CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-664

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

***Sponsor*:** Roxane Laboratories, Inc.

***Approval Date*:** November 5, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-664

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-664

APPROVAL LETTER

ANDA 76-664

NOV 5 2003

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated February 11, 2003, 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 11, and October 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 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.

Sincerely yours,

Robert L. Lesko for 11/5/2003

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

cc: ANDA 76-664
Division File
Field Copy
HFD-610/R. West
HFD-610/Orange Book
HFD-330
HFD-205

Endorsements:
HFD-625/M.Shaikh/ 11/4/03

HFD-625/M.Smela/ 11/4/03

HFD-617/P.Chen/ 11/4/03

HFD-613/A.Payne/ 11/4/03

HFD-613/J.Grace/ 11/4/2003

11/5/2003

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F/T by:

APPROVAL

10/14/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-664

LABELING

PATIENT'S INSTRUCTIONS FOR USE

IPRATROPIUM BROMIDE Nasal Solution 0.03% NASAL SPRAY 21 mcg/spray

NOV 5 2003

Ipratropium Bromide Nasal Spray 0.03% 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 Spray 0.03% 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.

APPROVED

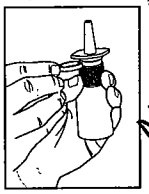


Figure 1

To Use:

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

2. The nasal spray pump must be primed before Ipratropium Bromide Nasal Spray 0.03% 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; repriming the pump will only require two sprays. If you have not used your nasal spray for more than seven days, repriming the pump will require seven sprays.

Figure 2

3. Before using Ipratropium Bromide Nasal Spray 0.03%, 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.

Figure 3

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.

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.

IPRATROPIUM BROMIDE Nasal Solution 0.03% NASAL SPRAY 21 mcg/spray

10001011/01

R_x only

NOV - 5 2003

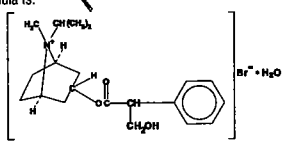
Prescribing Information

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

APPROVED

DESCRIPTION

The active ingredient in Ipratropium Bromide 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 Spray 0.03% is a metered-dose, manual pump spray unit which delivers 21 mcg (70 mcL) 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 to 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 α_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 to 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 Spray 0.06% (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 Spray 0.03% 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 Spray 0.03% (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 Spray 0.03% on degree of nasal congestion, sneezing, or postnasal drip. The response to Ipratropium Bromide Nasal Spray 0.03% 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 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. Ipratropium Bromide Nasal Spray 0.03% does not relieve nasal congestion, sneezing, or postnasal drip associated with allergic or nonallergic perennial rhinitis.

CONTRAINDICATIONS

Ipratropium Bromide Nasal Spray 0.03% 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 Spray 0.03% 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 Spray 0.03% comes into direct contact with the eyes. Patients should be instructed to avoid spraying Ipratropium Bromide Nasal Spray 0.03% 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 Spray 0.03% 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 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 Spray 0.03% 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 Spray 0.03% is administered to a nursing woman.

Pediatric Use

The safety of Ipratropium Bromide Nasal Spray 0.03% 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 to 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 Spray 0.03% for the treatment of rhinorrhea associated with allergic and nonallergic perennial rhinitis in this pediatric age group is based on an extrapolation of the demonstrated efficacy of Ipratropium Bromide Nasal Spray 0.03% in adults with these conditions and the likelihood that the disease course, pathophysiology, and the drug's effects are substantially similar to that of the adults. The recommended dose for the pediatric population is based on within and cross-study comparisons of the efficacy of Ipratropium Bromide Nasal Spray 0.03% in adults and pediatric patients and on its safety profile in both adults and pediatric patients. The safety and effectiveness of Ipratropium Bromide Nasal Spray 0.03% in patients under 6 years of age have not been established.

ADVERSE REACTIONS

Adverse reaction information on Ipratropium Bromide Nasal Spray 0.03% 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 Spray 0.03% three times daily, for eight weeks. In the other trial, Ipratropium Bromide Nasal Spray 0.03% 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 Spray 0.03%.

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 Spray 0.03% 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 Spray 0.03% (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 Spray 0.03% 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 Spray 0.03% 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 Spray 0.06%) 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. Allergic-type reactions such as skin rash, angioedema of the throat, tongue, lips and face, urticaria, laryngospasm, and anaphylactic reactions have been reported with Ipratropium Bromide Nasal Spray 0.03% and other ipratropium bromide products.

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

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Avoid freezing. Keep out of reach of children. Do not spray in the eyes.

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

Manufactured by:
Roxane Laboratories, Inc., Columbus, OH 43216

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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 clear plastic dust cap and safety clip.
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 Spray 0.03% without consulting your physician.

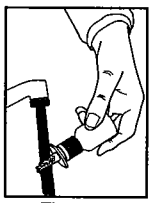
Figure 4

To Clean:
If the nasal tip becomes clogged, remove the clear 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.

Caution:
Ipratropium Bromide Nasal Spray 0.03% is intended to relieve your rhinorrhea (runny nose) with regular use. It is therefore important that you use Ipratropium Bromide Nasal Spray 0.03% 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 Spray 0.03%. Some patients may require up to two weeks of treatment to obtain maximum benefit.

Do not spray Ipratropium Bromide Nasal Spray 0.03% in your eyes. Should this occur, immediately flush your eye with cool tap water for several minutes. If you accidentally spray Ipratropium Bromide Nasal Spray 0.03% 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 Spray 0.03% should not be used during pregnancy or breast feeding 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 at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Avoid freezing. Keep out of reach of children. Do not spray in eyes.

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Dosage: Read full prescribing information and patient instructions.
Warning: Avoid spraying Ipratropium Bromide Nasal Spray in or around your eyes.
Other Ingredients: benzalkonium chloride, edetate disodium, sodium chloride, purified water.
Mfd. by: Roxane Laboratories, Inc.
Columbus, OH 43216

© RLI, 2003

NDC 0054-0045-44 **30 ml (345 metered sprays)**

IPRATROPIUM BROMIDE
Nasal Solution

0.03%

NASAL SPRAY
21 mcg/spray

Each spray contains 21 mcg ipratropium bromide.

Rx only

Roxane Laboratories, Inc. Columbus, Ohio 43216

1000:014/01

PROVIDED

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature.]

LOT EXP

ENLARGED TO 150%
BY FDI STAFF


IPRATROPIUM BROMIDE
Nasal Solution / NASAL SPRAY
0.03%
21 mcg/spray
NDC 0054-0045-44 30 ml (345 metered sprays)
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]
Avoid freezing.
NDC 0054-0045-44
30 ml (345 metered sprays)
IPRATROPIUM BROMIDE
Nasal Solution
0.03%
NASAL SPRAY
21 mcg/spray
Each spray contains 21 mcg ipratropium bromide in a pH-adjusted to 4.7, isotonic aqueous solution which also contains benzalkonium chloride, edetate disodium and sodium chloride.
Warning: Avoid spraying Ipratropium Bromide Nasal Spray in or around your
℞ only
Roxane Laboratories, Inc. Columbus, Ohio 43216
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Avoid freezing.
Manufactured by:
Roxane Laboratories, Inc.
Columbus, OH 43216
APPROVED
NDC 0054-0045-44
30 ml (345 metered sprays)
IPRATROPIUM BROMIDE
Nasal Solution
0.03%
NASAL SPRAY
21 mcg/spray
Each spray contains 21 mcg ipratropium bromide in a pH-adjusted to 4.7, isotonic aqueous solution which also contains benzalkonium chloride, edetate disodium and sodium chloride.
Warning: Avoid spraying Ipratropium Bromide Nasal Spray in or around your
℞ only
Roxane Laboratories, Inc. Columbus, Ohio 43216
Dosage:
Two sprays per nostril, two or three times daily.
Read accompanying full prescribing information and patient instructions.
NOV - 5 2003
10001013/01
© RLI, 2003
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Avoid freezing.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-664

LABELING REVIEWS

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

ANDA Number: **76-664** Date of Submission: February 11, 2003
Applicant's Name: Roxanne laboratories
Established Name: **Ipratropium Bromide Nasal Solution 0.03%, Nasal Spray - 0.021 mg/spray**

Labeling Deficiencies:

1. **CARTON and CONTAINER 21** mcg/spray (345 sprays)
   a. Revise the established name to read:

IPRATROPIUM BROMIDE
Nasal Solution

0.03%

NASAL SPRAY
21 mcg/spray

   b. Please revise storage recommendations to comply with our current standard storage temperature "Store at 20-25C(68-77F).[See USP controlled Room Temperature].

2. **INSERT** – See comments under CONTAINER. In addition, relocate the "Attention Pharmacist" statement so that it appears in the title section.

3. **PATIENT LEAFLET** – See comments under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit 12 final print labels and labeling or draft if you prefer.

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

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

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

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

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

ANDA Number	76-664
Date of Submission	
Applicant	Roxane Laboratories
Drug Name	Ipratropium Bromide Nasal Solution
Strength(s)	0.03% (Nasal Spray) 0.021 mg/spray

FPL Approval Summary		
Container Labels		**Submitted**
0.03%	30 mL	
Carton Labeling		
0.03%	1 x 30 mL	
Package Insert Labeling		
Patient Leaflet		

BASIS OF APPROVAL:

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 relief 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). The name should reflect the USP monograph as "Ipratropium Bromide Nasal Solution, XX% " with "(Nasal Spray)" added at the end. The orange book says NDA 20393 and 20394 Spray; metered; Nasal; 0.021mg/spray or 0.042 mg/spray for Ipratropium bromide. However, OGD has used the USP monograph as the established name and added (Nasal Spray) in parenthesis.

2. Storage Conditions:
NDA - Store tightly closed between 15-30C. Avoid Freezing, keep out of reach of children
ANDA - Revise to store at 20-25 C(68-77F).[See USP CRT]
USP – not applicable

3. Dispensing Recommendations:
NDA – Dispense with Patient instruction sheet.
ANDA - same
USP –

4. 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.

5. 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 5792 vol 1.13 .

6. Manufacturer by Roxane in columbus ohio page 5900 vol 1.2

Date of Review: April 1, 2003 **Date of Submission: Feb. 11, 2003**

cc: ANDA: 76-664
DUP/DIVISION FILE
HFD-613/APayne/ JGrace (no cc)
V:firmsam/roxane/let&rev/76664na1.lab
Review

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

ANDA Number	76-664
Date of Submission	Sept. 11, 2003
Applicant	Roxane Laboratories
Drug Name	Ipratropium Bromide Nasal Solution
Strength(s)	0.03% (Nasal Spray) 0.021 mg/spray

FPL Approval Summary		
Container Labels		Submitted FPL
0.03%	30 mL	Sep 11, 2003 vol 3.1 A&B
Carton Labeling		
0.03%	1 x 30 mL	Sep 11, 2003 vol 3.1 A&B
Package Insert Labeling	#10001011/01 Rev. Jul 2003	Sep 11, 2003 vol 3.1 A&B
Patient Leaflet	" "	Sep 11, 2003 vol 3.1 A&B

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**
None		None	

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 approved PI	S-004,
AP Date	5/23/03 rev.11/14/02

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-004, revised 11/14/02; approved 5/23/03 FPL). The name should reflect the USP monograph as "Ipratropium Bromide Nasal Solution, XX% " with "(Nasal Spray)" added at the end. The orange book says NDA 20393 and 20394 Spray; metered; Nasal; 0.021mg/spray or 0.042 mg/spray for Ipratropium bromide. However, OGD has used the USP monograph as the established name and added (Nasal Spray) in parenthesis.

2. Storage Conditions:
   NDA - Store tightly closed between 15-30C. Avoid Freezing, keep out of reach of children
   ANDA - Revise to store at 20-25 C(68-77F).[See USP CRT]
   USP – not applicable

3. Dispensing Recommendations:
   NDA – Dispense with Patient instruction sheet.
   ANDA - same
   USP –

4. Product Line:
   The innovator markets their product 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 maximum dose of 2 sprays per nostril 3 x daily.
   The applicant proposes to market their product in same as RLD except color of safety clip.

5. 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 5792 vol. 1.13 .

6. Manufacturer by Roxane in ColumbusOohio page 5900 vol 1.2

Date of Review: 9/23/03 **Date of Submission: Sep. 11, 2003**

cc: ANDA: 76-664
DUP/DIVISION FILE
HFD-613/APayne/ JGrace (no cc)
V:firmsam/roxane/let&rev/76664ap.lab
Review

9/23/03
9/24/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-664

CHEMISTRY REVIEWS

ANDA 76-664

Ipratropium Bromide Nasal Spray, 0.03%

Roxane Laboratories, Inc.
Columbus, OH

Mujahid L. Shaikh

Division Of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-664

2. REVIEW #: 1

3. REVIEW DATE: June 12- 23, 2003 (Revised on July 7, 2003)

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	February 11, 2003

Note: This ANDA is accepted for filing on February 12, 2003 and Acknowledgement letter is issued to the firm on March 17, 2003.

7. NAME & ADDRESS OF APPLICANT:

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

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

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Ipratropium Bromide Nasal Spray, 0.03%

9. LEGAL BASIS FOR SUBMISSION:
NDA 20393, Atrovent® Nasal Spray, 0.03%, Boehringer Ingelheim

Patent Expiration Date: 5-24-2000

10. PHARMACOLOGY CATEGORY:
Anticholinergic agent for seasonal perennial rhinitis.

11. DOSAGE FORM: Nasal Spray (Code: 836)

12. STRENGTH/POTENCY: 0.03%

13. ROUTE OF ADMINISTRATION: Nasal (Code: 014)

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

____X__Not a SPOTS product

APPEARS THIS WAY
ON ORIGINAL

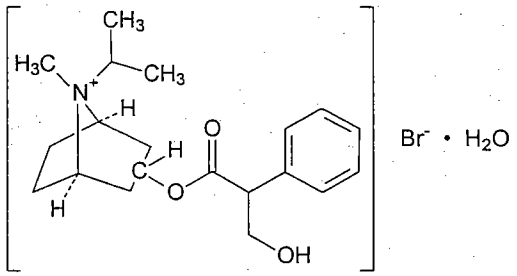
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
14259	II	Boehringer Ingelheim	Ipratropium Bromide	1	Adequate	7-7-03	
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

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

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

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

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	6-10-03	J.D. Ambrogio
Methods Validation	Waived		M. Shaikh
Labeling	Deficient	4/2/03	A. Payne
Bioequivalence	Pending Review		
EA	Adequate	6-23-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-664

The Executive Summary

I. Recommendations

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

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

II. Summary of Chemistry Assessments

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

Drug Product: The proposed drug product is Ipratropium Bromide Nasal Spray, 0.03%.

The Reference Listed Drug is Atrovent ® Nasal Spray, 0.03% (NDA 20-393) and it is approved for Boehringer Ingelheim (BI).

Atrovent ® Nasal Spray is currently manufactured at the same facility as the proposed Roxane drug product. The manufacturing process, source of the drug substance, and the specifications are essentially the same for both products.

Drug Substance: The active ingredient in this drug product is Ipratropium Bromide. It is a non-USP material and its acceptance specifications are based on BP and its manufacturer. The drug substance is provided by BI which is also the source of the drug substance for the Reference Listed Drug.

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

Ipratropium Bromide has been used for many years for treatment of patients for the symptomatic relief of rhinorrhea associated with the common cold or seasonal allergic rhinitis in adults and children age 5 years and older. Ipratropium Bromide Nasal Spray, 0.03% does not relieve nasal congestion or sneezing associated with the common cold or seasonal allergic rhinitis. It has been found to be safe and efficacious. It is used as nasal spray.

C. Basis for Approvability or Not-Approval Recommendation

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

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-625/MShaikh/7/7/03

HFD-625/MSmela/7/7/03

HFD-617/PChen/7/8/03

V:/Firmsnz/Roxane/ltrs&rev/76664.R01.doc

C. CC: **ANDA 76-664**
Division File
DUP Jacket
Field Copy

APPEARS THIS WAY
ON ORIGINAL

Redacted 29 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-664 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.03%, 21 mcg/spray

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. [redacted]
2.
3.
4.
5.
6.
7.
8.

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

1. Please respond to the labeling deficiencies.

2. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated to you separately.

3. Please provide any additional stability data that is available.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA: 76-664
ANDA DUP
Division File
Field Copy

Endorsements :

HFD-625 /M. Shaikh /7/7/03
HFD-6 25 /M. Smela /7/7/03
HFD-6 17 / PChen /7/8/03
F/t by: ard/7/9/03

V:\FIRMSNZ\Roxane\LTRS&REV\76664.R01.doc

NOT APPROVABLE – MINOR

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-664

Ipratropium Bromide Nasal Spray, 0.03%

Roxane Laboratories, Inc.
Columbus, OH

Mujahid L. Shaikh

Division Of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-664

2. REVIEW #: 2

3. REVIEW DATE: October 8, 2003 (Revised on November 3, 2003)

4. REVIEWER: Mujahid L. Shaikh

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original submission	February 11, 2003

6. SUBMISSION(S) BEING REVIEWED:*

Submission(s) Reviewed	Document Date
*Minor Amendment	September 11, 2003
Bio Amendment	July 10, 2003
*Telephone amendment	October 28, 2003

Note: This ANDA was accepted for filing on February 12, 2003 and Acknowledgement letter was issued to the firm on March 17, 2003.

7. NAME & ADDRESS OF APPLICANT:

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

Telephone: 614-272-4785

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

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None Used
b) Non-Proprietary Name (USAN): Ipratropium Bromide Nasal Spray, 0.03%

9. LEGAL BASIS FOR SUBMISSION:
NDA 20393, Atrovent® Nasal Spray, 0.03%, Boehringer Ingelheim

Patent Expiration Date: 5-24-2000

10. PHARMACOLOGY CATEGORY:
Anticholinergic agent for seasonal perennial rhinitis.

11. DOSAGE FORM: Nasal Spray (Code: 836)

12. STRENGTH/POTENCY: 0.03%

13. ROUTE OF ADMINISTRATION: Nasal (Code: 014)

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____SPOTS product – Form Completed

____X__Not a SPOTS product

APPEARS THIS WAY
ON ORIGINAL

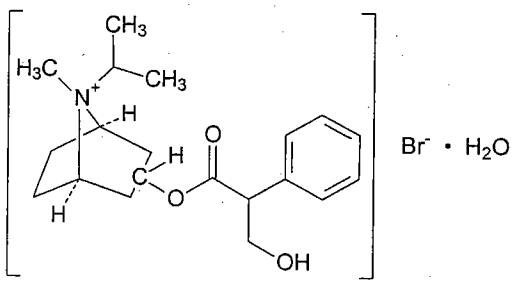
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
14259	II	Boehringer Ingelheim	Ipratropium Bromide	3	Adequate	7-7-03	
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

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

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

7 – Other (explain under "Comments")

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

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	6-10-03	J.D. Ambrogio
Methods Validation	Waived		M. Shaikh
Labeling	Acceptable	9/24/03	A. Payne/John Grace
Bioequivalence	Acceptable	9-16-03	Moheb Makary/Dale Conner
EA	Adequate	6-23-03	M. Shaikh
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

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The Chemistry Review for ANDA 76-664

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Approved.

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

II. Summary of Chemistry Assessments

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

Drug Product: The proposed drug product is Ipratropium Bromide Nasal Spray, 0.03%.

The Reference Listed Drug is Atrovent ® Nasal Spray, 0.03% (NDA 20-393) and it is approved for Boehringer Ingelheim (BI).

Atrovent ® Nasal Spray is currently manufactured at the same facility as the proposed Roxane drug product. The manufacturing process, source of the drug substance, and the specifications are essentially the same for both products.

Drug Substance: The active ingredient in this drug product is Ipratropium Bromide. It is a non-USP material and its acceptance specifications are based on BP and its manufacturer. The drug substance is provided by BI which is also the source of the drug substance for the Reference Listed Drug.

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

Ipratropium Bromide has been used for many years for treatment of patients for the symptomatic relief of rhinorrhea associated with the common cold or seasonal allergic rhinitis in adults and children age 5 years and older. Ipratropium Bromide Nasal Spray, 0.03% does not relieve nasal congestion or sneezing associated with the common cold or seasonal allergic rhinitis. It has been found to be safe and efficacious. It is used as nasal spray.

C. Basis for Approvability or Not-Approval Recommendation

Based on this CMC review for this ANDA, Roxane has submitted acceptable information regarding drug product formulation, manufacturing process, container/closure system and acceptance specifications for the drug substance,

release and stability specifications for the drug product. Referenced DMF is adequate and EER for all the listed facilities is acceptable.

III. Administrative

A. Reviewer's Signature: Mujahid L. Shaikh

B. Endorsements

HFD-625/MShaikh/11/3/03 mujahid shaikh 11/4/03
HFD-625/MSmela/11/3/03 M Smela 11/4/03
HFD-617/PChen/
V:/Firmsnz/Roxane/ltrs&rev/76664.R02.doc

C. CC: **ANDA 76-664**
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confidential commercial

information from

CHEMISTRY REVIEW #2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-664

BIOEQUIVALENCE REVIEWS

Ipratropium Bromide Nasal Spray 0.06% (42 µg/spray), 0.03% (21 µg/spray) **ANDA # 76-598 (0.06%)** **ANDA #76-664 (0.03%)** Reviewer: Moheb H. Makary W. 76598N1202.doc	Roxane Laboratories Columbus, OH Submission Date: December 23, 2002 February 11, 2003 September 5, 2003

REVIEW OF IN VITRO BIOEQUIVALENCE STUDY DATA

Executive Summary

This submission consisted of two in vitro bioequivalence studies. The studies were conducted on the ipratropium bromide 0.06% (42 µg/spray) and 0.03% (21 µg/spray) nasal spray comparing them with Boehringer Ingelhim's Atrovent^{R} Nasal Spray, 0.06% (42 µg/spray) and 0.03% (21 µg/spray), respectively. Consistent with the recommendations made in the revised Draft Nasal BA/BE guidance issued on April 3, 2003, the in vitro bioequivalence studies were conducted on the following testing for both strengths: the unit dose, droplet size distribution (laser diffraction and cascade impaction) and spray pattern. Additionally, the plume geometry test was conducted on the 0.06% strength only.

Statistical analyses of the *in vitro* performance data for ipratropium bromide nasal spray 0.06% (42 µg/spray) and 0.03% (21 µg/spray) for both studies demonstrate acceptable performance of the test products. The application is acceptable with no deficiencies.

Submission Summary

The firm submitted this application for Ipratropium Bromide Nasal Spray, 0.06% and 0.03% and requested a waiver of *in vivo* bioavailability requirements under 21 CFR 320.22 (b)(3).

Background

Based on the RLD labeling, Ipratropium bromide nasal spray 0.06% is a metered-dose, manual pump spray unit which delivers 42 ug ipratropium bromide per spray (70µL). It is indicated for the symptomatic relief of rhinorrhea associated with the common cold for adults and children age 5 years and older. It is a quaternary amine that is poorly absorbed into the systemic circulation from the nasal mucosa. The reference listed drug (RLD) is Atrovent^{R} Nasal Spray, 0.06% (42 µg/spray) manufactured by Boehringer Ingelheim. For Ipratropium Bromide Nasal Spray 0.06%, the recommended dose is two sprays (84 µg) per nostril three or four times daily. The drug is supplied as 15 mL of solution in a high density polyethylene bottle fitted with a metered nasal spray pump. The 15

mL bottle is designed to deliver 165 metered sprays of 0.07 mL each (42 µg/spray ipratropium bromide).

Ipratropium bromide nasal spray 0.03% is a metered-dose, manual pump spray unit which delivers 21 ug (70µL) ipratropium bromide per spray. It 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 reference listed drug (RLD) is Atrovent^{R} Nasal Spray, 0.03% (21 µg/spray) manufactured by Boehringer Ingelheim. The recommended dose of Atrovent® Nasal Spray 0.03% is 2 sprays (42 mcg) per nostril two or three times daily. 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).

Ipratropium Bromide Nasal Spray, 0.06%

Formulation:

Composition of the test product, ipratropium bromide nasal spray, 0.06%, is quantitatively and qualitatively the same as the reference listed drug. The formulations are provided below:

FORMULATION COMPARISON **(not for release under FOI)**

Ingredient	Test	RLD
	mg/mL	mg/mL
Ipratropium bromide		
Edetate disodium USP		
Sodium chloride, USP		
Benzalkonium chloride, NF		
Sodium hydroxide NF	To adjust pH	To adjust pH
Hydrochoric acid NF	To adjust pH	To adjust pH
Purified water USP		q.s.

Roxane Laboratories, Inc., a wholly owned subsidiary of Boehringer-Ingelheim also manufactures the reference-listed drugs.

Drug Products:

Test: Roxane's Ipratropium Bromide Nasal Spray, 0.06%, consisted of one lot of the drug solution formulation (Lot #25180S/Atrovent Bulk Solution Lot #256180, Lot size ——— with a nominal fill of 15 mL per bottle, 0.06%, manufactured date 4/2002) divided into three sublots using three separate batches of pumps (Roxane Nos. 10006625, 10006002 and 10004221).

Reference: Boehringer Ingelheim's Atrovent^{R} Nasal Spray, 0.06%, Lots 256644A, 256180B and 256930A, Exp. 5/2004, 4/2004 and 6/2004, respectively.

Comparability of Spray Devices:

Summary of Container/Closure System
The primary package consists of a white high-density polyethylene (HDPE) bottle fitted with a white metered nasal spray pump fitted with a clear plastic dust cap. These components and the corresponding packaging operation are design to yield a finished product with a nominal fill of 30 mL (345 metered sprays) for Ipratropium Bromide Nasal Spray, 0.03% and a nominal fill of 15 mL (165 metered sprays) for Ipratropium Bromide Nasal Spray, 0.06%. Roxane stated that these packaging components are identical to those used for the reference-listed drugs, Atrovent^{R} Nasal Spray, 0.03% and 0.06%. The physical data for the packaging components are providing on page 6257, Vol.1.14. The pump model used in both test and reference products is ———
The actuator model used in both the test and reference products is ———

Procedures and Information Applicable to All Tests:

——— provided data for all tests. All actuations of the nasal spray products were done using a mechanical actuator to actuate the nasal sprays in a reproducible manner. The mechanical actuator used was a proprietary unit designed by ——— for nasal spray actuation. The actuator operating conditions were as follows:

Force Rise Time:	0.1 sec
Min Travel Dist (mm)	2
Min Travel Time:	0.3 sec
Force Fall Time:	0.5 sec
Hold Time:	1 sec
Actuation Force:	7.0 kg

Unit dose (Unit Spray Content) and uniformity of unit dose

Roxane submitted data for the above-mentioned testing. The firm performed the uniformity of unit dose test using a stability-indicating method [Test Method Nos. M1-DC-IB06.0 and M1-DC-IB06.1, Assay of Ipratropium Bromide per Spray in Ipratropium Bromide Nasal Spray, Vol 1.2, page 13]. The labeled number of full medication doses per bottle is 165 sprays. The unit dose test was carried out on the entire bottle to determine the priming, re-priming and tail-off characteristics. According to the Patient's Instructions For Use leaflet for the reference listed drug, each unit is primed by wasting seven actuations. The unit should be re-primed by actuating the pump twice after 24 hours of non-use and by 7 actuations after 7 days of non-use.

The number of sprays required to prime the pump was determined by assaying the first seven sprays of each unit. A re-priming was performed after a 2-actuation (re-prime) preceded by 24-hour period without use, and drug content of the next spray (No. 13) was then analyzed immediately. Additional studies to evaluate the prime retention after 7 days of non-use were also performed.

For each test, ten (10) units from each of the three sub-lots of the test product and each of the three lots of the reference product were tested. Therefore, for each test a total of 30 units of the test product and 30 units of the reference product were tested. The amount of drug per spray was determined by a validated HPLC analysis (LOQ= ————————).

The Unit dose

Content uniformity summary results were reported at the beginning (actuation 8) and end of unit life (actuation 171). The following table provides a summary based on the reviewer's calculations.

Table I

UNIT DOSE (UNIT SPRAY CONTENT) DATA

PROD.	SECTOR	Mean* (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean (N = 30)	TEST/REF Geo Mean (N = 30)	p
TEST	BEG	99.79	1.57-2.22	0.84	2.03	1.01	1.01	0.15
	END	99.86	1.80-2.29	1.14	2.26	1.00	1.00	0.74
REF	BEG	98.89	1.04-2.35	2.00	2.25			
	END	100.03	1.49-2.39	0.47	1.84			

** The mean unit dose data are expressed % of label claim based on arithmetic means. Outcome of the statistical analysis remains the same whether the data are expressed as % LC or amount spray.*

Comments on the Unit Dose Data

1. For Roxane's Ipratropium Bromide 0.06%, the geometric mean values at actuations 8 and 171 values are similar to the corresponding reference product values. The test product exhibited almost the same variability (%CV) as the reference product with regard to the unit dose data.

2. The test/ref ratios are within the 90-111% limits, used by DBE for acceptance of *in vitro* performance of solution nasal spray products.

3. Based on the mean values, there was no change in the unit dose determined at the beginning and end sectors. Furthermore, the data did not show a particular trend in changes in variability through the container life.

4. The loss of prime was determined on the spray # 13 after a 2- actuation re-prime and spray #171 after 7-actuation re-prime by allowing the product to rest for a period of 24 hours and 7 days, respectively. Based on the data submitted (page 14, Vol.1.1), the test and reference products have same prime retention characteristics.

Droplet size distribution

a. Laser Diffraction:

Droplet size determination was performed on 10 units from each of the 3 unit lots of test and reference products. Each unit was tested at beginning, middle, and end sectors of unit life. At each sector of unit life, each unit was actuated at three distances (2.5 cm, 4.5 cm, and 6.5 cm) relative to the ⟶ laser beam. At each distance, measurements were taken at three delay times. The three delay times characterize three regions in the plume life based on % transmission:

Plume Region	Transmission Characteristic
Plume formation (Initial)	Drops
Fully formed plume (Middle)	Stable
Plume dissipation (End)	Rises

The three separate regions constitute the sampling points on which the droplet size distribution data are based. The delay times representing these regions vary with the actuation distances. The firm submitted D10, D50, D90 and SPAN data. Based on the revised draft of the Nasal BA/BE guidance, bioequivalence

evaluation is based only on D50 and SPAN data at the fully formed plume (Middle). A summary of these data based on the reviewer's calculations is given in Table II.

Table II
Droplet Size Distribution (D50 Data) – Test Product - Stable Plume

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo Mean(N=30)	p
TEST	BEG	2.5	Middle	25.25	2.3-3.4	1.8	3.09	0.99	0.99	0.001
		4.5	Middle	29.62	2.1-2.9	0.5	2.36	0.99	0.99	0.16
		6.5	Middle	34.40	2.9-3.8	0.2	3.31	1.00	1.01	0.59
	MIDDLE	2.5	Middle	25.71	1.8-4.5	1.5	3.14	0.99	0.99	0.17
		4.5	Middle	30.33	1.6-2.6	1.1	2.25	1.00	1.00	0.70
		6.5	Middle	35.09	2.6-2.8	0.9	2.82	0.99	0.98	0.11
	END	2.5	Middle	25.67	1.8-4.7	0.8	3.11	0.98	0.98	0.03
		4.5	Middle	30.43	1.6-3.5	1.5	2.70	1.00	1.00	0.89
		6.5	Middle	35.03	1.9-3.5	1.1	2.81	0.99	0.99	0.47

Droplet Size Distribution (D50 Data) – Reference Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
Ref	BEG	2.5	Middle	25.49	2.4-3.9	1.0	3.12
		4.5	Middle	29.88	1.8-2.2	0.6	2.01
		6.5	Middle	34.23	3.3-3.7	1.5	3.53
	MIDDLE	2.5	Middle	25.99	2.7-3.0	0.7	2.80
		4.5	Middle	30.41	1.1-2.6	0.5	2.08
		6.5	Middle	35.55	2.7-4.0	1.6	3.39
	END	2.5	Middle	26.17	3.7-4.3	0.8	3.72
		4.5	Middle	30.40	1.2-2.8	0.3	1.93
		6.5	Middle	35.20	1.8-3.6	0.6	2.73

Droplet Size Distribution (SPAN Data) – Test Product - Stable Plume

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo Mean(N=30)	p
TEST	BEG	2.5	Middle	1.53	3.0-7.7	3.3	6.09	0.99	0.99	0.001
		4.5	Middle	1.13	3.4-6.9	1.4	4.98	1.00	1.00	0.83
		6.5	Middle	1.07	5.0-6.7	1.5	5.67	1.01	1.01	0.63
	MIDDLE	2.5	Middle	1.51	3.1-7.4	2.8	5.76	0.99	0.99	0.39
		4.5	Middle	1.12	4.1-4.6	1.5	4.45	0.99	0.99	0.46
		6.5	Middle	1.05	4.8-6.4	0.6	5.22	1.02	1.02	0.28
	END	2.5	Middle	1.63	3.7-17.6	11.5	14.94	0.99	0.99	0.83
		4.5	Middle	1.14	3.9-10.4	3.5	7.63	0.99	0.99	0.64
		6.5	Middle	1.06	4.6-6.2	1.3	5.26	1.02	1.02	0.15

Droplet Size Distribution (D50 Data) – Reference Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
Ref	BEG	2.5	Middle	1.54	4.5-9.6	1.6	6.69
		4.5	Middle	1.12	4.7-6.1	0.2	5.14
		6.5	Middle	1.06	3.9-5.5	2.2	4.67
	MIDDLE	2.5	Middle	1.53	4.7-5.5	1.4	5.02
		4.5	Middle	1.13	5.2-7.0	0.6	5.85
		6.5	Middle	1.03	4.5-6.1	1.6	5.36
	END	2.5	Middle	1.64	4.6-20.9	11.3	16.94
		4.5	Middle	1.15	4.7-9.7	4.8	8.00
		6.5	Middle	1.04	2.5-7.8	0.2	5.25

Comments on Droplet Size Distribution

1. The ratios of the test geometric means to the reference geometric means for the fully formed (stable) plume D50 for the three distances are within the 0.98-1.01 range. For most comparisons the P values were insignificant.

2. The ratios of the test geometric means to the reference geometric means for SPAN for the three distances are within 0.99-1.02 range. For most of the comparisons the P values were insignificant.

3. For D50 and SPAN, the within-lot variability, between lot variability and total variability for the test product are comparable to that of reference product.

4. Based on the mean values:

- The D50 values did not change with the product life sectors. However, D50 increased with increase in distance between the actuator and laser beam.

- For the test and the reference products, total variability of D50 was generally less than that of the SPAN.

- Based on the geometric mean data the T/R ratio for D50 and SPAN are within the 0.9-1.11 range used hitherto by DBE for acceptance of *in vitro* performance of solution nasal spray products.

5. Based on these data, distribution of droplets in the test product spray is similar to that of the reference product spray.

b. Cascade impaction

The firm submitted the following data:

Collection #	Corresponding Stages	Aerodynamic Diameter (um)
Group 1	Collar, induction Port, Inlet Port, Stage 0, Valve stem & Actuator	ECD $\geq$9.0
Group 2	Stages 1 and 2	4.7<ECD$\leq$9.0
Group 3	Stages 3 to - and Filter	ECD$\leq$4.7

The drug deposited on corresponding stages was determined separately by HPLC method. For the HPLC method, the LOQ was ——— .

Ten units from each of the 3 unit lots of test and reference products were used to obtain cascade impaction data. Each unit was tested at the beginning and end of life. In each test five actuations of the products were used.

The procedure for determination of particle size distribution using ———— ———— Cascade Impactor with entry port of a one liter recovery flask (using Automated Spray Pump Actuation Station ———————— and HPLC method for the assay of Ipratropium Bromide Nasal Spray, 0.06% (42 ug/spray) was validated for precision, accuracy, specificity and linearity (Vol 1.2, page 13 and Vol.1.10, page 13). The flow rate used was 28.3 L/minute. A summary of cascade impaction data based on the reviewer calculation is presented in the Table III.

Table III
Material in ug

PROD.	SECTOR	Mean(N=30) Group 1	Variability %CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Geom Mean (N = 30)	p
				(>9.0 um)			
TEST	BEG	38.59	1.6-2.7	0.32	2.2	0.99 0.99	0.17
	END	39.46	1.0-2.7	1.4	2.2	1.00 1.00	0.45
REF	BEG	38.91	2.0-2.6	0.72	2.3		
	END	39.62	2.0-2.3	1.3	2.3		

PROD.	SECTOR	Mean(N=30) Group 2	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Geom Mean (N = 30)	P
				(<9.0 ->4.7 um)			
TEST	BEG	0.30	13.4-18.2	7.9	16.4	1.00 1.01	0.97
	END	0.32	12.8-23.8	4.2	18.4	1.16 1.16	0.00
REF	BEG	0.30	17.7-27.4	3.6	21.2		
	END	0.28	13.7-22.8	7.0	18.6		

PROD.	SECTOR	Mean(N=30)	Variability (%CV)			TEST/REF	
			Within-Lot	Between-lot	Total	Arith Geom	P
		Group 3	(N=10)	(N=3)	(N=30)	Mean (N = 30)	
				(<4.7 um)			
TEST	BEG	0.43	20.2-30.4	15.3	27.3	0.89 0.89	0.14
	END	0.67	12.0-36.6	19.6	27.3	1.33 1.31	0.00
REF	BEG	0.48	21.2-29.6	7.5	26.4		
	END	0.50	17.4-26.0	2.44	22.0		

Table based on combined data for the groups 2&3.

Comment on Cascade Impaction Data:

1. The Cascade Impaction results indicated that the amount of drug deposed in droplets >9 um is similar between test and reference products. The test/ref ratios are within the 90-111% limits, used by DBE for acceptance of *in vitro* performance of solution nasal spray products.

2. The group 2 and 3 data were separately analyzed for both the beginning and end stages. However, the revised Draft Nasal BA/BE guidance issued on April 3, 2003, recommends pooling of data below the impactor stage 1. Based on that guidance, the Agency requests cascade impaction data for only the beginning stage. Therefore, the cascade impaction data were reanalyzed. Based on that analysis for the beginning stage group 2 and 3 pooled data, the test and reference arithmetic means were 0.37 and 0.39, respectively. The geometric mean values were 0.35 and 0.37. The T/R ratios for the arithmetic and geometric means were 0.94 and 0.95, respectively, which are within the acceptable range. Furthermore, differences between test and reference data were insignificant (p=0.18), and the variability of the two products was comparable.

3. The amount of drug collected in groups 1, 2 and 3 constitutes 94.0% and 94.5% for the test and the reference products, respectively, at beginning life of the products (Beginning Sector) and 96.3% and 96.2% for the test and the reference products, respectively, at end life of the products (End Sector). As recommended in the Nasal BA/BE guidance, the total mass of drug collected on all stages and accessories is between 85 and 115 percent of label claim on a per actuation basis.

4. The cascade impaction data are acceptable.

Spray Pattern

The firm submitted spray pattern data at three distances (6.5, 4.5 and 2.5 cm) from TLC plate at beginning and end life sectors for the test product and the reference products. It provided individual results of spray pattern determination in term of longest diameter (D_{max}), shortest diameter (D_{min}) and ovality ratio (D_{max}/D_{min}).

The firm provided color photocopies of corresponding TLC plates with markings indicating D_{max} and D_{min} (page 5170, Vol.1.12). The staining agent ——— that reacts with drug was used to highlight the pattern of the TLC plate. Test Method No. M1-SP-IB06.1 (Spray Pattern Determination for Ipratropium Bromide Nasal Spray 0.06% (42 ug/spray)) can be found in Vol. 1.11, page 4959, along with its corresponding validation report. The firm employed manual analysis.

A summary of the spray pattern data based on the reviewer's calculations is presented in Table IV.

Table IV
Spray Pattern Data – Test Product

PROD.	Sector	Distance	Parameter	Mean	Variability (%CV)			TEST/REF		p
					Within-Lot	Between-lot	Total	Arith	Geo	
				(N = 30)	(N=10)	(N=3)	(N=30)	Mean(N=30)		
TEST	BEG	2.5	Long. Diam	55.94	4.7-7.6	3.8	6.8	1.00	0.99	0.74
		2.5	Short. Diam	49.63	4.7-7.8	6.6	8.0	1.02	1.02	0.30
		2.5	Oval. Ratio	1.13	3.2-9.7	4.1	7.1	0.98	0.98	0.13
		4.5	Long. Diam	84.16	3.7-10.2	2.9	6.8	0.98	0.98	0.18
		4.5	Short. Diam	71.61	4.5-7.5	7.7	8.5	1.00	1.00	0.89
		4.5	Oval. Ratio	1.18	4.4-8.9	4.9	8.0	0.98	0.98	0.27
		6.5	Long. Diam	117.30	4.4-7.2	5.7	7.7	1.02	1.02	0.26
		6.5	Short. Diam	96.00	6.3-8.4	4.4	7.8	1.08	1.08	0.00
		6.5	Oval. Ratio	1.23	5.7-9.0	4.1	8.1	0.95	0.94	0.01
	END	2.5	Long. Diam	52.74	4.7-7.7	3.2	6.6	1.00	1.00	0.75
		2.5	Short. Diam	43.33	3.7-6.2	3.7	5.6	1.03	1.03	0.05
		2.5	Oval. Ratio	1.22	3.8-8.4	5.3	7.3	0.98	0.98	0.19
		4.5	Long. Diam	80.11	3.4-10.7	4.8	8.1	1.03	1.03	0.19
		4.5	Short. Diam	66.22	5.0-8.3	12.1	12.0	1.04	1.04	0.23
		4.5	Oval. Ratio	1.22	5.8-13.7	7.8	11.6	1.00	0.99	0.84
		6.5	Long. Diam	110.72	3.6-12.0	5.6	8.66	1.05	1.05	0.04
		6.5	Short. Diam	89.29	5.8-12.7	18.4	17.5	**1.17**	**1.16**	0.00
		6.5	Oval. Ratio	1.27	5.6-11.8	12.9	14.6	0.91	0.91	0.01

Spray Pattern Data – Reference Product

PROD.	Sector	Distance	Parameter	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
Reference	BEG	2.5	Long. Diam	56.18	2.6-4.3	4.6	5.2
		2.5	Short. Diam	48.75	2.8-6.2	8.0	7.8
		2.5	Oval. Ratio	1.16	2.8-6.9	4.2	5.7
		4.5	Long. Diam	86.05	4.5-4.8	2.0	4.8
		4.5	Short. Diam	71.85	6.1-6.6	4.3	7.8
		4.5	Oval. Ratio	1.20	4.5-5.9	2.2	5.5
		6.5	Long. Diam	115.16	5.1-6.8	3.5	6.3
		6.5	Short. Diam	89.05	5.8-7.7	4.8	7.6
		6.5	Oval. Ratio	1.30	5.5-6.3	2.8	6.2
	END	2.5	Long. Diam	50.70	3.5-4.8	2.3	4.6
		2.5	Short. Diam	42.94	3.2-5.5	3.0	4.8
		2.5	Oval. Ratio	1.18	4.7-6.5	4.1	6.3
		4.5	Long. Diam	77.90	2.9-7.5	4.8	8.5
		4.5	Short. Diam	63.72	5.2-9.8	4.8	8.5
		4.5	Oval. Ratio	1.23	5.3-7.1	2.6	6.6
		6.5	Long. Diam	105.42	3.2-8.7	4.1	7.3
		6.5	Short. Diam	76.52	7.8-13.2	2.7	9.8
		6.5	Oval. Ratio	1.39	7.4-11.1	2.8	9.3

1. The ratios of the test geometric means to the reference geometric means for D_{max} and Ovality were within 0.98-1.05 and 0.91-0.99 range, respectively at the three distances. Test/ref ratios of geometric means are within the 90-111% limits used by DBE as an acceptance criteria for the solution nasal spray drug products.

2. For the D_{min}, the test/ref ratios based on geometric means are within 0.90-111% at 2.5 and 4.5 distances but outside this range at 6.5 distance. It is noted that the revised Draft Nasal BA/BE guidance issued on April 3, 2003, recommends measurements of Dmax and Ovality at 2 distances for manual analysis of the spray pattern test.

3. Based on the mean data, values of D_{max} and D_{min} did not significantly change between the beginning and end life sectors. The range of the total variability was not different between the beginning and end sectors.

4. Total variability in the three parameters was similar between the test and reference product.

The spray pattern data are acceptable.

Plume Geometry

The plume geometry test was performed by ———————— on behalf of Roxane Laboratories, Inc.

Plume geometry is described by two side views, at 90° at each other and relative to the axis of the plume, of the aerosol cloud when actuated into space.

High-speed video capture the spray plume (Plume Geometry) for ipratropium bromide nasal spray, 0.06% (w/v), method No. M1-PG.IB.1, page 5418, Vol.1.12.

The test consisted of using 10 units from each product lot to obtain plume geometry measurements at three times after a single actuation, the beginning (Early) of the plume, the fully formed plume (Intermediate), and the dissipation plume (End). The parameters used to characterize plume geometry are plume length, plume width, and plume (spray cone) angle. The results of the plume length, width and plume angle measurements are shown in Vol. 1.12, page 5423. Photographs of the spray plumes used to measure the plume length, width and angle are shown in Vol. 1.12, page 5325.

The plume geometry results calculated by the reviewer are shown in Table V. The Draft Nasal BA/BE guidance issued on April 3, 2003, recommends measurements of plume fully developed and still intact with the actuator. Of the three phases of plume studied by the sponsor, the early and intermediate phases represent delay times at which the plume is still intact with actuator. Therefore, the following tables include data for these two phases only.

Table V
Plume Geometry Data (Plume Length)

PROD.	Plume Stage	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith (N = 30)	Geo (N = 30)	p
			0-Degree View					
TEST	Early	93.83	11.2-18.5	2.1	13.8	0.96	0.96	0.25
	Intermed	138.97	6.7-9.3	4.3	8.6	1.00	1.00	0.97
REF	Early	97.80	13.5-15.1	5.7	14.6			
	Intermed	136.98	7.9-10.7	1.3	9.4			
			90-Degree View					
TEST	Early	94.30	15.0-23.1	6.9	20.1	1.02	1.02	0.74
	Intermed	139.35	10.5-12.6	4.0	11.4	1.02	1.01	0.49
REF	Early	92.81	7.2-16.7	6.7	15.0			
	Intermed	136.87	6.9-9.1	2.4	8.1			

Plume Geometry Data (Plume Width)

PROD.	Plume Stage	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith (N = 30)	Geo (N = 30)	P
			0-Degree View					
	Early	80.90	10.1-14.3	2.4	11.5	0.99	0.99	0.81
TEST	Intermed	105.95	6.3-11.5	0.9	8.5	1.04	1.03	0.14
	Early	81.46	9.1-12.7	6.5	11.7			
REF	Intermed	102.53	7.0-7.6	4.8	8.1			
			90-Degree View					
	Early	81.54	9.5-12.7	2.3	11.5	1.00	1.01	0.89
TEST	Intermed	108.67	8.0-10.5	3.0	9.6	1.05	1.05	0.04
	Early	81.16	4.3-15.5	10.6	14.9			
REF	Intermed	103.61	5.3-9.8	4.1	8.3			

Plume Geometry Data (Plume Angle)

PROD.	Plume Stage	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith (N = 30)	Geo (N = 30)	P
			0-Degree View					
	Early	88.25	3.0-3.6	1.2	3.3	0.99	0.99	0.28
TEST	Intermed	91.67	3.0-4.4	0.5	3.6	1.00	1.00	0.80
REF	Early	89.18	1.9-5.6	2.2	4.1			
	Intermed	91.43	1.5-5.9	1.6	4.0			
			90-Degree View					
	Early	89.53	2.2-4.4	0.97	3.2	1.01	1.01	0.37
TEST	Intermed	91.95	3.1-4.3	0.96	3.3	1.01	1.01	0.44
	Early	88.82	2.6-5.8	1.0	4.4			
REF	Intermed	91.33	2.5-5.0	0.8	4.0			

Comments on Plume Geometry Data:

1. The mean values and variability (%CV) for angle, length and width for both views and the two plume stages are summarized in the Table above.
2. For angle, length and width, the means are comparable between the test and reference formulations. The overall variability for the test and reference

products is similar for the three parameters and geometric mean ratios ranged from 0.96 to 1.05, supporting equivalence.

3. Plume Geometry Data are acceptable.

Ipratropium Bromide Nasal Spray, 0.03%

Based on the revised draft Nasal BA/BE Guidance the in vitro testing requirements for the lower strength products represent the following abbreviated testing:

In vitro test	High Strength	Low Strength
Single Actuation Content Through Container Life	B, E[a]	B, E
Priming and Repriming	Yes	Yes
Droplet Size Distribution by Laser Diffraction	B, E	B
Drug in Small Particles/Droplets by Cascade Impactor	B	No
Spray Pattern	B	B
Plume Geometry	B	No

[a] Beginning (B), Middle (M), End (E)

Drug Products:

Test: Roxane's Ipratropium Bromide Nasal Spray, 0.03%, consisted of one lot of the drug solution formulation (Lot #256181S/Atrovent Bulk Solution Lot #256181, Lot size ——— , with a nominal fill of 30 mL per bottle, 0.03%, manufactured date 3/2002) divided into three sublots using three separate batches of pumps (Roxane Nos. 10004751, 10002678 and 10006253).

Reference: Boehringer Ingelheim's Atrovent[R] Nasal Spray, 0.03%, Lots 158431A, 256181C and 256881A, Exp. 11/2003, 3/2004 and 5/2004, respectively.

Unit dose (Unit Spray Content) and uniformity of unit dose

Roxane submitted data for the above-mentioned testing. As mentioned for the 0.06% product, the firm performed the uniformity of unit dose test using a stability-indicating method [Test Method Nos. M1-DC-IB03.0 and M1-DC-IB03.1, Assay of Ipratropium Bromide per Spray in Ipratropium Bromide Nasal Spray, Vol 1.2, page 13]. The labeled number of full medication doses per bottle is 345 sprays of 0.07 mL each (21-ug ipratropium bromide). The unit dose test was carried out on the entire bottle to determine the priming, re-priming and tail-off

characteristics. As mentioned for the 0.06% product, the labeling of the 0.03% product also 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 re-prime."

The number of sprays required to prime the pump was determined by assaying the first seven sprays of each unit. A re-priming was performed after a 2-actuation (re-prime) preceded by 24-hour period without use, and drug content of the next spray (No. 13) was then analyzed immediately. Additional studies to evaluate the prime retention after 7 days of non-use were also performed.

For each test, ten (10) units from each of the three sub-lots of the test product and each of the three lots of the reference product were tested. Therefore, for each test a total of 30 units of the test product and 30 units of the reference product were tested. The amount of drug per spray was determined by a validated HPLC analysis (LOQ= ————).

Content uniformity summary results were reported at the beginning (actuation 8) and end of unit life (actuation 351). The following table provides a summary based on the reviewer's calculations.

Table I

UNIT DOSE (UNIT SPRAY CONTENT) DATA

PROD.	SECTOR	Mean* (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean (N = 30)	TEST/REF Geo Mean (N = 30)	p
TEST	BEG	101.54	1.43-1.66	1.81	2.11	0.99	0.99	0.02
	END	101.99	1.20-2.27	1.85	2.33	1.00	1.00	0.91
REF	BEG	102.57	0.99-1.91	0.70	1.68			
	END	102.05	1.48-3.09	0.87	2.42			

**The mean unit dose data are expressed % of label claim based on arithmetic means. Outcome of the statistical analysis remains the same whether the data are expressed as % LC or amount spray.*

Comments on the Unit Dose Data

1. For Roxane's Ipratropium Bromide 0.06%, the geometric mean values at actuations 8 and 351 values are similar to the corresponding reference product values. The test product exhibited almost the same variability (%CV) as the reference product with regard to the unit dose data.

2. The test/ref ratios are within the 90-111% limits, used by DBE for acceptance of *in vitro* performance of solution nasal spray products.

3. Based on the mean values, there was no change in the unit dose determined at the beginning and end sectors. Furthermore, the data did not show a particular trend in changes in variability through the container life.

4. The loss of prime was determined on the spray # 3 after a 2- actuation re-prime and spray #351 after 7-actuation re-prime by allowing the product to rest for a period of 24 hours and 7 days, respectively. Based on the data submitted, the test and reference products have same prime retention characteristics.

Droplet size distribution

a. Laser Diffraction:

Droplet size determination was performed on 10 units from each of the 3 unit lots of test and reference products. The method used for determination of droplet size distribution, data collection and analysis were the same as mentioned for the 0.06% product.

Table II
Droplet Size Distribution (D50 Data) – Test Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo Mean(N=30)	p
Test	BEG	2.5	Middle	25.43	3.5-7.2	1.1	5.2	1.01	1.01	0.29
		4.5	Middle	30.18	1.9-2.9	0.7	2.3	1.01	1.01	0.26
		6.5	Middle	34.69	1.9-3.2	1.1	2.5	1.00	1.00	0.76

Droplet Size Distribution (D50 Data) – Reference Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
Ref	BEG	2.5	Middle	25.12	1.9-2.8	1.3	2.5
		4.5	Middle	29.95	2.1-3.1	1.0	2.6
		6.5	Middle	34.60	2.8-3.3	0.8	3.0

Droplet Size Distribution (Span Data) – Test Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo Mean(N=30)	p
Test	BEG	2.5	Middle	1.52	6.2-9.3	2.2	7.8	1.01	1.01	0.72
		4.5	Middle	1.12	6.6-13.2	2.8	9.8	1.02	1.01	0.49
		6.5	Middle	1.05	4.4-7.2	3.3	6.4	1.00	1.00	0.95

Droplet Size Distribution (Span Data) – Reference Product

PROD.	Sector	Distance	Plume Formation	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
Ref	BEG	2.5	Middle	1.51	6.3-9.0	1.5	7.2
		4.5	Middle	1.10	4.5-8.8	1.9	6.9
		6.5	Middle	1.05	3.7-4.4	2.0	4.2

Comments on Droplet Size Distribution

1. The ratios of the test geometric means to the reference geometric means for D50 for the fully formed plume for the three distances are within 1.00-1.01 range. For all comparisons the P values were insignificant.

2. The ratios of the test geometric means to the reference geometric means for SPAN for the fully formed plume for the three distances are within 0.49-0.95 range. For all of the comparisons the P values were insignificant.

3. For D50 and SPAN, the within-lot variability, between lot variability and total variability at the initial of plume formation for the test product are comparable to that of reference product.

4. Based on the geometric mean data the T/R ratio for D50 and SPAN are within the 0.9-1.11 range used hitherto by DBE for acceptance of *in vitro* performance of solution nasal spray products.

Based on these data, distribution of droplets in the test product spray is similar to that of the reference product spray.

Spray Pattern

The firm submitted spray pattern data at three distances (6.5, 4.5 and 2.5 cm) from TLC plate at beginning of life sector for the test product and the reference products. It provided individual results of spray pattern determination in term of longest diameter (D_{max}), shortest diameter (D_{min}) and ovality ratio (D_{max}/D_{min}).

The firm provided color photocopies of corresponding TLC plates with markings indicating D_{max} and D_{min} (page 4961, Vol.1.11). The staining agent (————) that reacts with drug was used to highlight the pattern of the TLC plate. Test Method No. M1-SP-IB03.1 (Spray Pattern Determination for Ipratropium Bromide Nasal Spray 0.03% (21 ug/spray)) can be found in Vol. 1.11, page 4967, along with its corresponding validation report. The firm employed manual analysis.

A summary of the spray pattern data based on the reviewer's calculations is presented in Table III.

Table III
Spray Pattern Data – Test Product

PROD.	Sector	Distance	Parameter	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	TEST/REF Arith Mean(N=30)	Geo Mean(N=30)	p
Test	BEG	2.5	Long. Diam	55.11	2.6-5.2	7.6	7.4	1.08	1.07	0.00
		2.5	Short. Diam	48.09	4.1-6.7	5.5	6.7	1.08	1.08	0.00
		2.5	Oval. Ratio	1.15	3.6-4.9	3.7	5.0	1.00	1.00	0.89
		4.5	Long. Diam	78.86	2.4-7.5	8.5	9.1	1.04	1.04	0.07
		4.5	Short. Diam	64.26	3.9-8.3	3.5	7.6	1.01	1.01	0.79
		4.5	Oval. Ratio	1.23	5.8-9.0	3.3	7.4	1.03	1.03	0.07
		6.5	Long. Diam	109.85	2.8-8.9	5.8	7.6	1.04	1.04	0.06
		6.5	Short. Diam	86.84	5.5-8.6	4.4	7.8	0.99	0.99	0.73
		6.5	Oval. Ratio	1.27	5.0-10.0	8.6	10.5	1.04	1.04	0.08

Spray Pattern Data – Reference Product

PROD.	Sector	Distance	Parameter	Mean (N = 30)	Variability (%CV) Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
	BEG	2.5	Long. Diam	51.26	3.5-3.8	5.6	5.8
		2.5	Short. Diam	44.66	3.6-4.5	4.1	5.1
		2.5	Oval. Ratio	1.15	3.3-6.0	1.6	5.2
		4.5	Long. Diam	75.66	4.2-6.3	4.8	6.4
		4.5	Short. Diam	63.84	6.2-6.9	5.0	7.6
		4.5	Oval. Ratio	1.19	5.5-7.3	4.0	7.0
		6.5	Long. Diam	105.89	4.5-5.7	2.0	5.2
		6.5	Short. Diam	87.43	5.1-6.6	7.8	8.6
		6.5	Oval. Ratio	1.22	6.9-9.5	7.8	10.2

Comments on Spray Pattern Analysis:

1. The total variability (%CV) for the test product is similar to the reference product for the various distances.

2. The ratios of the test geometric means to the reference geometric means for D_{max}, D_{min} and Ovality were within 1.04-1.07 and 0.99-1.08, 1.00-1.04 range, respectively. Based on the geometric mean data the T/R ratio for D_{max}, D_{min} and Ovality are within the 0.9-1.11 range used hitherto by DBE for acceptance of *in vitro* performance of solution nasal spray products.

3. The spray pattern data are acceptable.

Recommendations:

1. The *in vitro* performance data submitted by Roxane Laboratories, Inc. comparing its ipartropium bromide nasal spray (0.06%) with the reference product, Atrovent® nasal spray (0.06%) have been found to be acceptable by the Division of Bioequivalence. The studies demonstrate equivalent *in vitro* performance of Roxane's ipartropium bromide nasal spray, 0.06%, and the reference listed drug product Atrovent®, Nasal Solution, 0.06%, manufactured by Boehringer Ingelheim.

2. The *in vitro* performance data submitted by Roxane Laboratories, Inc. comparing its ipartropium bromide nasal spray (0.03%) with the reference product, Atrovent® nasal spray (0.03%) have been found to be acceptable by the Division of Bioequivalence. The studies demonstrate equivalent *in vitro* performance of Roxane's ipartropium bromide nasal spray, 0.03%, and the reference listed drug product Atrovent®, Nasal Solution, 0.03%, manufactured by Boehringer Ingelheim.

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

APPEARS THIS WAY
ON ORIGINAL

The firm should be informed of the above recommendations.

Moheb H. Makary
Moheb H. Makary, Ph.D. Date: 9/15/03
Review Branch III
Division of Bioequivalence

for RD INITIALLED PWNAKANT PATRICK NWAKANMA
FT INITIALLED GJP SINGH_____ Date: 9/15/03

Concur: Dale Conner Date: 9/16/03
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/7-28-03, 9-2-03, 9-10-03, 9-15-03, 76598N1203.doc
cc: ANDA #76-598, 76-664, original, HFD-658 (Makary), Drug File, Division File.

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-598 APPLICANT: Roxane Laboratories, Inc.
ANDA: 76-664

DRUG PRODUCT: Ipartropium Bromide Nasal Spray, 0.06% and 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,

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 #76-598
ANDA #76-664
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
for HFD-658/ Bio team Leader GJP Singh PATRICK NWAKAMA Per

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Printed in final on 9/15/03

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary MHM
for HFD-658/ Bio team Leader GJP Singh PATRICK NWAKAMA Per
HFD-650/ D. Conner MM 9/16/03

BIOEQUIVALENCY - ACCEPTABLE

submission date: 12-23-03
ANDA #76-598 (0.06%)
submission date: 02-11-03
ANDA #76-664 (0.03%)

ANDA #76-598

1. **STUDY** (STA) — Strengths: 0.06% **Outcome: AC**
2. **STUDY** (STA) — Strengths: 0.06% **Outcome: AC**
3. **STUDY** (STA) — Strengths: 0.06% **Outcome: AC**
4. **STUDY** (STA) — Strengths: 0.06% **Outcome: AC**

ANDA #76-664

5. **STUDY** (STA) — Strengths: 0.03% **Outcome: AC**
6. **STUDY** (STA) — Strengths: 0.03% **Outcome: AC**
7. **STUDY** (STA) — Strengths: 0.03% **Outcome: AC**
8. **STUDY** (STA) — Strengths: 0.03%

9. ~~**Study Amendment**~~ (new correspondence)
September 5, 2003 — Strengths: 0.03% and 0.06%
Outcome: ~~**AC**~~ WC

Outcome Decisions: **AC** – Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # :76-598 and ANDA #76-664 SPONSOR : Roxane Laboratories, Inc.
DRUG AND DOSAGE FORM : Ipartropium Bromide Nasal Spray
STRENGTH(S) : 0.06% and 0.03%
TYPES OF STUDIES : In Vitro Studies

CLINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : _____

STUDY SUMMARY : In Vitro Studies are acceptable.

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 9/15/03

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

INITIAL : per PATRICK NWAKAMA DATE : 9/15/03

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

INITIAL : DPC DATE : 9/16/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-664

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA #76-664
Drug Ipratropium Bromide Nasal Spray

Applicant Roxane Laboratories, Inc.
Strength 0.03% (0.021 mg/spray)

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

REVIEWER:

1. Project Manager, Peter Chen
   Review Support Br Team 2

DRAFT Package
Date 11/3/03
Initials PC

FINAL Package
Date 11/3/03
Initials PC

Application Summary:

Original Rec'd date 2/2/03
Date Acceptable for Filing 2/2/03
Patent Certification (type) I
Date Patent/Exclus.expires N.A.
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD =
Date checked _____ NDA# _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 6/10/03
Date of Office Bio Review 9/16/03
Date of Labeling Approv. Sum 9/24/03
Date of Sterility Assur. App. N.A.
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

Gregg Davis **PPIII and PPIV ANDAs Only**
Supv., Reg. Support Branch/

Date 11/5/03
Initials RW

Date 11/5/03
Initials RW for

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days? Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled: N/A
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Comments:

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked 11/5/03
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

RLD = Atrovent Nasal Spray 0.03% Boehringer Ingelheim Pharmaceuticals, Inc. (0.021 mg/spray) NDA 20,393

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

3. Div. Dir./~~Deputy Dir.~~
   Chemistry Div. I ~~or II~~
   Comments:

Date 11-4-03
Initials RC

The conclusion is satisfactory.

REVIEWER: **FINAL ACTION**

4. Frank Holcombe
Assoc. Dir. For Chemistry
Date _____
Initials _____
Comments: (First generic drug review)
N/A. ANDAs for this product were previously approved for Dey LP (3/31/03), NovaPharma (4/18/03), and Bausch+Lomb (3/31/03).

5. Peter Rickman
Director, DLPS
Date 11/5/03
Initials for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable LES dated 6/10/03 (Verified 11/5/03). No D.A.I. alerts noted. Bioequivalence established through in vitro methodology. Drug product is "Q1Q" to the RLD. Office-level bio endorsed 9/16/03 (See ANDA 76-598 for 0.06% strength). FPQ found acceptable for approval 9/24/03. CMC found acceptable 11/4/03. Methods validation for this ANDA was waived pending M.V. for "sister" ANDA 76-598 for 0.06% strength.

OR

5. Robert L. West
Deputy Director, OGD
Date 11/5/2003
Initials
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Comments:

This ANDA is recommended for approval.

6. Gary Buehler
Director, OGD
Date 11/5/03
Initials for
Comments:

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

7. Project Manager, Peter Chen
Review Support Branch Team 2
Date 11/5/03
Initials

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
1320 Time notified of approval by phone 1325 Time approval letter faxed

FDA Notification:
11/5/03 Date e-mail message sent to "CDER-OGDAPPROVALS☐ distribution list.
11/5/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-664

CORRESPONDENCE

3/17/03
NDE for Filing
505(j)(2)(A)
J. Middleton

Concur.
17-MAR-2003
Gregory E. Davis

Boehringer Ingelheim
Roxane Laboratories

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

February 11, 2003

Abbreviated New Drug Application
Ipratropium Bromide Nasal Spray, 0.03%

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

Dear Madam/Sir:

In accordance with 21 CFR 314.94, Roxane Laboratories, Inc. is submitting an Abbreviated New Drug Application (ANDA) for Ipratropium Bromide Nasal Spray, 0.03%. This ANDA consists of 14 volumes. This ANDA was formatted in accordance with the Guidance for Industry, Organization of an ANDA, February 1999.

The reference-listed drug is ATROVENT® (ipratropium bromide) Nasal Spray, 0.03% manufactured by Boehringer Ingelheim. The active ingredient is Ipratropium Bromide Monohydrate. The formulation, manufacturing process, equipment, and primary container/closure system used for Atrovent® (ipratropium bromide) Nasal Spray, 0.03% and Roxane Laboratories' Ipratropium Bromide Nasal Spray, 0.03% are identical. Roxane Laboratories, Inc., a wholly owned subsidiary of Boehringer-Ingelheim manufactures the reference-listed drug.

Four complete copies of the draft labeling are contained in the Archival and CMC Review copies of this application. The drug product will be manufactured, tested, labeled, packaged and released by Roxane Laboratories, Inc. No contract manufacturers or packagers are used for the proposed drug product. *In vitro* bioequivalence study reports and diskettes containing electronic data in SAS Transport format are included in this application. Furthermore, two copies of the ANDA Section XV, Analytical Methods, are enclosed separately along with this application.

Samples and the methods validation package will be submitted upon the request and direction of the Office of Generic Drugs. Roxane Laboratories, Inc. commits to provide full cooperation to resolve any problems that may arise during the methods validation testing as part of the "Post-Approval" for the above listed drug product.

RECEIVED
FEB 12 2003
OGD / CDER

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen D. Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs at (614) 241-4133.

Respectfully,

Virginia J. Fojas for

Elizabeth Ernst
Associate Director, DRA-Multisource Products

ANDA 76-664

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

MAR 17 2003

Dear Madam:

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

NAME OF DRUG: Ipratropium Bromide Nasal Spray, 0.03%

DATE OF APPLICATION: February 11, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 12, 2003

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

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

Should you have questions concerning this application, contact:

Peter Chen
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

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

ANDA 76-664
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 17-MAR-2003 date
HFD-615/SMiddleton, CSO date 3/17/03
Word File
V:\FIRMSNZ\ROXANE\LTRS&REV\76664.ACK
F/T StM 3/17/03
ANDA Acknowledgment Letter!

Boehringer Ingelheim
Roxane Laboratories

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150 (Documents Room)
Rockville, MD 20855-2773

July 10, 2003

NAE Cor 11/5/03

Attention: Steve Mazella

ANDA 76-664
Ipratropium Bromide Nasal Spray, 0.03%

AMENDMENT
Response to Request for Electronic Submission of the *In Vitro Bioequivalence* Data

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

Dear Mr. Mazella:

In response to your telephone request of July 7, 2003, attached is a diskette containing the *in vitro* bioequivalence electronic data in SAS Transport format. Also included in the diskette is a document (in WORD) describing the contents of the diskette.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

RECEIVED
JUL 11 2003
OGD/CDER

MINOR AMENDMENT

ANDA 76-664

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 14 2003

APPLICANT: Roxane Laboratories, Inc. TEL: 614-272-4785

ATTN: Elizabeth Ernst FAX: 614-276-2470

FROM: Peter Chen PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 11, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Solution, 0.03% (Nasal Spray).

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 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 and labeling comments included.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

PC 7/14/03

JUL 14 2003

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-664 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.03%, 21 mcg/spray

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. [redacted]
2.
3.
4.
5.
6.
7.
8.

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

1. Please respond to the labeling deficiencies.

2. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated to you separately.

3. Please provide any additional stability data that is available.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 76-664 Date of Submission: February 11, 2003
Applicant's Name: Roxanne laboratories
Established Name: **Ipratropium Bromide Nasal Solution 0.03%, Nasal Spray - 0.021 mg/spray**

Labeling Deficiencies:

1. CARTON and CONTAINER 21 mcg/spray (345 sprays)

   a. Revise the established name to read:

   IPRATROPIUM BROMIDE
   Nasal Solution

   0.03%

   NASAL SPRAY
   21 mcg/spray

   b. Please revise storage recommendations to comply with our current standard storage temperature "Store at 20-25C(68-77F).[See USP controlled Room Temperature].

2. INSERT – See comments under CONTAINER. In addition, relocate the "Attention Pharmacist" statement so that it appears in the title section.

3. PATIENT LEAFLET – See comments under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit 12 final print labels and labeling or draft if you prefer.

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

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

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

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

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT
N/A AM

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

September 11, 2003

Attention: Peter Chen

ANDA 76-664
Ipratropium Bromide Nasal Solution, 0.03%
Nasal Spray, 21 mcg/spray

MINOR AMENDMENT
Chemistry/Labeling Deficiencies

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

Dear Mr. Chen:

We wish to amend the ANDA. Enclosed please find a point-by-point response to the questions in the facsimile deficiency letter dated July 14, 2003.

We have also submitted a copy of this amendent to Ms. Kathleen D. Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

RECEIVED
SEP 12 2003

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT
N/AM

October 28, 2003

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

Attention: Peter Chen
Mujahid Shikh

ANDA 76-664
Ipratropium Bromide Nasal Solution, 0.03%
Nasal Spray, 21 mcg/spray

TELEPHONE AMENDMENT
Chemistry Deficiency

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

Dear Mr. Chen and Mr. Shikh:

We wish to amend the ANDA. Enclosed please find the response to the telephone amendment requested by Mr. Shikh in a conference call with me and Virginia Fojas on October 14, 2003. This was to revise the release and stability limits stated in [redacted] of the product specification. The limits were revised as follows:

From: [redacted]

To: [redacted]

Attached is a revised copy of the product specification, Specification No. 1623-02 for Ipratropium Bromide Nasal Solution 0.03%, Nasal Spray – 21 mcg/spray

We have also submitted a copy of this amendent to Ms. Kathleen D. Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

RECEIVED
OCT 29 2003
OGD/CDER

10/31