Ipratropium Bromide Nasal Solution, 0.03%

Re: Ipratropium Bromide Nasal Spray, 0.03% ANDA Submission

Dear Sir or Madam:

In accordance with the provisions set forth in 21 CFR 314.94, we are submitting this abbreviated new drug application, in duplicate, for Ipratropium Bromide Nasal Spray, 0.03%. This application consists of 3 volumes of chemistry information, including a summary of the bioequivalence data, and 13 additional volumes of bioequivalence data (a total of 16 volumes).

An analytical methods validation package, which includes 2 additional copies of non-compendial assay procedures and the corresponding validation studies, is provided under separate cover. We will commit to resolve any issues identified in the methods validation process after approval. The Chemistry, Manufacturing and Control (CMC) information in this submission will be provided in the electronic format within 30 days following this application. This ANDA contains bioequivalence data provided in 14 separate volumes.

Changes which influence the manufacture of Ipratropium Bromide Nasal Spray, 0.03% will be reported to the Agency as established in 21 CFR 314.70.

In accordance with 21 CFR 314.50, we certify that a true copy of the information contained in this application has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 975-7775 or fax (813) 975-7757.

Sincerely,

J. B. Hawkins

Joseph B. Hawkins
Manager
Regulatory Affairs

Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV 13 2000
OGD

Pharmaceuticals,Inc. 8500 Hidden River Parkway Tampa, FL 33637 813 975 7700 Fax 813 975 7757

BAUSCH & LOMB

December 15, 2000

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

NEW CORRESP
NC

Re: ANDA 76-025
Ipratropium Bromide Nasal Spray, 0.03%
Revised Patent Certification Submission

Dear Sir or Madam:

This correspondence is provided in response to a December 14, 2000 telephone request from the Agency. This submission includes a revised (Paragraph II) patent certification for the above referenced application.

In accordance with 21 CFR 314.50, we certify that a true copy of the information contained in this application has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence, please contact me at the above address, by telephone at (813) 975-7775 or fax (813) 975-7757.

Sincerely,

J.B. Hawk

Joseph B. Hawkins
Manager
Regulatory Affairs

Enclosures

ANDA 76-025

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

DEC 19 2000

Dear Sir:

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

Reference is also made to the telephone conversation dated December 13, 2000 and your correspondence dated December 15, 2000.

NAME OF DRUG: Ipratropium Bromide Nasal Solution, 0.03%

DATE OF APPLICATION: November 10, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 13, 2000

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:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

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

ANDA 76-025
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 19-DEC-2000 date
HFD-615/BFritsch, CSO 12/19/00 date
Word File
V:\FIRMSAM\bausch\ltrs&rev\76025.ack
F/T
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

MAJOR AMENDMENT

ANDA 76-025

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

MAY - 7 2001

TO: APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

ATTN: Joseph B. Hawkins

TEL: (813) 975-7700, Ext, 7102

FAX: (813) 975-7757

FROM: Michelle Dillahunt

PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 10, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Solution, 0.03%.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (9 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance

SPECIAL INSTRUCTIONS: Chemistry comments included

5/7/01

Redacted 8 page(s)

of trade secret and/or

confidential commercial

information from

5/7/2001 FDA FAX

2. Please provide any additional long term stability data that may be available.

3. We require an acceptable Methods Validation to support the ANDA and will schedule the study after the test method issues are resolved. Please provide a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion. Additionally, please provide all current methods for drug substance acceptance and drug product release in a separate section of your amendment to facilitate the process.

4. Your labeling information is pending review. Deficiencies, if any, will be communicated separately.

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

Sincerely yours,

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

8500 Hidden River Parkway
Tampa FL 33637
813 975 7700
Fax 813 975 7757

BAUSCH & LOMB

May 7, 2001

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

ORIG AMENDMENT
AA

Re: ANDA 76-025, Ipratropium Bromide Nasal Spray, 0.03%
Amendment – Alternate Test Laboratory

Dear Sir or Madam:

This correspondence is provided to notify the Agency that we will be using an alternate laboratory for testing of the drug product described in the above referenced ANDA.

Bausch & Lomb is adding our laboratory in Rochester, New York as an alternate test site for drug product. The laboratory will be used for chemical and microbiological testing of drug product samples, including the remaining exhibit batch stability samples for the above referenced ANDA. Testing described in the pre-marketed stability protocol may be performed at the following facility, from this date forward:

Bausch & Lomb, Incorporated
1400 N. Goodman Street
Rochester, NY 14603

A letter certifying compliance of this laboratory with current Good Manufacturing Practices is enclosed. This change affects pre-marketed batches only at test stations from this date forward. All stability testing to date, including data previously submitted to the Agency, was performed at the Bausch & Lomb facility in Tampa, Florida.

If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775.

Sincerely,

Joseph B. Hawkins
Manager,
Regulatory Affairs

enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
MAY 0 8 2001
OGD

BIOEQUIVALENCY AMENDMENT

ANDA 76-025

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

JUN - 8 2001

TO: APPLICANT: Bausch & Lomb Pharmaceuticals, Inc. TEL: 813-975-7700

ATTN: Joseph B. Hawkins FAX: 813-975-7757

FROM: Krista M. Scardina, Pharm.D. PROJECT MANAGER: 301-827-5847

Dear Mr. Hawkins:

This facsimile is in reference to the bioequivalency data submitted on November 10, 2000, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Spray, 0.021mg/spray (0.03%).

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __3___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

1.1

JUN -8 2001

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:76-025 APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Spray 0.03%

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

1. All In vitro tests:

You have used *single lots* of the test and reference products to determine comparative data for all in vitro testing. The in vitro studies were conducted approximately a year after the issuance of the draft guidance "*Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*" issued in June 1999. The draft guidance recommends in vitro equivalence based on three lots of the test and reference products, because the proposed method of evaluation takes into consideration the relative within-lot and lot-to-lot variations of the test and reference products.

Your in vitro performance testing is therefore unacceptable. You are advised to submit data using three lots of the test and reference products for the following in vitro tests:

1. Unit Dose/Content Uniformity
2. Priming, loss of prime, and tail off
3. Droplet size distribution by at least two methods
4. Spray pattern
5. Plume geometry

2. On the Droplet Size Distribution:

With regard to the testing procedure, you have not stated the stage of plume formation for which the D50 and SPAN data were collected. When you repeat this test using three lots of the test and reference products, data should be collected at the beginning, middle and end of product life and at three distances between the orifice and the laser beam. For each spray, please submit D10, D50, D90 and SPAN data for the following three stages of the plume formation based on obscuration (or %transmission) of the laser beam:

(1) Plume formation characterized by increase in obscuration.
(2) Fully formed plume characterized by a period of relatively stable obscuration.
(3 Dissipating plume characterized by decrease in obscuration relative to the stable obscuration.

The above data should be accompanied by representative (≥ 20%) graphs of obscurations vs. time (msec). These graphs should also contain plots of D10, D50 and D90 vs. time data. Furthermore, if possible, please submit data regarding the duration of the "fully formed" plume as well as the entire spray of test and reference products.

Additionally, the Agency recommends the following:

1. **On comparability of spray devices:**
   Please submit technical/engineering drawings of the test and reference pumps, if possible.

2. **On Plume Geometry data:**
   The Agency considers that using only 3 time-delays - e.g., 0.033, 0.066 and 0.100 seconds may be sufficient, instead of the 6 time-delays - 0.0167, 0.0334, 0.0501, 0.0668, 0.0835, 0.1002 seconds used in your Plume Geometry study.

3. **Data Submission:**
   Please submit data for the three lots of the test and reference products in Excel spread sheets format attached herewith. Test/Reference ratios based on geometric means are also requested.

It is also noted that you have submitted separate applications on ipratropium bromide 0.06% and 0.03% nasal sprays. Please note that based on the *Draft Nasal BA/BE Guidance*, full in vitro testing on the lower strength product (0.03%) is not required if the lower and higher strength products use the same pump and actuator. In that case abbreviated in vitro testing on the lower strength product may be sufficient. The recommended abbreviated testing includes:

In vitro test	Low strength
Dose content uniformity	Yes, Beginning and End only
Priming and repriming	Yes

Tail off	Yes
Droplet size distribution	
By laser diffraction	Yes, Beginning only
By cascade impactor	Not requested
Spray Pattern	Beginning only
Plume Geometry	Not requested

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

BAUSCH & LOMB

8500 Hidden River Parkway
Tampa, Florida 33637

Facsimile Transmission Cover

NUMBER OF PAGES (Including cover): 8

DATE: September 26, 2001

ORIG. BIOAVAILABILITY N/A

TO: Krista Scardina Phone: 301-827-5847
Fax: 301-594-0181

From: Joe Hawkins Phone: 813-866-2102
Fax: 813-975-7757

Subject: ANDA August 10 Conference regarding ANDAs 76-025 & 76-103

Krista,

We participated in a conference call with the Agency on August 10, 2001 regarding the subject ANDAs. FDA requested that we provide data demonstrating the stage of plume development where droplet size is evaluated. Please evaluate the attached proposal for evaluating droplet size and let me know if it is acceptable to the Division of Bioequivalence.

FDA also indicated that they want us to submit the data obtained from additional studies in a format of a template to be provided by the Agency. We have not received the template and would like to obtain it in electronic format if possible.

To reply or if you have any questions regarding this fax you may contact me at 813-866-2102 or by e-mail at: joe_hawkins@bausch.com.

Redacted 7 page(s)

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confidential commercial

information from

9/26/2001 BAUSCH & LOMB FAX

8500 Hidden River Parkway
Tampa FL 33637
www.bausch.com

BAUSCH & LOMB

December 7, 2001

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

TPL
AC

Re: ANDA 76-025, Ipratropium Bromide Nasal Spray, 0.03%
Major Amendment – Chemistry Issues

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's May 7, 2001, "not approvable" facsimile for the above referenced application. In that letter, the Agency indicated that our response would be considered a major amendment. A copy of the Agency's letter is provided in Attachment 1.

To facilitate the Agency's review, each of the questions and our corresponding response is included following the FDA form 365h. Necessary supporting documentation for each response is provided in attachments to this amendment.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's May 7, 2001 correspondence. The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence or need additional information, please contact Joe Hawkins by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

J.B. Hawkins

Joseph B. Hawkins
Manager,
Regulatory Affairs

enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 13 2001

8500 Hidden River Parkway
Tampa FL 33637
www.bausch.com

BAUSCH & LOMB

January 24, 2002

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

N/AA

ORIG AMENDMENT

Re: ANDA 76-025, Ipratropium Bromide Nasal Spray, 0.03% Gratuitous Amendment – minor corrections

Dear Sir or Madam:

This correspondence is submitted to correct minor typographical errors noted during an internal review of the application referenced above.

The summary table for sodium chloride provided on page 102 of the December 7, 2001 amendment listed the incorrect lot number. This was a typographical error only and the results presented in the table were for the correct lot (1117199). Worksheets for lot 1117199 were also included in the original application (pages 319 – 322). A corrected summary table is enclosed.

The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence or need additional information, please contact Joe Hawkins by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

Joseph B. Hawkins
Manager,
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 25 2002

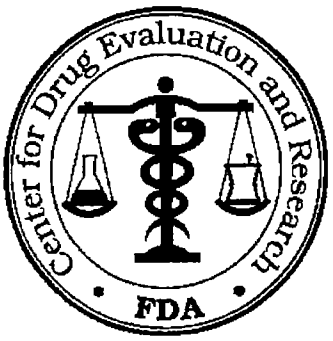
enclosure

MINOR AMENDMENT

ANDA 76-025

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

JUL 11 2002



TO: APPLICANT: Bausch and Lomb Pharmaceuticals, Inc.
ATTN: Joseph B. Hawkins

TEL: 813-866-2102

FAX: 813-975-7757

FROM: Peter Chen

PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 10, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Spary, 0.03%.

Reference is also made to your amendment(s) dated: May 7 and December 7, 2001 and January 24, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

PC 7/11/02

JUL 11 2002

38. Chemistry Comments to be Provided to the Applicant

ANDA: 76-025

APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Solution, 0.03%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

2.

3.

4.

5.

6.

7.

8. Your have provided an equation in response to deficiency # 9.d which can give percentage RSD from the recovery values. You failed to give a definition of each parameter used in the equation.

9. Please submit revised acceptance specifications for Ipratropium Bromide drug substance, and revised release and stability specifications for the drug product incorporating the revisions suggested above.

10. Bioequivalence for the drug product has not been demonstrated. Please reply to the deficiencies dated June 8, 2001.

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

   1. Please provide any additional long term stability data that may be available.

   2. We require an acceptable Methods Validation to support the ANDA. We have scheduled the validation with the laboratory. Please provide samples promptly when contacted.

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

Sincerely yours,

Paul Schwartz

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

8500 Hidden River Parkway
Tampa FL 33637
www.bausch.com

BAUSCH
& LOMB

August 13, 2002

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

ORIG AMENDMENT
N/Am

Re: ANDA 76-025, Ipratropium Bromide Nasal Spray, 0.03%
Minor Amendment – Chemistry Issues

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's July 11, 2002, "not approvable" facsimile for the above referenced application. In that letter, the Agency indicated that our response would be considered a Minor Amendment. A copy of the Agency's facsimile is enclosed in Attachment 1.

To facilitate the Agency's review, each of the questions and our corresponding response is included following the FDA form 365h. Necessary supporting documentation for each response is provided in attachments to this amendment.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's July 11, 2002 correspondence. The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence or need additional information, please contact Joe Hawkins by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

J B. Hawk

Joseph B. Hawkins
Manager,
Regulatory Affairs

enclosure

RECEIVED
AUG 1 4 2002
OGD / CDER

8500 Hidden River Parkway
Tampa FL 33637

www.bausch.com

BAUSCH
& LOMB

September 12, 2002

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

ORIG AMENDMENT
NIAB

Re: ANDA 76-025, Ipratropium Bromide Nasal Spray, 0.03%
Bioequivalence Amendment

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's June 8, 2001, facsimile regarding bioequivalence issues for the above referenced application. In that letter, the Agency indicated that our response would be considered a major amendment. A copy of the Agency's letter is provided in Attachment 1.

To facilitate the Agency's review, a table of contents for the enclosed information is provided following the FDA form 365h. Necessary supporting documentation for each response is provided in attachments to this amendment. We believe that this correspondence provides a complete response to the questions raised in the Agency's June 8, 2001 correspondence.

The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this correspondence or need additional information, please contact Joe Hawkins by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

Joseph B. Hawkins
Manager,
Regulatory Affairs

Enclosure

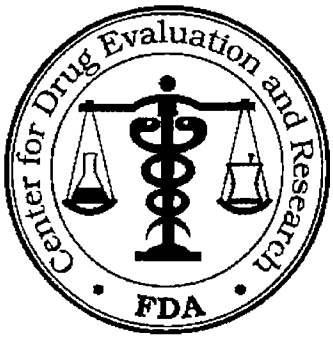
RECEIVED
SEP 13 2002
OGD / CDER

MINOR AMENDMENT

ANDA 76-025

SEP 18 2002

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



TO: APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.
ATTN: Joseph B. Hawkins

TEL: 813-866-2102

FAX: 813-975-7757

FROM: Peter Chen

PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 10, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Solution, 0.03%.

Reference is also made to your amendment(s) dated: August 13, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS: Chemistry Comments included.

PC 9/18/02

SEP 18 2002

38. Chemistry Comments to be Provided to the Applicant

ANDA: 76-025

APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Solution, 0.03%

The deficiencies presented below represent MINOR deficiencies.

1. Bioequivalence for the drug product has not been demonstrated. Please reply to this communication no earlier than your reply to the bioequivalence deficiencies dated June 8, 2001.

2. [redacted]

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

1. An acceptable compliance evaluation is needed for approval and the evaluation is pending.

2. An acceptable Methods Validation is needed to support the ANDA and the study is in process.

Sincerely yours,

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

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

BAUSCH & LOMB

October 3, 2002

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

ORIG AMENDMENT
N/am

Re: ANDA 76-025, Ipratropium Bromide Nasal Spray, 0.03%
Minor Amendment – Chemistry Issues

Dear Sir or Madam:

This correspondence is submitted in response to the Agency's September 18, 2002, "not approvable" facsimile for the above referenced application. In that letter, the Agency indicated that our response would be considered a Minor Amendment. A copy of the Agency's facsimile is enclosed in Attachment 1.

To facilitate the Agency's review, each of the questions and our corresponding response is included following the FDA form 365h. Necessary supporting documentation for each response is provided in attachments to this amendment.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's September 18, 2002 correspondence. The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence or need additional information, please contact Joe Hawkins by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

J. B. Hawk

Joseph B. Hawkins
Manager,
Regulatory Affairs

enclosure

RECEIVED
OCT 04 2002
OGD / CDER

10-4-02

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

January 28, 2003

BAUSCH & LOMB

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

ORIG AMENDMENT
N/A

Re: ANDA 76-025, Ipratropium Bromide Nasal Spray, 0.03%
Telephone Amendment – Bioequivalence

Dear Sir or Madam:

This correspondence is submitted in response to a January 23, 2003, telephone request from Dr. Nina Nwaba in the Office of Generic Drugs Division of Bioequivalence.

The Agency's requests and our corresponding responses are enclosed following the FDA form 365h. Necessary supporting documentation for each response is provided in attachments to this amendment.

We believe that this correspondence provides a complete response to the Agency's January 23, 2003 telephone request. The information contained in this amendment is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence or need additional information, please contact Joe Hawkins by telephone at (813) 866-2102, or by fax at (813) 975-7757.

Sincerely,

J. B. Hawk

Joseph B. Hawkins
Manager,
Regulatory Affairs

Enclosure

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JAN 29 2003
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NC

March 20, 2003

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

Re: ANDA 76-025, Ipratropium Bromide Nasal Spray, 0.03%
Telephone Amendment – Method Validation Commitment

Dear Sir or Madam:

This correspondence is submitted in response to a March 19, 2003, from Sara Ho regarding the above referenced application. Sara requested that we provide certification that we would work with the Agency to resolve any method validation issues, should the application be approved prior to completion of the FDA method validation.

Bausch & Lomb commits to work with the Agency to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion.

If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 866-2102.

Sincerely,

Joseph B. Hawkins
Manager,
Regulatory Affairs

Enclosure