CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-552

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

***Sponsor*:** Dey, L.P.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-552

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Tentative Approval Letter	
Labeling	X
Labeling Reviews	X
Medical Review(s)	
Chemistry Reviews	X
Bioequivalence Reviews	X
Statistical Review(s)	
Microbiology Review(s)	
Administrative Documents	
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-552

APPROVAL LETTER

ANDA 75-552

MAR 31 2003

Dey, L.P.
Attention: Michelle A. Carpenter
2751 Napa Valley Corporate Drive
Napa, CA 94558

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 31, 1998, 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 30 mL per bottle fitted with a metered nasal spray pump.

Reference is also made to your amendments dated August 9, 1999; and February 28, April 2, and November 18, 2002.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Ipratropium Bromide Nasal Solution, 0.03%, (Nasal Spray), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Atrovent® Nasal Spray, 0.03% of Boehringer Ingelheim Pharmaceuticals, Inc.)

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

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

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

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

Sincerely yours,

Gary Buehler 3/31/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-552
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-625/M.Shaikh/ 3/10/03
HFD-625/M.Smela/ 3/10/03
HFD-617/P.Chen/ 3/7/03
HFD-613/A.Payne/ 3/5/03
HFD-613/J.Grace/ 3/5/2003

V:\FIRMSAM\DEY\LTRS&REV\75552.ap.doc

F/T by

APPROVAL PJ 3/11/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-552

LABELING

75-552 AP 3/31/03

DEY

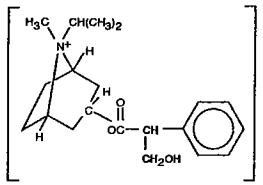
00356001

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)

Rx only

Prescribing Information

DESCRIPTION The active ingredient in Ipratropium Bromide Nasal Solution (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:



$Br^- \cdot H_2O$

MAR 31 2003

APPROVED

ipratropium bromide monohydrate

$C_{20}H_{30}BrNO_3 \cdot H_2O$
Mol. Wt. 430.4

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

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

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

Pharmacokinetics

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

Distribution: Ipratropium bromide is minimally bound (0 to 9% *in vitro*) to plasma albumin and α1-acid glycoprotein. Its blood/plasma concentration ratio was estimated to be about 0.89. Studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier.

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

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

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

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

Pharmacodynamics: In two single-dose trials (n=17), doses up to 336 mcg of ipratropium bromide did not significantly affect pupillary diameter, heart rate, or systolic/diastolic blood pressure. Similarly in patients with induced-colds, Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) (84 mcg/nostril four times a day), had no significant effects on pupillary diameter, heart rate or systolic/diastolic blood pressure.

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

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

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

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

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

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

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

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

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

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

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

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

Pregnancy *TERATOGENIC EFFECTS Pregnancy Category B.* Oral reproduction studies were performed at doses of 10 mg/kg in mice, 1,000 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

ATTENTION PHARMACIST – DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

DEY

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)

Patient's Instructions for Use

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

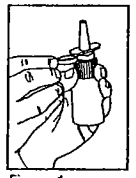


Figure 1

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.

APPROVED

MAR 31 2003

2. The nasal spray pump must be primed before Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is used for the first time. To prime the pump, hold the bottle with your thumb at the base and your index and middle fingers on the white shoulder area. Make sure the bottle points upright and away from your eyes. Press your thumb firmly and quickly against the bottle seven times (Figure 2). The pump is now primed and can be used. Your pump should not have to be reprimed unless you have not used the medication for more than 24 hours; 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 Solution 0.03% (Nasal Spray), blow your nose gently to clear your nostrils if necessary.

Figure 3

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

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

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

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

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

9. Replace the 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 Solution 0.03% (Nasal Spray) without consulting your physician.

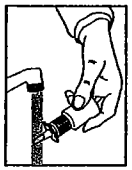


Figure 4

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

Do not spray Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) in your eyes. Should this occur, immediately flush your eye with cool tap water for several minutes. If you accidentally spray Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) in your eyes, you may experience a temporary blurring of vision and increased sensitivity to light, which may last a few hours. Should eye pain or blurred vision occur, contact your doctor.
Should you experience excessive nasal dryness or episodes of nasal bleeding contact your doctor.
You should not use this drug if you have glaucoma or difficult urination due to an enlargement of the prostate, unless directed by a physician.

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) should not be used during pregnancy or 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 between 15°C to 30°C (59°F to 86°F). Avoid freezing. Keep out of reach of children.

DEY

Manufactured by
Dey
Napa, CA 94558

03-560-01 November 2001

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

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

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

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

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

	% of Patients Reporting Events+			
	Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) (N=356)		Vehicle Control (N=347)	
	Incidence%	Discontinued%	Incidence%	Discontinued%
Headache	9.8	0.6	9.2	0
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	0.9	0.3
Nasal irritation[2]	2.0	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
Nausea	2.2	0.3	0.9	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 nasal mucus by 2.0% of ipratropium bromide patients and 2.3% of vehicle patients.
[2] Nasal irritation includes reports of nasal itching, nasal burning, nasal irritation and ulcerative rhinitis.
[3] Other nasal symptoms include reports of nasal congestion, increased rhinorrhea, increased rhinitis, posterior nasal drip, sneezing, nasal polyps and nasal edema.
* All events are listed by their WHO term; rhinitis has been presented by descriptive terms for clarification.

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

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

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

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

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

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

DOSAGE AND ADMINISTRATION The recommended dose of Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is two sprays (42 mcg) per nostril two or three times daily (total dose 168 to 252 mcg/day) for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older. Optimum dosage varies with the response of the individual patient.

Initial pump priming requires seven sprays of the pump. If used regularly as recommended, no further priming is required. If not used for more than 24 hours, the pump will require two sprays, or if not used for more than seven days, the pump will require seven sprays to reprime.

HOW SUPPLIED Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is supplied 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 31.1g of product formulation, 345 sprays, each delivering 21 mcg (70 µL) of ipratropium per spray, or 28 days of therapy at the maximum recommended dose (two sprays per nostril three times a day).

Store between 15°C to 30°C (59°F to 86°F). 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.

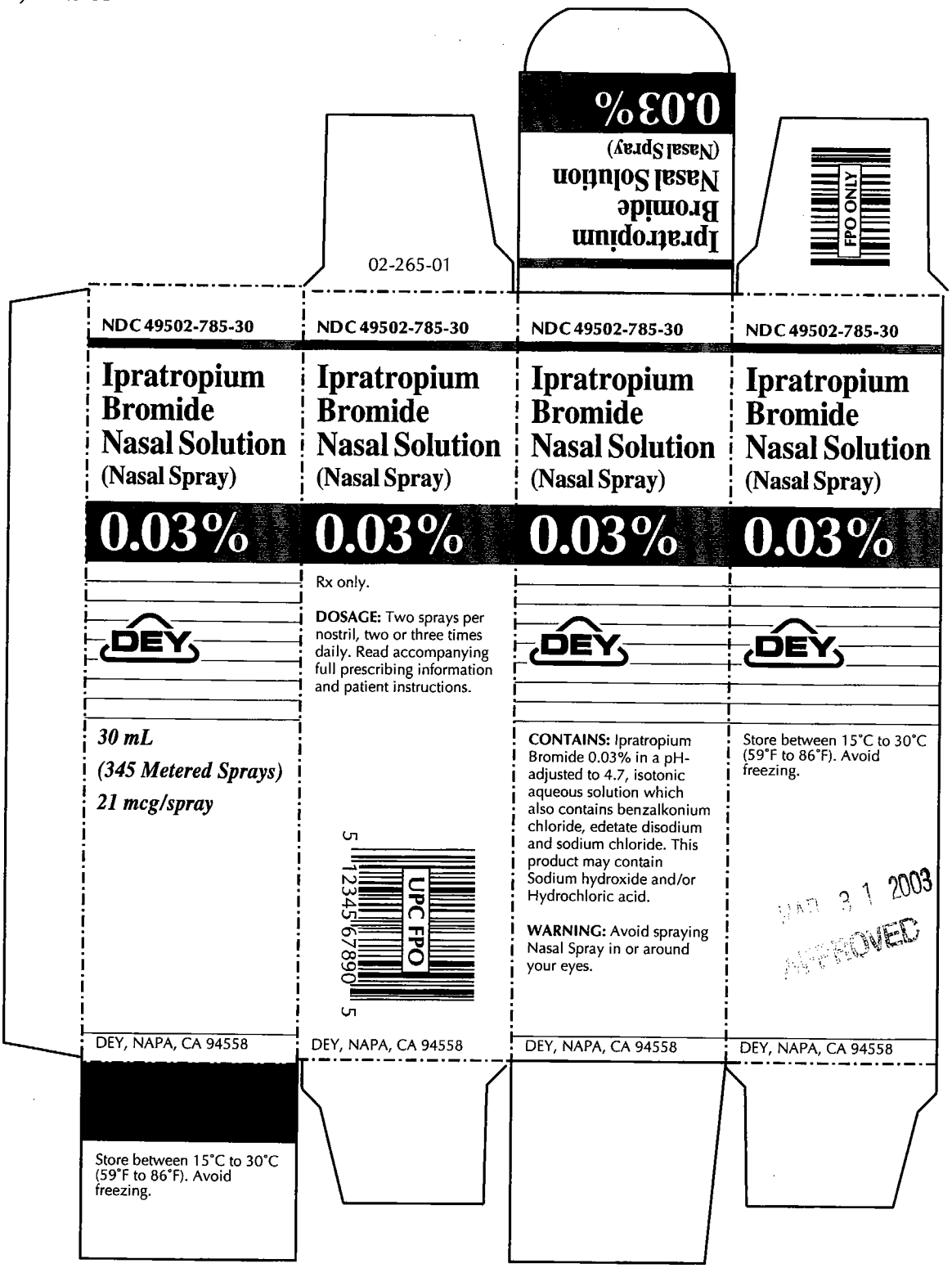
Rx only.

DEY

DEY
Napa, CA 94558

03-560-01 Printed: November 2001

A (round #12) 11-15-01



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-552

LABELING REVIEWS

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

ANDA Number: 75-552 **Date of Submission: February 22, 1999**

Applicant's Name: Dey Labs

Established Name: Ipratropium Bromide Nasal Solution, 0.03%

Labeling Deficiencies:

1. GENERAL COMMENT

   a. The established name for this product is Ipratropium Bromide Nasal Solution. Revise all labels and labeling accordingly. Note: "Spray" may appear on labels and labeling separate and away from the established name.

2. CONTAINER (30 mL bottle)

   a. Revise "CAUTION: Federal law…" statement to read "Rx only".

   b. Include the following statement:

      This product may contain Sodium hydroxide and/or Hydrochloric acid.

   c. Revise your storage recommendation to read as follows:

      Store between 15°C to 30°C (59°F to 86°F).

   d. See comment (a) under GENERAL COMMENTS.

3. CARTON (1 X 30 mL)

   a. See comments under CONTAINER.

4. PHYSICIAN'S INSERT

   a. TITLE

      We encourage the inclusion of "Rx only" in this section.

b. Please note, the most recent labeling for the reference listed drug, ATROVENT® Nasal Spray, 0.03%, was approved April 1, 1998. Please revise your insert labeling to be in accord.

c. See comment (a) under GENERAL COMMENTS.

5. PATIENT PACKAGE INSERT

a. Revise your storage recommendation to read as follows:

Store between 15°C to 30°C (59°F to 86°F).

b. See comment (a) under GENERAL COMMENTS.

Please revise your container labels and carton, physician's insert and patient package insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of carton labeling. Submit 4 copies of draft physician's insert and patient package insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: (30 mL)

Carton Labeling: (1 x 30 mL, shrink wrapped in trays of 12)

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: ATROVENT® Nasal Spray, 0.03%

NDA Number: 20-393/S-001
NDA Drug Name: Ipratropium Bromide Nasal Spray, 0.03%
NDA Firm: Boerhinger Ingelheim

Date of Approval of NDA Insert and supplement #: April 1, 1998
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No
If yes, give date of labeling guidance:

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.

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	
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. The reference listed drug for this product is ATROVENT® Nasal Spray (Boerhinger Ingelheim; NDA#20-393/S-001; Approved April 1, 1998.

2. Patents/Exclusivities

   Patent#438504 - U-119 (Treatment of Nasal Hypersecretion)
   Expires May 24, 2000
   Exclusivity- New Drug Formulation
   Expired October 20, 1998
   Exclusivity- I-223 (Use in the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in children age 6 to 11)
   Expires April 1, 2001.

   The applicant certifies that it will not market until after the expiration dates of both the patent and exclusivity. See Vol. 1.1, page 3.

3. The product is manufactured by Dey, 2751 Napa Valley Corporate Drive, Napa, CA 94558. See Vol. 1.1, page 253.

4. Outside firms are utilized for testing purposes only. See Vol. 1.2, page 264.

5. Container/Closure

   A high-density polyethylene bottle and nasal pump assembly. The bottle has a pre-printed pressure sensitive label that will be ——— stamped with lot number and expiration date. See Vol. 1.2, page 455.

6. Finished Product

   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. See Vol. 1.1, page 26A.

7. Product Line

Supplied as 30 mL of solution in a HDPE 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 of ipratropium bromide nasal spray is designed to deliver 345 sprays of 0.07 mL each (21 mcg), or 28 days of therapy at the maximum recommended dose (two sprays in each nostril three times a day). See Vol. 1.1, page 26A.

8. Components/compositon

Innovator:
Active: Ipratropium Bromide, 0.03%
Inactive: benzalkonium chloride
Edetate disodium
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Purified water
pH adjusted to 4.7

Applicant:
Active: Ipratropium Bromide, 0.03%
Inactive: Benzalkonium chloride
Edetate disodium
Sodium chloride
Purified water
Sodium hydroxide
Hydrochloric acid

See Vol. 1.1, page 6 and page 40.

9. Storage/Dispensing

NDA: Store tightly closed between 59°F (15°C) and 86°F (30°C). Avoid freezing. Keep out of reach of children. Do not spray in eyes.

ANDA: Store tightly closed between 59°F (15°C) and 86°F (30°C). Avoid freezing. Keep out of reach of children. Avoid spraying in or around the eyes.
See Vol. 1.1, page 26A.

Date of Review: March 24, 1999
Date of Submission: February 22, 1999

Reviewer: J Watkins Date: 4/14/99

Team Leader: Date:

John J. Grace 4-15-1999

cc:

ANDA: 75-552
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
V:\FIRMSAM\DEY\LTRS&REV\75552na1.l
Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 75-552 **Date of Submission: April 27, 2001**
Applicant's Name: Dey Labs
Established Name: Ipratropium Bromide Nasal Solution, 0.03%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: (30 mL)
Carton Labeling: (1 x 30 mL, shrink wrapped in trays of 12)
Professional Package Insert Labeling: # 03-560-01 r/Mar.2001 satisfactory in FPL submitted April 27, 2001 vol. 2.1 page 01316
Patient Package Insert Labeling: attached to Insert satisfactory in FPL submitted April 27, 2001
Revisions needed post-approval: Need to revise name to Ipratropium Bromide Nasal Solution, 0.03% (Nasal Spray). Firm elected not to revise their product name. April 27, 2001 cover letter.
BASIS OF APPROVAL:
No Unexpired patent or exclusivity issues.
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: ATROVENT® Nasal Spray, 0.03%
NDA Number: 20-393/S-001
NDA Drug Name: Ipratropium Bromide Nasal Spray, 0.03%
NDA Firm: Boerhinger Ingelheim
Date of Approval of NDA Insert and supplement #: April 1, 1998
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
If yes, give date of labeling guidance:
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.
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	
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. The reference listed drug for this product is ATROVENT® Nasal Spray (Boerhinger Ingelheim; NDA#20-393/S-001; Approved April 1, 1998.
2. Patents/Exclusivities
   Patent#438504 – U-119 (Treatment of Nasal Hypersecretion)
   Expires May 24, 2000

Exclusivity- New Drug Formulation
Expired October 20, 1998

Exclusivity- I-223 (Use in the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in children age 6 to 11)
Expires April 1, 2001.

The applicant certifies that it will not market until after the expiration dates of both the patent and exclusivity. See Vol. 1.1, page 3.

3. The product is manufactured by Dey, 2751 Napa Valley Corporate Drive, Napa, CA 94558. See Vol. 1.1, page 253.
4. Outside firms are utilized for testing purposes only. See Vol. 1.2, page 264.
5. Container/Closure
A high-density polyethylene bottle and nasal pump assembly. The bottle has a pre-printed pressure sensitive label that will be ——— stamped with lot number and expiration date. See Vol. 1.2, page 455.
6. Finished Product
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. See Vol. 1.1, page 26A.
7. Product Line
Supplied as 30 mL of solution in a HDPE 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 of ipratropium bromide nasal spray is designed to deliver 345 sprays of 0.07 mL each (21 mcg), or 28 days of therapy at the maximum recommended dose (two sprays in each nostril three times a day). See Vol. 1.1, page 26A.
8. Components/compositon
Innovator:
Active: Ipratropium Bromide, 0.03%
Inactive: benzalkonium chloride
Edetate disodium
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Purified water
pH adjusted to 4.7

Applicant:
Active: Ipratropium Bromide, 0.03%
Inactive: Benzalkonium chloride
Edetate disodium
Sodium chloride
Purified water
Sodium hydroxide
Hydrochloric acid
See Vol. 1.1, page 6 and page 40.
9. Storage/Dispensing
NDA: Store tightly closed between 59°F (15°C) and 86°F (30°C). Avoid freezing. Keep out of reach of children. Do not spray in eyes.
ANDA: Store tightly closed between 59°F (15°C) and 86°F (30°C). Avoid freezing. Keep out of reach of children. Avoid spraying in or around the eyes.
See Vol. 1.1, page 26A.

Date of Review: August 2, 2001 **Date of Submission: April 27, 2001**

---

cc:
ANDA: 75-552
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:/firmsam/dey/let&rev/75552ap.L
Review

APayne 8/2/01
JGrace 9/17/2001

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

ANDA Number: 75-552 **Date of Submission: December 3, 2001 supercedes the April 27, 2001 submission.**

Applicant's Name: Dey Labs
Established Name: Ipratropium Bromide Nasal Solution, 0.03%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: (30 mL) submitted on December 3, 2001, vol 3.1
Carton Labeling: (1 x 30 mL, shrink wrapped in trays of 12) submitted on December 3, 2001, vol. 3.1
Professional Package Insert Labeling: # 03-560-01 r/Nov. 2001 satisfactory in FPL submitted on December 3, 2001, vol.
Patient Package Insert Labeling: attached to Insert satisfactory in FPL submitted ~~April 27, 2001~~ December 3, 2001 vol 3.1 cmp
Revisions needed post-approval:
BASIS OF APPROVAL:
No Unexpired patent or exclusivity issues.
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: ATROVENT® Nasal Spray, 0.03%
NDA Number: 20-393/S-001
NDA Drug Name: Ipratropium Bromide Nasal Spray, 0.03%
NDA Firm: Boerhinger Ingelheim
Date of Approval of NDA Insert and supplement #: April 1, 1998
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
If yes, give date of labeling guidance:
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.
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		X	

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)			
		X	

Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			
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	
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. The reference listed drug for this product is ATROVENT® Nasal Spray (Boerhinger Ingelheim; NDA#20-393/S-001; Approved April 1, 1998.
2. Patents/Exclusivities
   Patent#438504 – U-119 (Treatment of Nasal Hypersecretion)
   Expires May 24, 2000
   Exclusivity- New Drug Formulation

Expired October 20, 1998

Exclusivity- I-223 (Use in the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in children age 6 to 11)
Expires April 1, 2001.

The applicant certifies that it will not market until after the expiration dates of both the patent and exclusivity. See Vol. 1.1, page 3.

3. The product is manufactured by Dey, 2751 Napa Valley Corporate Drive, Napa, CA 94558. See Vol. 1.1, page 253.
4. Outside firms are utilized for testing purposes only. See Vol. 1.2, page 264.
5. Container/Closure
A high-density polyethylene bottle and nasal pump assembly. The bottle has a pre-printed pressure sensitive label that will be ——— stamped with lot number and expiration date. See Vol. 1.2, page 455.
6. Finished Product
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. See Vol. 1.1, page 26A.
7. Product Line
Supplied as 30 mL of solution in a HDPE 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 of ipratropium bromide nasal spray is designed to deliver 345 sprays of 0.07 mL each (21 mcg), or 28 days of therapy at the maximum recommended dose (two sprays in each nostril three times a day). See Vol. 1.1, page 26A.
8. Components/compositon

Innovator:
Active: Ipratropium Bromide, 0.03%
Inactive: benzalkonium chloride
Edetate disodium
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Purified water
pH adjusted to 4.7

Applicant:
Active: Ipratropium Bromide, 0.03%
Inactive: Benzalkonium chloride
Edetate disodium
Sodium chloride
Purified water
Sodium hydroxide
Hydrochloric acid

See Vol. 1.1, page 6 and page 40.

9. Storage/Dispensing
NDA: Store tightly closed between 59°F (15°C) and 86°F (30°C). Avoid freezing. Keep out of reach of children. Do not spray in eyes.
ANDA: Store tightly closed between 59°F (15°C) and 86°F (30°C). Avoid freezing. Keep out of reach of children. Avoid spraying in or around the eyes.
See Vol. 1.1, page 26A.

Date of Review: December 10 2, 2001 **Date of Submission: December 3, 2001**

---

cc:

ANDA: 75-552
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:/firmsam/dey/let&rev/75552ap2.L
Review

12/10/01

12/10/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-552

CHEMISTRY REVIEWS

1. CHEMISTRY REVIEW NO. 1

2. ANDA # **75-552**
75-553

3. NAME AND ADDRESS OF APPLICANT
Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

4. LEGAL BASIS FOR SUBMISSION
Listed Drug Product: Atrovent[R] Nasal Spray, 0.03% and 0.06% by Boehringer Ingelheim

Patent Expiration date: 5-24-2000

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

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
ANDA 75-552: Ipratropium Bromide Nasal Spray 0.03%
ANDA 75-553: Ipratropium Bromide Nasal Spray 0.06%

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

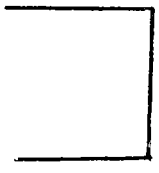
9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-31-98 (Both ANDAs)
Amendment: 2-22-99 (Both ANDAs) [Response to 2-4-99 letter]
NC: 5-19-99 (ANDA 75-553)

FDA:
Refuse to file ltr: 2-4-99 (Both ANDAs)
Accepted for filing: 2-25-99 (Both ANDAs) [Acknowledgment letter: 3-16-99]

10. PHARMACOLOGICAL CATEGORY
Anticholinergic Agent

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)



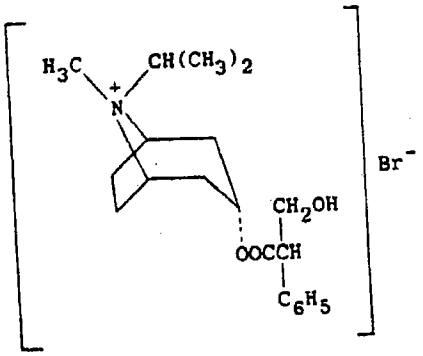
13. DOSAGE FORM
Solution

14. POTENCY
0.03% & 0.06%

15. CHEMICAL NAME AND STRUCTURE

Chemical name: (endo,syn)-(±)-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-Azoniabicyclo [3.2.1]-octane bromide.

Structure:



16. RECORDS AND REPORTS

N/A

17. COMMENTS

1. Referenced DMF —— for ———————— the manufacturer of ———————— is adequate per N. Takiar's review dated 7-15-98. No new information is submitted.
2. Adequate information is provided for the contract testing facilities.
3. Ipratropium Bromide drug substance and the Ipratropium Bromide Nasal Spray are not USP 23 materials.
4. Dey's specifications for Ipratropium Bromide are based on current EP and additional specification adopted by the manufacturer of the active.
5. Samples for MV will be requested after all the issues regarding release specifications and analytical methods are resolved.
6. Bio status: Deficient per bio review and bio deficiency letter to the firm dated 6-7-99 to ANDA 75-552 and dated 6-29-99 to ANDA 75-553. No response yet.
7. EER need to be submitted for additional facilities listed in this ANDA (section # 33) which are not included in already submitted EER.
8. During review of this ANDA, CR #1 for first submitted ANDA —— —— for Ipratropium Bromide Nasal Spray is consulted.

B. COMMENTS TO BE INCLUDED IN NA LETTER:

All the comments included in the section nos. 20, 23, 25, 26, 28, 29, 31, 32, 33 and 34.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approved. A NA letter with MAJOR amendment is being faxed to the firm including all the deficiencies identified in this review.

19. REVIEWER: Mujahid L. Shaikh

DATE COMPLETED: 8-9-99

Revision of this review is completed on 8-13-99 to included Mike Smela comments.

Redacted 29 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

f. [redacted]

g.

h.

i.

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

1. The cGMP compliance of all facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Please be advised that samples of the drug product for methods validation will be requested at a later date once the testing issues have been resolved.

3. Please submit the currently available stability data for both exhibit batches.

4. Labeling deficiencies will also need to be addressed in your reply.

5. We await your response to deficiency letters issued by the Division of Bioequivalence on June 7, 1999 and June 29, 1999 for these ANDAs.

6. Please submit revised drug substance specifications, drug product specifications and stability specifications and also submit copies of all current analytical methods in a separate section of your amendment to facilitate the method validation package.

Sincerely yours,

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

cc: AND 75-552 & 75-553
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/8/13/99 Mujadid Shaikh 8/20/99
HFD-625/M.Smela/8/13/99 for M Smela 8/20/99

Project Manager:

HFD-617/M.Dillahunt/8/17/99 MDillahunt 8/18/99

V:\firmsam\dey\ltrs&rev\75552REV.1
F/T by: gp/8/17/99

CHEMISTRY REVIEW - NOT APPROVABLE - MAJOR

1. CHEMISTRY REVIEW NO. 2

2. ANDA # **75-552**
75-553

3. NAME AND ADDRESS OF APPLICANT
Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

4. LEGAL BASIS FOR SUBMISSION
Listed Drug Product: Atrovent[R] Nasal Spray, 0.03% and 0.06% by Boehringer Ingelheim

Patent Expiration date: 5-24-2000

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

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
ANDA 75-552: Ipratropium Bromide Nasal Spray 0.03%
ANDA 75-553: Ipratropium Bromide Nasal Spray 0.06%

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-31-98 (Both ANDAs)
Amendment: 2-22-99 (Both ANDAs) [Response to 2-4-99 letter]
NC: 5-19-99 (ANDA 75-553)
NC: 8-30-99
NC: 11-15-99
NC: 4-18-00
NC: 8-18-00
*Major Amendment: 4-27-01 (Both ANDAs) [Response to bio deficiency letters dated June 7 and 29, 1999 and NA letter dated August 26, 1999]
* NC: 5-10-01
* Amendment: 7-31-01

FDA:
Refuse to file ltr: 2-4-99 (Both ANDAs)
Accepted for filing: 2-25-99 (Both ANDAs) [Acknowledgment letter: 3-16-99]
Bio deficiency letter: 6-7-99 (ANDA 75-552)
Bio Deficiency letter: 6-29-99 (ANDA 75-553)
NA letter (Chemistry): 8-26-99 (Both ANDAs)

10. PHARMACOLOGICAL CATEGORY
Anticholinergic Agent

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

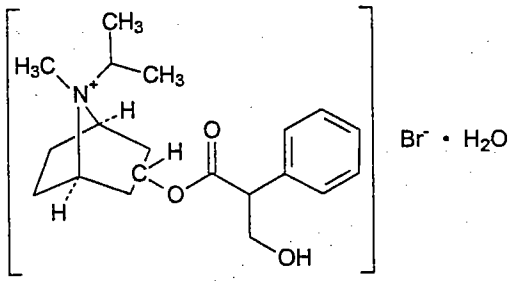
[redacted]

13. DOSAGE FORM
Solution

14. POTENCY
0.03% & 0.06%

15. CHEMICAL NAME AND STRUCTURE
Chemical name: (endo,syn)-(.)-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-Azoniabicyclo [3.2.1]-octane bromide.

Structure:



16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. Referenced DMF [redacted] for [redacted] - the manufacturer of [redacted] is adequate per review dated 6-21-01. No new information is submitted.
2. EER: Acceptable for all the facilities in both ANDAs.
3. Ipratropium Bromide drug substance and the Ipratropium Bromide Nasal Spray are not USP 24 materials, therefore, MV is being requested concurrent to this review.
4. Dey's specifications for Ipratropium Bromide are based on current EP and additional in-house specifications adopted by the manufacturer of the active.
5. Bio status: Bio response submitted on April 27, 2001 is under review for both ANDAs.
6. Labeling: Pending review

B. COMMENTS TO BE INCLUDED IN NA LETTER:
All the comments included in the section nos. 20, 28, 29, 30, 33 and 34.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approved. A NA letter with MINOR amendment is being faxed to the firm including all the deficiencies identified in this review.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 10-29-01

Revised on 11-5-01 to include K. Furnkranz's comments

Redacted 24 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

36. 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:

SPOT? Yes_____ No___x___

If yes, complete a SPOT form.

APPEARS THIS WAY
ON ORIGINAL

37. **DMF CHECKLIST FOR ANDA # 75-552 and 75-553 REVIEW # 2**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
II/		3	Adequate	6-21-01
	Comments:			
III/		4	-	-
	Comments: None			
III/		3	Adequate	5-30-01
	Comments:			
	Comments:			
	Comments:			
	Comments:			
	Comments:			
	Comments:			

ACTION CODES: (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").

Mujahid L. Shaikh Mujahid Shaikh 11/14/01
Reviewer Signature Date

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-552 & 75-553 APPLICANT: Dey L.P.

DRUG PRODUCT: Ipratropium Bromide Nasal Solution, 0.03% and 0.06%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. [redacted]

2.

3.

4.

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

1. Please be advised that samples of the drug substance and drug product for methods validation are being requested concurrent to this letter.

2. Your response must also address the labeling deficiencies identified for ANDA 75-553.

3. Your response regarding bioequivalence of the drug products is pending review.

Sincerely yours,

11/19/01

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

cc: AND 75-552 & 75-553
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/11/5/01 11/14/01
HFD-625/K.Furnkranz for M.Smela/11/6/01 11/14/01

Project Manager:

HFD-617/M.Dillahunt/11/6/01

V:\firmsam\dey\ltrs&rev\75552REV.2
F/T by: gp/11/6/01

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 3

2. ANDA # **75-552**
75-553

3. NAME AND ADDRESS OF APPLICANT
Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

4. LEGAL BASIS FOR SUBMISSION
Listed Drug Product: Atrovent[R] Nasal Spray, 0.03% and 0.06% by Boehringer Ingelheim

Patent Expiration date: 5-24-2000

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

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
ANDA 75-552: Ipratropium Bromide Nasal Spray 0.03%
ANDA 75-553: Ipratropium Bromide Nasal Spray 0.06%

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-31-98 (Both ANDAs)
Amendment: 2-22-99 (Both ANDAs) [Response to 2-4-99 letter]
NC: 5-19-99 (ANDA 75-553)
NC: 8-30-99
NC: 11-15-99
NC: 4-18-00
NC: 8-18-00
Major Amendment: 4-27-01 (Both ANDAs) [Response to bio deficiency letters dated June 7 and 29, 1999 and NA letter dated August 26, 1999]
NC: 5-10-01
Amendment: 7-31-01 (ANDA 75-552)
Amendment: 8-15-01 (ANDA 75-553)
*Amendment: 12-3-01 (Both ANDAs) [Response to 11-14-01 NA letter]

FDA:
Refuse to file ltr: 2-4-99 (Both ANDAs)
Accepted for filing: 2-25-99 (Both ANDAs) [Acknowledgment letter: 3-16-99]
Bio deficiency letter: 6-7-99 (ANDA 75-552)

Bio Deficiency letter: 6-29-99 (ANDA 75-553)
NA letter (Chemistry): 8-26-99 (Both ANDAs)
NA letter: 11-14-01 (Both ANDAs)

10. PHARMACOLOGICAL CATEGORY
Anticholinergic Agent

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

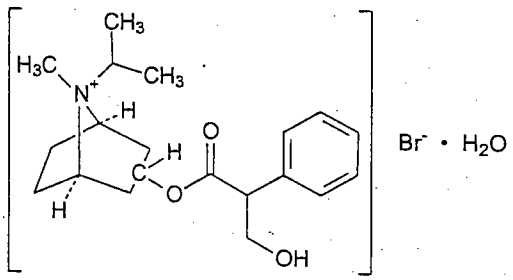
[redacted]

13. DOSAGE FORM
Solution

14. POTENCY
0.03% & 0.06%

15. CHEMICAL NAME AND STRUCTURE
Chemical name: (endo,syn)-(.)-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-Azoniabicyclo [3.2.1]-octane bromide.

Structure:



16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. Referenced DMF [redacted] for [redacted] the manufacturer of [redacted] is adequate per review dated 6-21-01. No new information is submitted.
2. EER: Acceptable for all the facilities in both ANDAs.
3. Ipratropium Bromide drug substance and the Ipratropium Bromide Nasal Spray are not USP 24 materials, therefore, MV has been requested on 12-15-01.
4. Dey's specifications for Ipratropium Bromide are based on current EP and additional in-house specifications adopted by the manufacturer of the active.
5. Bio status: Bio response submitted on April 27, 2001 is under review for both ANDAs.
6. Labeling: Acceptable.
7. EER: Acceptable for both ANDAs.

B. COMMENTS TO BE INCLUDED IN NA LETTER:
See Item # 38.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approved. A NA (Minor) letter

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 2-6-02
Revised on 2-11-02

APPEARS THIS WAY
ON ORIGINAL

Redacted 17 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

11. Please provide a copy of your revised drug product release and stability specifications for both strengths incorporating the changes requested in this communication.

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

1. Your response regarding bioequivalence of the drug products is under review. Deficiencies, if any, will be communicated separately.

2. The Method Validation study is currently in progress.

Sincerely yours,

Paul Seligman for 2/12/02
Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AND 75-552 & 75-553
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/2/11/02 Mujahid Shaikh 2/12/02
HFD-625/M.Smela/2/11/02 M Smela 2/12/02

Project Manager:

HFD-617/M.Dillahunt/2/11/02 M Dillahunt 2/12/02

V:\firmsam\dey\ltrs&rev\75552REV.3
F/T by: gp/2/12/02

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-552
75-553

3. NAME AND ADDRESS OF APPLICANT
Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

4. LEGAL BASIS FOR SUBMISSION
Listed Drug Product: Atrovent[R] Nasal Spray, 0.03% and 0.06% by Boehringer Ingelheim

Patent Expiration date: 5-24-2000

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

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
ANDA 75-552: Ipratropium Bromide Nasal Spray 0.03%
ANDA 75-553: Ipratropium Bromide Nasal Spray 0.06%

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-31-98 (Both ANDAs)
- Minor Amendment: 2-28-02 [Response to 2-12-02 NA letter]
- Telephone Amendment: 4-26-02 [CMC issues. Both ANDAs]
- Bio Amendment to 75-552: 4-2-02
- Bio Amendment to 75-553: 5-2-02

10. PHARMACOLOGICAL CATEGORY
Anticholinergic Agent

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

[redacted]

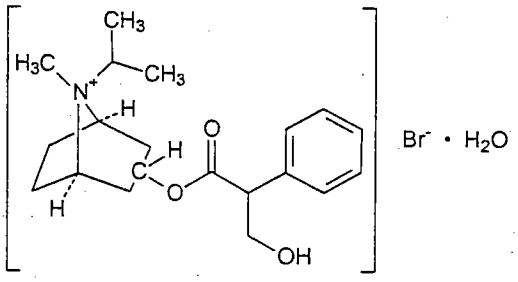
13. DOSAGE FORM
Solution

14. POTENCY
0.03% & 0.06%

15. CHEMICAL NAME AND STRUCTURE

Chemical name: (endo,syn)-( )-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-Azoniabicyclo [3.2.1]-octane bromide.

Structure:



16. RECORDS AND REPORTS

N/A

17. COMMENTS

1. Referenced DMF ——— for ——————— the manufacturer of ——————— is adequate per review dated 6-21-01. No new information is submitted.
2. EER acceptable status is more than 2 years old. Therefore, FUR is required.
3. MV is completed on 4-18-02 for ANDA 75-552.
4. Dey's specifications for Ipratropium Bromide are based on current EP and additional in-house specifications adopted by the manufacturer of the DS.
5. Bio status: Bio response for ANDA 75-552 submitted on April 27, 2001 has been reviewed and is unacceptable per March 20, 2002 deficiency letter. Firm has submitted a response on April 2, 2002 that is pending review. Similarly, bio status for ANDA 75-553 is deficient and deficiencies have been faxed on 4-18-02. Firm has submitted their response on 5-2-02 which is pending review.
6. Labeling: Acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Chemistry Closed.

Bio and EER FUR are pending.

19. REVIEWER: Mujahid L. Shaikh

DATE COMPLETED: 4-30-02
Revised on 5-13-02

cc: AND 75-552 & 75-553
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/ Mujahid Shaikh 5/13/02
HFD-625/M.Smela/

Project Manager:

~~HFD-617/M.Dillahunt/~~ M Smela 5/13/02

V:\firmsam\dey\ltrs&rev\75552REV.4
F/T by:

APPEARS THIS WAY
ON ORIGINAL

Redacted 16 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #4

ANDA 75-552: Deficient as of March 20, 2002 bio deficiency letter. Dey's response of April 2, 2002 is pending review.

ANDA 75-553: Deficient per April 18, 2002 bio deficiency letter. Dey's response of May 2, 2002 is pending review,

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
Dey requested a categorical exclusion per 21 CFR 25.24(c)(1) for both ANDAs.

36. ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes_____
No ___x____

If no, explain reason(s) below: Minor Amendment

SPOT? Yes_____ No__x___

If yes, complete a SPOT form.

APPEARS THIS WAY
ON ORIGINAL

37. **DMF CHECKLIST FOR ANDA # 75-552 and 75-553 REVIEW # 4**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
II/	[redacted]	3	Adequate	6-21-01

Comments: NO new information is submitted.

III/ [redacted]	4	-	-

Comments: None

III/ [redacted]	3	Adequate	5-30-01

Comments: Reviewed by Ken Furnkranz

Comments:

Comments:

Comments:

Comments:

Comments:

ACTION CODES: (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").

Mujahid L. Shaikh Mujahid Shaikh 5/13/02
Reviewer Signature Date

Addendum to Chemist Review # 4 for:

ANDA 75-552

Ipratropium Bromide Nasal Spray, 0.03%

This addendum is being written to issue a MINOR amendment action based on the bioequivalence deficiencies identified in the bioequivalence review completed by J. Lee on 8-16-02. Item # 38 is written to request a Minor amendment from the firm.

Following items are also checked:

Status of DMF ——: A recently submitted annual report is adequate per review completed by this reviewer on August 27, 2002.

EER Status: FUR is acceptable on June 26, 2002 by J. D. Ambrogio.

APPEARS THIS WAY
ON ORIGINAL

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-552 APPLICANT: Dey L.P.

DRUG PRODUCT: Ipratropium Bromide Nasal Solution, 0.03%

The deficiencies presented below represent Minor deficiencies.

Bioequivalence for this product has not been demonstrated. Please submit your response to the deficiency letter dated August 20, 2002. If a new batch(es) of drug product is manufactured to address the bioequivalence deficiencies, please provide a Certificate of Analysis and confirmation that the process and controls currently provided in the ANDA were used to manufacture the batch(es).

Sincerely yours,

Paul S Lee 8/29/02

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: AND 75-552
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/8/27/02 M Shaikh
HFD-625/M.Smela/8/27/02 M Smela 8/28/02 8/28/02

Project Manager:
HFD-617/P.Chen/8/27/02 P Chen 8/27/02

V:\firmsam\Dey\ltrs&rev\75552RV4.ad1

F/T by: gp/8/28/02

APPEARS THIS WAY
ON ORIGINAL

1. CHEMISTRY REVIEW NO. 5

2. ANDA # **75-552**

3. NAME AND ADDRESS OF APPLICANT
Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

4. LEGAL BASIS FOR SUBMISSION
Listed Drug Product: Atrovent[R] Nasal Spray, 0.03% by Boehringer Ingelheim

Patent Expiration date: 5-24-2000

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

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
ANDA 75-552: Ipratropium Bromide Nasal Spray 0.03%

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-31-98
- Minor Amendment: 2-28-02 [Response to 2-12-02 NA letter]
- Telephone Amendment: 4-26-02
- Bio Amendment to 75-552: 4-2-02
- Minor Amendment to 75-552: 11-18-02 (Response to August 29, 2002 deficiency letter based on bio comments)

10. PHARMACOLOGICAL CATEGORY
Anticholinergic Agent

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

[redacted]

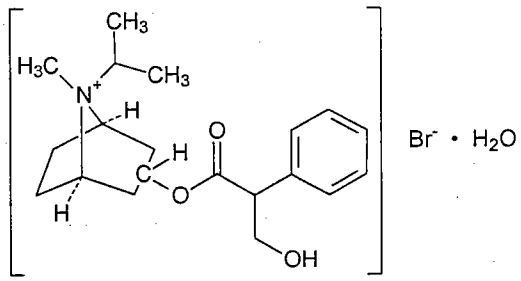
13. DOSAGE FORM
Solution

14. POTENCY
0.03%

15. CHEMICAL NAME AND STRUCTURE

Chemical name: (endo,syn)-( )-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-Azoniabicyclo [3.2.1]-octane bromide.

Structure:



16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. Referenced DMF ——— for ——————— - the manufacturer of ——————— is adequate per last review (CR # 8) dated 8-27-02. No new information is submitted.
2. EER acceptable as of June 26, 2002 by J.D. Ambrogio.
3. MV is completed on 4-18-02 for ANDA 75-552.
4. Dey's specifications for Ipratropium Bromide are based on current EP and additional in-house specifications adopted by the manufacturer of the DS.
5. Bio status: Dey's bio response on November 18, 2002 is pending review.
6. Labeling: Acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Chemistry Closed.

Bio response is pending review.

Bio: Acceptable as of 2-13-03. Shaikh 3-4-03

19. REVIEWER: Mujahid L. Shaikh

DATE COMPLETED: 12-4-02

M Shaikh 3/4/03

cc: AND 75-552
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/ mujaid Shaikh 12/4/02
HFD-625/M.Smela/ M Smela 12/4/02

V:\firmsam\dey\ltrs&rev\75552.R05
F/T by:

APPEARS THIS WAY
ON ORIGINAL

Redacted 13 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #5

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-552

FIRM: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

DOSAGE FORM: Metered Nasal Spray

STRENGTH: 0.03%

DRUG: Ipratropium Bromide

CGMP STATEMENT/EIR UPDATED STATUS:
EER for all facilities listed in section # 33 of this ANDA (CR # 5) is acceptable on 6-26-02.

BIO STUDY:
Bio status: Acceptable as of 2-13-03.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Satisfactory as per CR #4.

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

LABELING:
Acceptable for approval per A. Payne's review completed on 12-10-01.

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

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Original bio data provided on sublots W083, W084A and W084B. Additional Spray Pattern data are provided for new batches W141, W142 and W143.

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

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Exhibit batch (lot # W008) and its size is [redacted]. This exhibit batch was submitted with the original submission. An additional stability batch (lot #W083) was manufactured to qualify new [redacted] equipment.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Intended production batch size: ————————.

Manufacturing process for the intended production size batch is identical to that used for the stability batch. The applicant has certified that the new biobatches were manufactured consistent with the process proposed in the ANDA.

cc: ANDA 75-552

Endorsements:

HFD-625/M.Shaikh/3/9/03 mujahid shaikh 3/10/03

HFD-625/M.Smela/3/4/03 M Smela 3/10/03

V:\firmsam\Dey\ltrs&rev\75552.appsum

F/t by: gp/3/6/03

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-552

BIOEQUIVALENCE REVIEWS

Ipratropium bromide
0.03% nasal solution
ANDA #75-552
Reviewer: J. Lee
75552IVO.299

Dey Labs
Napa, Calif.
Submission date:
February 22, 1999

Review of an In-vitro Study

The sponsor has submitted an application for ipratropium bromide 0.03% nasal solution and has requested a waiver of in-vivo bioavailability requirements under 21 CFR 320.22 (b)(3). The sponsor has submitted a series of in-vitro tests to demonstrate comparable performance of the delivery system for the proposed drug product vs Atrovent® Nasal Spray 0.03% (Boerhinger Ingelheim).

In-vitro Data

Note: In-vitro data is reported for lot #W008 (Dey) and #816015A (Atrovent).

Unit Spray Content

Unit spray content through bottle life was obtained according to the procedure on page 557 (vol. 1.3) of this submission . Three bottles of the nasal spray were sampled at the beginning (actuations 11 & 12), middle (actuations 172 & 173) and end (actuations 344 & 345) of each bottle to determine (by weight difference) the concentration of ipratropium bromide per unit spray. The results showed:

	Spray	Bottle 1	Bottle 2	Bottle 3	
	11	102.5	103.2	102.9	
	12	104.3	101.6	101.9	values are expressed as
Dey	172	105.5	103.9	104.2	percent of label claim
	173	104.9	103.8	104.3	
	344	104.6	103.8	103.5	
	345	106.3	103.2	104.5	

The unit spray content test was not conducted for Atrovent.

Content Uniformity

Content uniformity was performed on 10 bottles of the Dey product (by weight difference) at actuations 11 and 12 according to the procedure on page 558 (vol. 1.3).

Results show an average of 103.4% of label claim (n=20; %CV=1.2). Content uniformity information was not provided for Atrovent.

Spray Pattern

Measurement of spray pattern employed the use of hard manual actuation ("quick and firm") at 1 and 2.5 cm from the target TLC plate. Four spray patterns (for 3 bottles) were prepared at each distance (at 0°, 90°, 180° and 270°) [see validation on pages 639-71 in Vol. 1.3); the plates were placed in a TLC tank and developed with ——— staining reagent. The plates were then covered with a clear plastic sheet and the spray pattern demarcated and measured. The validation stated that placebo plates showed similar patterns to plates with the formulation products, indicating that the method was not drug-specific. It is the formulation as a whole that produced the spray pattern samples.

See attachment for results.

Particle Size Distribution

Particle size distribution was evaluated using two methods - by ——————— and by Cascade Impaction.

———————

The ——————— particle sizer uses a laser light-scattering method to characterize the size and distribution of droplets in nasal spray aerosol plumes.

Particle size is typically reported for d_{10}, d_{50}, and d_{90}, the diameters at the 10th, 50th and 90th percentiles. Span is a measure of the symmetry of the particle distribution about the median diameter (d_{50}) and is defined as: Span = $[d_{90} - d_{10}]/d_{50}$. [validation on pp. 723-47, vol. 1.3]

Cascade Impactor

Particle size distribution was also measured using the ——————— cascade impactor. The nasal sprays were manually actuated (20 times) and the deposition of ipratropium bromide on the various components of the impactor was measured using an HPLC method. [validation on pp. 672-709, vol. 1.3]

See attachment for results.

Plume Geometry

Plume geometry was measured using manual actuation and high-speed photography. The number of priming actuations was not reported. Photocopies of the scanned photographs were submitted. Concrete plume geometry data was omitted. [Validation on pp. 748-69, Vol. 1.3]

See attachment for results.

Priming and Tail-off Data

Information not provided.

Comment:

The submitted in-vitro tests are wholly deficient. All tests should be repeated as follows:

1. The requirements below apply to the following tests:

   A. Unit Spray/Content Uniformity.
   B. Priming, loss of prime and tail off
   C. Droplet size distribution by Malvern Mastersizer/Cascade Impaction
   D. Spray pattern.
   E. Plume geometry

   For all these comparative *in vitro* tests:

   - ☞ The bottles should be actuated using a validated automated actuation device to increase reproducibility. Validation data including the effect of actuation force, actuation velocity and other factors should be submitted.
   - ☞ No fewer than 10 units each of the test and reference products should be tested in a blinded manner.
   - ☞ Data from three batches each of the test and reference products should be submitted, including batch records for all batches of the test product.
   - ☞ SOPs for all tests effective at the time of testing should be submitted. SOPs should describe the automated actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s).
   - ☞ Raw data for all tests should be submitted in the form of paper copies (tables) as well as electronic files (Excel 5.0 spread sheets).
   - ☞ For tests performed at the beginning (B), middle (M), and end (E) or B and E of use life sectors, comparative performance of test and reference products will be assessed at each sector.

With regard to specific tests:

2. Unit Spray/Content Uniformity

   Consistent with the Potency Test described in the 27 June 1989 *Division of Bioequivalence Guidance for the in vitro portion of bioequivalence requirements for metaproterenol sulfate and albuterol inhalation aerosols (metered dose inhalers)*, this test should be performed at beginning, middle, and end of use life of the product after product priming.

The amount of drug per single spray should be determined using a validated analytical procedure (chemical/chromatographic). Assay validation data should be submitted. Determination of amount of drug per spray by weight difference of the bottles is an unacceptable procedure.

3. Spray Pattern

Spray patterns should be determined at three distances from the TLC plate at the beginning and end life sectors, based on single actuations. The spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products. Visualization of the spray patterns should be accomplished using a drug-specific reagent (that will not develop color when tested with placebo). Photographs (not photocopies of photographs) of spray patterns, in color if appropriate, should be analyzed to measure the shortest (D_{min}) and widest (D_{max})diameters. Reported data should include values of D_{min}, D_{max} and ovality ratio (D_{min}/D_{max}), along with photographs (with superimposed grid for quantitation) and markings indicating D_{min} and D_{max}.

4. Laser Diffraction (———————)

Testing should be done at beginning, middle, and end of use life of the product. Measurements should be made at three distances from the orifice to the laser beam. At each distance, measurements should be made at different delay times (minimum of 3) in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time(s). Data should be reported in the form of D_{10}, D_{50}, D_{90} and SPAN $[(D_{90}-D_{10}/D_{50})]$. Data should be reported based on mass (volume). All instrument/computer printouts should also be submitted, including cumulative percent undersize tables and histograms of particle size distribution. Obscuration should be reported for each run, along with the instrument manufacturer's recommended obscuration ranges. The sponsor's reported obscuration range of —— % (set in the SOP) is too low.

The sponsor should also explain how the equipment was calibrated for optimum droplet size.

5. Cascade Impactor

Cascade impactor data based on a validated assay should account for mass balance and be reported in the following groups:

1. Adaptor to throat or separator and stage 0,
2. Stage 1
3. Stage 2 to filter.

Because the purpose of the cascade impactor test for this product is to characterize fines only, and not to provide a particle size distribution, the sponsor may provide cascade impactor studies only at the beginning and end of canister through-life testing.

6. Plume Geometry

Plume geometry data should describe two side views, at a 90° angle to each other and relative to the axis of the plume, of the aerosol cloud when actuated into space. Plume geometry need only be performed at the beginning of use life. Plumes should be characterized at three or more different delay times after actuation. These times should be chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time(s). Photographs of spray plumes should be used to measure plume length, plume width, and plume (spray cone) angle. The sponsor is requested to provide all photographs and data characterizing plume dimensions. Photographs should be overlaid with marked grids for quantitation.

7. Priming and Tail-off Data

The sponsor should submit data to support comparative priming characteristics (priming, loss of prime) of the test and reference products. In addition, evidence for comparable tail-off characteristics should be submitted. Data should be based on the amount of drug per actuation using a validated analytical procedure.

Loss of prime data should be submitted for the test and reference products after 24 hours and after 7 days. Prime retention properties of the Dey product should be comparable to Atrovent per labeling:

> *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.*

8. Since the device and formulation are integral components of a nasal spray, the sponsor should provide information to support sameness of test and reference devices. The sponsor should provide to the extent possible a side-by-side comparison of the pumps and actuators used in the test and reference products. This information should include the manufacturer, model numbers of the pumps, actuators, actuator inserts and the overcaps. Technical drawings with dimensions should also be submitted, if available.

9. The sponsor should provide a quantitative formulation table of their product in terms of amount/spray.

Recommendation:

1. The in-vitro studies submitted by Dey Labs on their ipratropium bromide 0.03% nasal solution is incomplete per comments #1-9.

R. Lee 5/26/99

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR _____ 5/27/1999

Concur: _____ Date: 5/27/99

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

JLee/jl/05-26-99

cc: NDA #75-552 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

Spray Pattern

SPRAY PATTERN TEST FOR IPRATROPIUM BROMIDE NASAL SPRAY UNITS

Product: Dey Nasal Spray 0.03%
Timepoint: T = 0
Lot #: W008

Test Method: 6730-03
Lab. Reference: 24185-26

Distance (cm)	Orientation	Unit # 3 Vertical (mm)	Unit # 3 Horizontal (mm)	Unit # 3 Ratio	Unit #8 Vertical (mm)	Unit #8 Horizontal (mm)	Unit #8 Ratio	Unit #12 Vertical (mm)	Unit #12 Horizontal (mm)	Unit #12 Ratio	Mean Vertical (mm)	Mean Vertical % RSD	Mean Horizontal (mm)	Mean Horizontal % RSD	Mean ± Std. Dev. Ratio	Mean ± Std. Dev. % RSD
1.0	0°										25.8	2.2	27.5	3.6	0.94 ± 0.056	5.9
	90°										27.8	9.0	27.0	10.3	1.03 ± 0.012	1.1
	180°										28.2	13.3	29.2	11.0	0.97 ± 0.05	5.2
	270°										28.5	9.8	26.7	6.6	1.07 ± 0.036	3.4
	Mean	29.3	28.6	1.03	25.4	25.6	0.99	28.1	26.5	0.99	27.6		27.6		0.98 ± 0.039	
	% RSD	8.4	8.8	2.5	2.5	5.1	5.7	8.9	5.7	10.4	4.3		4.0		3.98%	
	Orientation															
2.5	0°										36.8	7.8	39.8	9.4	0.93 ± 0.012	1.2
	90°										38.3	2.0	37.5	3.5	1.02 ± 0.017	1.7
	180°										39.8	5.9	38.8	1.5	1.03 ± 0.047	4.6
	270°										39.3	5.3	38.2	3.3	1.03 ± 0.026	2.6
	Mean	38.0	38.4	0.99	38.9	39.3	0.99	38.8	38.1	1.02	38.6		38.6		0.99 ± 0.025	
	% RSD	2.4	6.8	5.2	2.2	4.7	5.5	10.2	5.0	5.8	3.4		2.6		2.63%	

SPRAY PATTERN TEST FOR IPRATROPIUM BROMIDE NASAL SPRAY UNITS

Product: Atrovent® Nasal Spray 0.03%
Timepoint: T = 0
Lot #: 816015A

Test Method: 6730-03
Lab. Reference: 24185-41

Distance (cm)	Orientation	Unit # 2 Vertical (mm)	Unit # 2 Horizontal (mm)	Unit # 2 Ratio	Unit #4 Vertical (mm)	Unit #4 Horizontal (mm)	Unit #4 Ratio	Unit #15 Vertical (mm)	Unit #15 Horizontal (mm)	Unit #15 Ratio	Mean Vertical (mm)	Mean Vertical % RSD	Mean Horizontal (mm)	Mean Horizontal % RSD	Mean ± Std. Dev. Ratio	Mean ± Std. Dev. % RSD
1.0	0°										20.2	13.7	21.0	14.9	0.96 ± 0.032	3.3
	90°										20.0	4.3	20.8	2.8	0.96 ± 0.017	1.8
	180°										20.8	3.7	21.3	4.9	0.98 ± 0.038	3.9
	270°										21.2	9.5	21.7	13.9	0.98 ± 0.045	4.6
	Mean	20.0	21.1	0.95	21.0	21.5	0.98	20.6	21.0	0.99	20.5		21.2		0.97 ± 0.029	
	% RSD	11.4	11.8	0.5	3.4	5.0	1.7	8.7	12.0	4.7	2.7		1.7		2.99%	
	Orientation															
2.5	0°										36.3	2.9	36.0	7.2	1.01 ± 0.044	4.3
	90°										36.2	3.2	36.5	3.6	0.99 ± 0.026	2.7
	180°										36.3	2.9	36.7	5.5	0.99 ± 0.07	7.1
	270°										35.8	9.8	37.3	4.3	0.96 ± 0.061	6.3
	Mean	36.0	36.5	0.98	36.5	35.8	0.99	36.0	37.6	1.01	36.2		36.6		1.00 ± 0.047	
	% RSD	4.8	5.4	5.9	0.0	4.4	4.4	2.6	4.1	4.2	0.7		1.5		4.70%	

Data Analysis

Particle Sizing by ——— Laser Diffraction

August 13, 1997

Drug: **Ipratropium Bromide**
Product: **0.03% Dey Nasal Spray**
Lot# : **W008**
Stability Study Time Point: **Time = 0**

Storage Condition: N/A

Spray Bottle Unit # 3

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	33.2	52.94	312.34
StdDev	5.98	5.31	222.66
% RSD	18.0%	10.0%	71.3%

Spray Bottle Unit # 8

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	28.62	45.48	91.94
StdDev	1.35	3.9	31.97
% RSD	4.7%	8.6%	34.8%

Spray Bottle Unit # 12

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	29.61	49.21	98.41
StdDev	1.89	4.11	18.47
% RSD	6.4%	8.4%	18.8%

Mean Data for Units# 3, 8, 12

	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
mean	30.48	49.21	167.56
StdDev	3.83	5.05	156.63
% RSD	12.6%	10.3%	93.5%

Data Analysis

Particle Sizing by ——— Laser Diffraction

August 13, 1997

Drug: **Ipratropium Bromide**
Product: **0.03% Atrovent Nasal Spray**
Lot# : **816015A**
Stability Study Time Point: **Time = 0**

Storage Condition: N/A

Spray Bottle Unit # 4

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	28.4	48.15	212.07
StdDev	1.6	2.58	209.31
% RSD	5.6%	5.4%	98.7%

Spray Bottle Unit # 9

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	31.27	51.47	221.44
StdDev	5.01	8.86	244.57
% RSD	16.0%	17.2%	110.4%

Spray Bottle Unit # 15

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	24.74	42.08	104.7
StdDev	0.6	0.6	30.71
% RSD	2.4%	1.4%	29.3%

Mean Data for Units # 4, 9, 15

	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
mean	28.14	47.23	179.40
StdDev	3.88	6.19	171.17
% RSD	13.8%	13.1%	95.4%

Cascade Impactor

[redacted] CASCADE IMPACTION
FOR IPRATROPIUM BROMIDE NASAL SPRAY UNITS

Timepoint: T = 0

Product	Dey Nasal Spray Units 0.03%				
Test Method	TM 6730-04				
Lot #	W008				
Bottle #	3	8	12	Mean	%RSD
%Material Balance:	—	—	—	94.9	1.64
% of drug with Particle Size > 9 µm	100.0%	100.0%	100.0%	100.0%	0.00
Amount of drug per spray (µg)	—	—	—	20.54	2.43
Shot Weight (mg)	—	—	—	72.2	0.90

[redacted] CASCADE IMPACTION
FOR IPRATROPIUM BROMIDE NASAL SPRAY UNITS

Timepoint: T = 0

Product	Atrovent® Nasal Spray Units 0.03%				
Test Method	TM 6730-04				
Lot #	816015A				
Bottle #	7	15	4	Mean	%RSD
%Material Balance:	—	—	—	88.0	7.84
% of drug with Particle Size > 9 µm	100.0%	100.0%	100.0%	100.0%	0.00
Amount of drug per spray (µg)	—	—	—	19.21	5.21
Shot Weight (mg)	—	—	—	72.8	2.66

Plume Geometry

Test Method: TM 6730-05
Test Name: 2D Still Image Plume Geometry
Product: Dey 0.03% Ipratropium Bromide Nasal Spray
Company: Dey Laboratories

Time Point: T = 0
Condition: NA
Orientation: NA
Lot Number: W008

Sample Unit ID	*Image Number*	*Initial Angle °*	*Mean Statistics*
Bottle 3	1		*Overall Mean 83.0 °*
	2		*% RSD 2.8%*
	3		
	mean	*80.6*	*Mean of Means 83.0 °*
	% RSD	*3.7%*	*% RSD 2.5%*
Bottle 8	1		
	2		
	3		
	mean	*84.3*	
	% RSD	*0.7%*	
Bottle 12	1		
	2		
	3		
	mean	*84.0*	
	% RSD	*0.0%*	

Test Method: TM 6730-05
Test Name: 2D Still Image Plume Geometry
Product: Atrovent® (ipratropium bromide) Nasal Spray 0.03%
Company: Dey Laboratories

Time Point: T = 0
Condition: NA
Orientation: NA
Lot Number: 816015A

Sample Unit ID	*Image Number*	*Initial Angle °*	*Mean Statistics*
Bottle 4	1		*Overall Mean 69.1 °*
	2		*% RSD 7.7%*
	3		
	mean	*65.9*	*Mean of Means 69.1 °*
	% RSD	*7.6%*	*% RSD 5.8%*
Bottle 7	1		
	2		
	3		
	mean	*67.8*	
	% RSD	*3.1%*	
Bottle 15	1		
	2		
	3		
	mean	*73.6*	
	% RSD	*8.3%*	

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-552 APPLICANT: Dey Labs

DRUG PRODUCT: Ipratropium bromide 0.03% nasal solution

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

The submitted in-vitro tests are deficient. All tests should be repeated as follows:

1. The requirements below apply to the following tests:

   A. Unit Spray/Content Uniformity.
   B. Priming, loss of prime and tail off
   C. Droplet size distribution by Malvern Mastersizer/Cascade Impaction
   D. Spray pattern.
   E. Plume geometry

   For all these comparative *in vitro* tests:

   - ☞ The bottles should be actuated using a validated automated actuation device to increase reproducibility. Validation data including the effect of actuation force, actuation velocity and other factors should be submitted.
   - ☞ No fewer than 10 units each of the test and reference products should be tested in a blinded manner.
   - ☞ Data from three batches each of the test and reference products should be submitted, including batch records for all batches of the test product.
   - ☞ SOPs for all tests effective at the time of testing should be submitted. SOPs should describe the automated actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s).
   - ☞ Raw data for <u>all tests</u> should be submitted in the form of paper copies (tables) as well as electronic files (Excel 5.0 spread sheets).
   - ☞ For tests performed at the beginning (B), middle (M), and end (E) or B and E of use life sectors, comparative performance of test and reference products will be assessed at each sector.

With regard to specific tests:

2. <u>Unit Spray/Content Uniformity</u>

   Consistent with the Potency Test described in the 27 June 1989 *Division of Bioequivalence Guidance for the in vitro portion of bioequivalence requirements for metaproterenol sulfate and*

albuterol inhalation aerosols (metered dose inhalers), this test should be performed at beginning, middle, and end of use life of the product after product priming.

The amount of drug per single spray should be determined using a validated analytical procedure (chemical/chromatographic). Assay validation data should be submitted. Determination of amount of drug per spray by weight difference of the bottles is an unacceptable procedure.

3. Spray Pattern

Spray patterns should be determined at three distances from the TLC plate at the beginning and end life sectors, based on single actuations. The spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products. Visualization of the spray patterns should be accomplished using a drug-specific reagent (that will not develop color when tested with placebo). Photographs (not photocopies of photographs) of spray patterns, in color if appropriate, should be analyzed to measure the shortest (D_{min}) and widest (D_{max}) diameters. Reported data should include values of D_{min}, D_{max} and ovality ratio (D_{min}/D_{max}), along with photographs (with superimposed grid for quantitation) and markings indicating D_{min} and D_{max}.

4. Laser Diffraction (——————————)

Testing should be done at beginning, middle, and end of use life of the product. Measurements should be made at three distances from the orifice to the laser beam. At each distance, measurements should be made at different delay times (minimum of 3) in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time(s). Data should be reported in the form of D_{10}, D_{50}, D_{90} and SPAN $[(D_{90}-D_{10}/D_{50})]$. Data should be reported based on mass (volume). All instrument/computer printouts should also be submitted, including cumulative percent undersize tables and histograms of particle size distribution. Obscuration should be reported for each run, along with the instrument manufacturer's recommended obscuration ranges. The sponsor's reported obscuration range of ——% (set in the SOP) is too low.

Please also explain how the equipment was calibrated for optimum droplet size.

5. Cascade Impactor

Cascade impactor data based on a validated assay should account for mass balance and be reported in the following groups:

1. Adaptor to throat or separator and stage 0,

2. Stage 1

3. Stage 2 to filter.

Because the purpose of the cascade impactor test for this product is to characterize fines only, and not to provide a particle size distribution, you may provide cascade impactor studies only at the beginning and end of canister through-life testing.

6. Plume Geometry

Plume geometry data should describe two side views, at a 90° angle to each other and relative to the axis of the plume, of the aerosol cloud when actuated into space. Plume geometry need only be performed at the beginning of use life. Plumes should be characterized at three or more different delay times after actuation. These times should be chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time(s). Photographs of spray plumes should be used to measure plume length, plume width, and plume (spray cone) angle. Please provide all photographs and data characterizing plume dimensions. Photographs should be overlaid with marked grids for quantitation.

7. Priming and Tail-off Data

Please submit data to support comparative priming characteristics (priming, loss of prime) of the test and reference products. In addition, evidence for comparable tail-off characteristics should be submitted. Data should be based on the amount of drug per actuation using a validated analytical procedure.

Loss of prime data should be submitted for the test and reference products after 24 hours and after 7 days. Prime retention properties of the Dey product should be comparable to Atrovent per labeling:

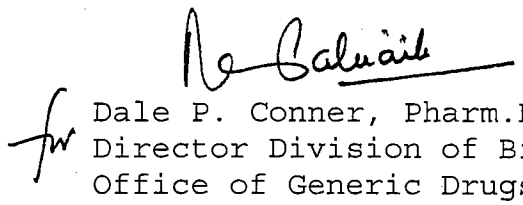
> *Initial pump priming requires seven sprays of the pump. If used regularly as recommended, no further priming is required. If not used for more than 24 hours, the pump will require two sprays, or if not used for more than seven days, the pump will require seven sprays to reprime.*

8. Since the device and formulation are integral components of a nasal spray, you should provide information to support sameness of test and reference devices. Please provide to the extent possible a side-by-side comparison of the pumps and actuators used in the test and reference products. This information should include the manufacturer, model numbers of the pumps, actuators,

actuator inserts and the overcaps. Technical drawings with dimensions should also be submitted, if available.

9. Please provide a quantitative formulation table of your test product in terms of amount/spray.

Sincerely yours,



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

CC: ANDA 75-552
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements:
HFD-658/ J. Lee E.J. 5/26/99
HFD-650/ SG Nerurkar 5/27/99
HFD-617/ Mahmud
HFD-650/ Conner for Dur 5/27/99

Printed in draft on \ \
Printed in final on \ \
V:\firmsam\Dey\ltrs&rev\75552IVO.299

BIOEQUIVALENCY - DEFICIENCIES

9. **OTHER OPTIONS** (less common): Strengths: 0.03%

Bio study (STU) [in-vitro study]

Outcome: IC

OUTCOME DECISIONS:
UN - Unacceptable (fatal flaw) **IC** - Incomplete

WINBIO COMMENTS:
Gross deficiencies. All tests must be repeated.

Ipratropium bromide
0.03% nasal solution
~~ANDA #75-552~~
ANDA #75-553
Reviewer: J. Lee
75552C.899

Dey Labs
Napa, Calif.
Submission date:
August 9, 1999

Review of Correspondence

The sponsor is seeking clarification of several items contained in the deficiency letters (for the 0.03% and 0.06% nasal solution) issued in the review of original in-vitro data for their ipratropium bromide nasal solutions.

Comment:

1. " 'SOPs should describe the automated actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s).' If mechanical actuations are being performed for all tests, is blinding of products necessary? And if so, to what extent? It seems there is no possibility of bias if the analysts have no role in the performance of the actuator."

Res: Blinding of products is necessary not only to remove potential bias in the actuations, but extends to postacutuation evaluations, where knowledge of the identity of the product could influence the interpretation of the results. The sponsor should describe in the SOPs for each in-vitro test the blinding measures taken (see p. 10 of Draft Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action).

2. Priming and Tail-off Data: " 'Data should be based on the amout of drug per actuation using a validated analytical procedure.' Will spray weight calculations suffice since these tests are a measure of pump performance which is strictly a function of spray weight for solution products? Unit spray through bottle life and content uniformity analyses should provide sufficient data to show that the pump is delivering the required amount of drug per spray."

Res: Spray weight calculations will not suffice. Amount of drug per actuation should be based on a validated chemical analysis.

3. " 'Spray patterns should be determined at three distances from the TLC plate...' Dey's spray pattern development efforts have shown that a third distance of scientific merit cannot be visualized given the staining techniques available. Will two distances be acceptable?"

Res: The Division of Bioequivalence requires that spray patterns be determined at three distances (e.g. 1, 2.5-3, 5 cm). Based on the Division's experience with aqueous nasal

spray products, spray patterns can be measured at distances even greater than 5 cm. The sponsor should endeavor to find a staining technique that is specific and can differentiate spray patterns at three different distances.

4. . . " 'Unit Dose and Uniformity of Unit Dose states, . . .this test should be performed at beginning, middle, and end of use life of the product after product priming. However, page 10 of . . Draft Guidance . . beginning of unit life, at the middle of unit life, and at the end of unit life for nasal aerosols, and at the beginning and end of unit life for nasal sprays.' Is beginning and end testing acceptable?"

Res: Beginning and end testing is acceptable for this drug product per Draft Guidance.

4. "The June 7 facsimile would require Dey to perform the full amount of bioequivalence testing on the 0.03% product whereas the table on page 29 of the Draft Guidance mentioned above outlines a reduced testing regime for low strength products. Can Dey follow the testing regime outlined in the Draft Guidance?"

Res: Dey may follow the reduced testing regime for the 0.03% product per Draft Guidance.

Recommendation:

1. Clarification is provided for the sponsor's inquiries to the deficiency letters as stated in the comments above.

   All comments should be forwarded to the sponsor.

E. Lee 9/22/99

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

9/23/1999

Concur: Date: 10/1/99

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

JLee/jl/09-22-99

cc: NDA #75-552 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:75-552 and 75-553 APPLICANT: Dey Labs

DRUG PRODUCT: Ipratropium bromide, 0.03% and 0.06% Nasal Solution

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following responses are provided:

1. " 'SOPs should describe the automated actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s).' If mechanical actuations are being performed for all tests, is blinding of products necessary?" etc.

Res: Blinding of products is necessary not only to remove potential bias in the actuations, but extends to postacutuation evaluations, where knowledge of the identity of the product could influence the interpretation of the results. You should describe in the SOPs for each in-vitro test the blinding measures taken (see p. 10 of Draft Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action).

2. Priming and Tail-off Data: " 'Data should be based on the amount of <u>drug per actuation</u> using a validated analytical procedure.' Will spray weight calculations suffice since these tests are a measure of pump performance which is strictly a function of spray weight for solution products?" . . . etc.

Res: Spray weight calculations will not suffice. Amount of <u>drug per actuation</u> should be based on a validated chemical analysis.

3. " 'Spray patterns should be determined at <u>three</u> distances from the TLC plate…' Dey's spray pattern development efforts have shown that a third distance of scientific merit cannot be visualized given the staining techniques available. Will two distances be acceptable?"

Res: The Division of Bioequivalence requires that spray patterns be determined at <u>three</u> distances (e.g. 1, 2.5-3, 5 cm). Based on the Division's experience with aqueous nasal spray products, spray patterns can be measured at distances even greater than 5 cm. You should endeavor to find a staining technique that is <u>specific</u> and can differentiate spray patterns at three <u>different</u> distances.

4. . . " 'Unit Dose and Uniformity of Unit Dose states, . . .this test should be performed at beginning, middle, and end of use life of the product after product priming. However, page 10 of . . Draft Guidance . . beginning of unit life, at the middle of unit life, and at the end of unit life for nasal aerosols, and at

the beginning and end of unit life for nasal sprays.' Is beginning and end testing acceptable?"

Res: Beginning and end testing is acceptable for this drug product per Draft Guidance.

4. "The June 7 facsimile would require Dey to perform the full amount of bioequivalence testing on the 0.03% product whereas the table on page 29 of the Draft Guidance mentioned above outlines a reduced testing regime for low strength products. Can Dey follow the testing regime outlined in the Draft Guidance?"

Res: Dey may follow the reduced testing regime for the 0.03% product per Draft Guidance.

Sincerely yours,

Dale P. Conner

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

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements:
HFD-658/ J.Lee E.S. 9/22/99
HFD-650/ Bio Team Leader 9/23/99
HFD-617/ Fan 10/1/99
HFD-650/ Conner 10/1/99

Printed in draft on \ \
Printed in final on \ \
V:\firmsam\Dey\ltrs&rev\75552C.899

BIOEQUIVALENCY - DEFICIENCIES

8. **OTHER** (OTH) 8/9/99 Strengths: 0.03% & 0.06%
Outcome: IC

OUTCOME DECISIONS:
UN - Unacceptable (fatal flaw) **IC** - Incomplete

WINBIO COMMENTS:
Clarification of some items in previous deficiency letters.

Ipratropium Bromide
Nasal Spray, 0.03% (21 µg/spray)
ANDA #75-552
Reviewer: J. Lee
75552IVO401.doc

Dey Laboratories
Napa, Calif
Submission date:
April 27, 2001
December 6, 2001

Review of In-vitro Performance Studies and DSI Inspection Report

Ipratropium Bromide Nasal Spray (IPBR NS) 0.03% is indicated for the relief of rhinorrhea associated with the common cold for adults and children age 12 years and older. The active drug 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, 0.03% (21 µg/spray) manufactured by Boehringer Ingelheim.

The RLD recommended dose is two sprays (42 µg) per nostril three or four times daily. The drug is supplied as a solution in a high-density polyethylene bottle fitted with a *metered nasal spray pump*. Each bottle is designed to deliver 345 metered sprays of 0.07 mL each (21 µg/spray) of ipratropium bromide.

FORMULATION COMPARISON (not for release under FOI)

	mg/ml		
Ingredient	Test	Ref	Test/Ref
Ipratropium bromide	0.3	0.3	1.00
Edetate disodium USP Sodium chloride USP Benzalkonium chloride NF			
Sodium hydroxide NF	To adjust pH*	To adjust pH*	-
Hydrochloric acid NF	To adjust pH*	To adjust pH*	-
Purified water USP	q.s.	q.s.	

pH = ——— (Test) and 4.7 (Ref)

IN VITRO TESTING RECOMMENDATIONS

This application contains in vitro performance data for the lower of the two marketed strengths (0.03% and 0.06%) of IPBR NS. Dey uses the same models of pumps and actuators for its IPBR NS, 0.03% and 0.06%. The firm has submitted full in vitro testing on its IPBR NS 0.06% (ANDA #75-553) and abbreviated testing on the 0.03% product.

Based on the Draft Nasal BA/BE guidance, only abbreviated testing is required for the lower strength, provided the sponsor uses the same pump and actuator for the lower- and higher-strength products. The testing recommendations for the multiple-strength solution nasal sprays in the Agency's draft Guidance are as follows:

TEST	STRENGTH	
	HIGHER	LOWER
Unit Dose Content	At Beg. & End	At Beg. & End
Priming	Recommended	Recommended
Tail Off	Recommended	Recommended
Laser Diffraction Analysis	At Beg. , Mid. & End	At Beg. Only
Cascade Impaction	At Beg. & End	Not Necessary
Spray Pattern	At Beg. & End	At Beg. Only
Plume Geometry	At Beg. Only	Not Necessary

Beg. and Mid. = Beginning and middle sectors of the product use life.

DRUG PRODUCTS

Test: Dey's Ipratropium Bromide Nasal Spray, 0.03%, consisted of lots # W083, W084A and W084B. Mnfg date: 11/99
Reference: Boehringer Ingelheim's Atrovent[R] Nasal Spray, 0.03%, consisted of lots 819012S, 819014A and 819015A. The expiry dates for all three batches were not given.

COMPARABILITY OF SPRAY DEVICES

The pump supplier, ———, has stated that the metered dose pump supplied for Dey's Ipratropium Bromide Nasal Spray, 0.03% is the same as that used in Atrovent® Nasal Spray (also supplied by ———). Physical comparative data with the test and reference metering devices were provided (Vol 2.1, p 387).

IN VITRO PERFORMANCE TESTING

Procedures and Information Applicable to All Tests

All actuations of the nasal spray products were made using an automated actuator (designed by ———) to actuate the nasal sprays in a reproducible manner. The procedure used for operation of the actuator is described in SOP# PDTM-700-01 (p 230-4, vol. 2.7). The actuator operating conditions were as follows:

Dose time:	11-15 msec
Return Time:	35-50 msec
Hold Time:	2 sec
Actuation Force:	5.6 kg

The firm performed the unit dose content test using Test Method No. DY01-06 [vol. 2.5, p 196 - 203]. Since the labeled number of full medication doses per bottle is 345 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, and 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 eight sprays of each unit.

For each test, ten (10) units from each of the three lots of the test and reference products were tested (in duplicate or triplicate).

The weight of individual sprays was also determined by weighing bottles before and after each spray collection, and the amount of drug per spray was determined by a validated HPLC analysis (TM-DY01-02; LT 01-156, vol 2.7, p 145 - 50).

The unit spray content data were reported for the beginning (actuation 8, 9) and end of unit life (actuation 344, 345). The following table provides a summary based on the reviewer's calculations.

Unit Spray Content Data

RODUC	Sector	Mean		Variability (%CV)			TEST/REF		p
		Arith (N=60)	Geo (N=60)	Within-Lot (N=20)	Between-lot (N=3)	Total (N=60)	Arith	Geo	
TEST	BEG	21.036	21.02	2.11 - 6.22	0.81	4.10	0.99	0.99	0.329
	END	21.389	21.353	5.35 - 6.10	1.16	5.62	1.00	1.00	0.698
REF	BEG	21.206	21.189	3.25 - 5.10	1.05	3.94			
	END	21.488	21.441	1.70 - 9.78	2.08	6.24			

Mean data are expressed in mcg/spray.

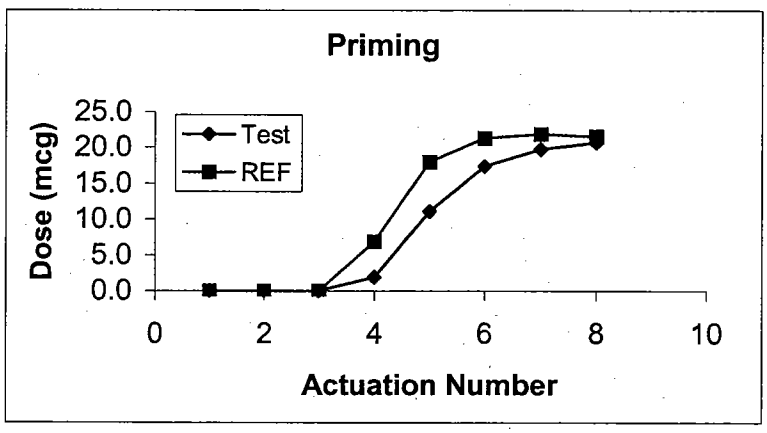
For the Dey product, the geometric mean values at actuations 8 and 345 values are ≤ 1% lower than the corresponding reference product values. The test product exhibited slightly lower variability (%CV) than the reference product. The test/ref ratios (geometric) are within the 90-111% limits employed by DBE for acceptance of nasal solution sprays.

Based on the mean values, there was no change in the unit dose determined at the beginning and end sectors.

Priming/Re-priming

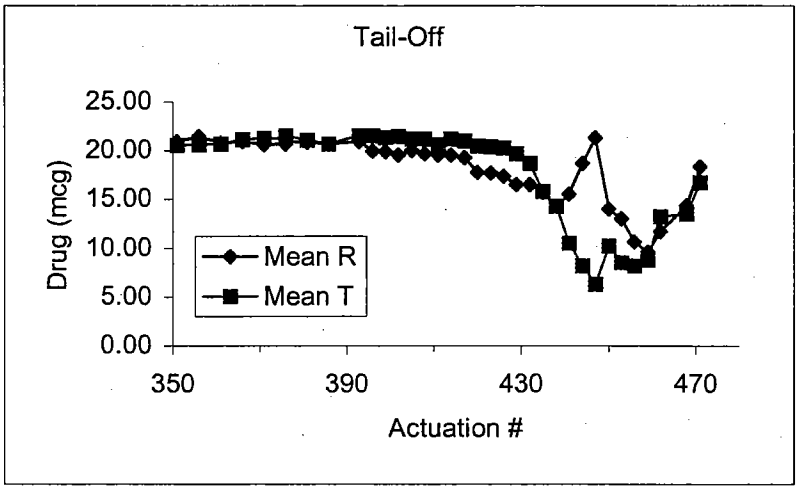
Based on the data submitted, the test product is fully primed at the 8th spray. A re-priming study was performed by leaving the bottle for 24 hours in an upright position, and drug content of the spray was analyzed after 2 sprays (per Atrovent® pkg insert). Another re-priming study was performed after 7 days of inactivity. Drug content of the spray was analyzed after 7 sprays (per Atrovent® pkg insert). Both re-priming studies showed labeled delivery of drug (~21 mcg).

	Test		REF	
Act #	Mean	%CV	Mean	%CV
1	0.0	-	0.0	-
2	0.0	-	0.0	-
3	0.0	-	0.0	-
4	1.9	183	6.9	80
5	11.0	68	18.0	18
6	17.3	39	21.3	6
7	19.8	26	21.9	6
8	20.7	20	21.6	8



Tail-off

The tail off profile characterizes the decrease in emitted dose following delivery of the labeled number of actuations based on the HPLC assay (up to actuation 360) and by tabulating the spray weights up to actuation 470 to product exhaustion. The firm has demonstrated good correlation between unit spray contents based on spray weights and the HPLC data. The data indicate that the test product delivers the labeled numbers of doses and its tail off is no more erratic than that of the reference product.



Droplet size distribution

a. Laser Diffraction

Droplet size determination was performed based on TM 6730-02 (vol. 2.7) on 10 units from each of the 3 unit lots of test and reference products. Each unit was tested only at the beginning sector of unit life. Each unit was actuated at three distances relative to the ——— laser beam (1 cm, 2.5 cm, and 5 cm). At each distance, measurements were taken at different 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 (Intermediate)	Stable
Plume dissipation (End)	Rises

The three separate regions constitute the sampling areas on which the droplet size distribution data are based. The delay times representing these regions vary with the actuation distance.

The firm submitted D_{10}, D_{50}, D_{90} and SPAN data. Equivalence evaluation is based on D_{50} and SPAN data. A summary of these data based on the reviewer's calculations is show below:

Droplet Size Distribution - D50 Data (Test Product) and Test/Ref Ratios

Distance	Plume Formation	Mean Arith (N=90)	Mean Geo (N=90)	Variability (%CV) Within-Lot (N=30)	Variability (%CV) Between-lot (N=3)	Variability (%CV) Total (N=90)	TEST/REF Arith	TEST/REF Geo	p
1	Initial	144.36	124.76	44.0 - 57.7	9.93	52.35	0.90	0.88	0.17
1	Intermediate	49.65	41.02	77.4 - 109	13.14	96.08	0.9101	0.95	0.55
1	Dissip.	81.95	78.84	26.1 - 28.9	5.26	27.09	1.08	1.07	0.04
2.5	Initial	121.73	106.93	114 - 136	10.46	55.86	0.89	0.89	0.16
2.5	Intermediate	29.73	29.54	7.85 - 17.8	3.56	12.55	0.95	0.96	0.07
2.5	Dissip.	79.45	77.34	20.0 - 23.4	6.80	23.43	0.9698	0.99	0.46
5	Initial	99.79	80.46	77.9 - 84.8	14.52	80.61	0.98	0.98	0.89
5	Intermediate	31.58	31.55	2.97 - 4.30	2.36	4.14	0.98	0.98	0.001
5	Dissip.	58.74	48.35	37.1 - 96.5	36.10	89.45	1.10	1.07	0.49

Droplet Size Distribution - D50 Data (REF Product)

Stage	Distance	Plume Formation	Mean Arith (N=90)	Mean Geo (N=90)	Variability (%CV) Within-Lot (N=30)	Variability (%CV) Between-lot (N=3)	Variability (%CV) Total (N=90)
	1	Initial	160.33	142.00	40.2 - 48.4	9.3	45.7
	1	Intermediate	54.55	43.23	84.6 - 114	23.3	104
	1	Dissip.	76.14	73.97	16.3 - 27.9	9.8	25.3
	2.5	Initial	136.95	119.52	49.0 - 65.0	5.2	56.1
BEG	2.5	Intermediate	31.14	30.81	7.7 - 29.5	3.1	18.8
	2.5	Dissip.	81.93	78.11	28.4 - 33.6	8.0	31.6
	5	Initial	101.52	82.24	75.1 - 80.8	11.3	78.0
	5	Intermediate	32.29	32.27	3.67 - 4.66	0.88	4.1
	5	Dissip.	53.49	45.13	68.6 - 96.8	13.8	90.6

Droplet Size Distribution - SPAN Data (Test Product) and Test/Ref Ratios

stage	Distance	Plume Formation	Mean Arith (N=90)	Mean Geo (N=90)	Variability (%CV) Within-Lot (N=30)	Variability (%CV) Between-lot (N=3)	Variability (%CV) Total (N=90)	TEST/REF Arith	TEST/REF Geo	p
	1	Initial	2.29	2.08	39.2 - 54.0	5.3	47.7	1.02	1.01	0.80
	1	Intermediate	1.73	1.71	10.3 - 21.2	1.4	16.6	0.98	0.99	0.55
	1	Dissip.	1.69	1.65	14.0 - 28.6	9.7	23.1	0.96	0.95	0.16
	2.5	Initial	2.57	2.37	37.7 - 44.4	13.8	42.1	0.98	0.99	0.75
BEG	2.5	Intermediate	1.85	1.78	6.48 - 66.2	10.4	43.5	1.06	1.03	0.29
	2.5	Dissip.	1.77	1.75	9.6 - 15.3	2.10	12.4	1.00	0.99	0.80
	5	Initial	3.38	49.97	45.8 - 54.5	14.2	50.0	1.01	1.04	0.93
	5	Intermediate	1.25	1.18	6.37 - 104	11.8	68.5	1.09	1.04	0.24
	5	Dissip.	4.67	3.89	34.0 - 65.8	27.5	50.3	0.91	0.96	0.21

Droplet Size Distribution - SPAN Data (REF Product)

stage	Distance	Plume Formation	Mean Arith (N=90)	Mean Geo (N=90)	Variability (%CV) Within-Lot (N=30)	Between-lot (N=3)	Total (N=90)
	1	Initial	2.25	2.05	41.1 - 53.0	10.5	47.1
	1	Intermediate	1.77	1.73	5.03 - 50.7	4.7	31.5
	1	dissip.	1.76	1.74	16.5 - 17.5	1.2	16.8
	2.5	Initial	2.62	2.40	29.6 - 55.5	3.6	42.0
BEG	2.5	Intermediate	1.75	1.73	6.3 - 29.0	3.5	18.3
	2.5	dissip.	1.77	1.76	8.7 - 12.8	2.5	11.3
	5	Initial	3.35	2.79	46.6 - 61.2	11.1	54.3
	5	Intermediate	1.14	1.13	6.6 - 8.5	4.5	8.6
	5	dissip.	5.12	4.04	49.7 - 59.1	6.1	53.8

The test/reference ratios of the geometric means of D_{50} at initial, middle and end of plume formation for the three distances are in the range of 0.88 - 1.07. For most comparisons the p values were insignificant.

The ratios of the test geometric means to the reference geometric means for SPAN at initial, middle and end of plume formation for the three distances are in the range of 0.95 - 1.04. For all comparisons the p values were insignificant.

For D_{50} and SPAN, the within-lot, between-lot and total variability at the initial, middle, and end of plume formation for the test product are mostly comparable to that of reference product.

Based on the mean values:

The DBE evaluation of droplet size distribution using laser diffraction analysis is based on data for the fully formed plume, characterized by stable transmission. In the above table these data are labeled as 'Intermediate'. Based on the data for the Intermediate plume, T/R ratios of geometric means were within the 0.9 - 1.11 range, used hitherto by DBE for acceptance of nasal spray data.

The D_{50} values were greater at the beginning of plume formation than at the middle and end of plume formation.

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

b. Cascade impaction: This test is not required for lower strength products.

Spray Pattern

The firm submitted spray pattern data at three distances (1, 2.5 and 4 cm) from the TLC plate at beginning and end life sectors for the test and reference products. It provided individual results of spray pattern determination in terms of D_{max}, D_{min} and ovality ratio (D_{max}/D_{min}).

Test Method No. TM-6730-03 (Spray Pattern Testing for Ipratropium Bromide Nasal Spray 0.03%) can be found in Vol. 2.7, p 256-9. Validation in Vol. 2.5, p 214-260.

Spray Pattern Data (Test Product) and Test/Ref Ratios

Distance	Plume Formation	Mean Arith (N=90)	Mean Geo (N=90)	Variability (%CV) Within-Lot (N=30)	Between-lot (N=3)	Total (N=90)	TEST/REF Arith	TEST/REF Geo	p
1	Dmax	2.091	2.0825	5.93 - 11.12	11.40	9.01	1.10	1.10	1.231E-12
1	Dmin	1.924	1.9167	6.10 - 10.40	10.37	9.17	1.10	1.11	1.584E-11
1	Oval. Ratio	1.090	1.0877	4.45 - 10.70	10.89	7.39	0.99	0.99	0.491
2.5	Dmax	4.426	4.402	8.46 - 10.85	12.08	10.52	**1.13**	**1.14**	1.399E-10
2.5	Dmin	3.906	3.889	7.96 - 10.16	10.54	9.28	1.09	1.10	5.984E-06
2.5	Oval. Ratio	1.136	1.132	6.69 - 10.56	10.67	9.12	1.04	1.04	0.001
4	Dmax	6.5322	6.5012	8.10 - 11.42	8.27	9.65	**1.13**	**1.15**	1.873E-08
4	Dmin	5.7422	5.6907	11.17 - 15.16	14.17	13.17	**1.12**	**1.14**	1.969E-06
4	Oval. Ratio	1.1468	1.1425	7.77 - 9.11	10.06	8.88	1.01	1.01	0.483

Spray Pattern Data (REF Product)

Sector	Distance	Plume Formation	Mean Arith (N=90)	Mean Geo (N=90)	Variability (%CV) Within-Lot (N=30)	Between-lot (N=3)	Total (N=90)
	1	Dmax	1.904	1.897	7.19 - 9.62	7.07	8.54
	1	Dmin	1.742	1.733	8.37 - 10.15	6.42	10.04
	1	Oval. Ratio	1.098	1.095	3.381 - 7.53	6.63	7.44
	2.5	Dmax	3.906	3.860	9.40 - 16.51	13.11	14.31
BEG	2.5	Dmin	3.584	3.536	11.43 - 17.06	13.87	15.30
	2.5	Oval. Ratio	1.095	1.092	5.88 - 8.56	9.15	7.32
	4	Dmax	5.774	5.670	16.00 - 20.28	16.19	18.29
	4	Dmin	5.126	5.002	17.89 - 24.97	19.69	21.18
	4	Oval. Ratio	1.138	1.134	6.14 - 9.74	9.65	8.69

The within-lot, between-lot and total variability of the test/reference products are similar. Most of the p-values show significant differences. For Dmax at 2.5 cm and Dmax and Dmin at 4 cm, the T/R arithmetic and geometric ratios are greater than 1.1. The acceptable T/R range is 0.90 - 1.11.

Plume Geometry: Not required for lower strength products

DSI Inspection Report:

The in-vitro studies were sent out for inspection by the Division of Scientific Investigations (DSI) [Date of inspection report: December 6, 2001]. The data audit revealed inconsistencies in the manual quantitation of the spray patterns. The firm currently uses the image analysis software to analyze spray patterns. During the inspection, representative spray patterns were reanalyzed using this image software. The Dmin and Dmax values of the reanalyzed patterns were found to be significantly different from the original values, especially at the 2.5 and 4 cm distances between the spray nozzle and TLC plate. The firm was therefore requested to reanalyze all the spray patterns for 0.03% and 0.06% ipratropium bromide nasal spray products. The reanalyzed spray pattern data using image software analysis as calculated by the Reviewer is presented below:

Spray Pattern Data (Test Product) and Test/Ref Ratios

PROD.	Sector	Distance	Plume Formation	Mean Arith (N=30)	Mean Geo (N=30)	Variability (%CV) Within-Lot (N=10)	Variability (%CV) Between-lot (N=3)	Variability (%CV) Total (N=30)	TEST/REF Arith	TEST/REF Geo	p
		1	Dmax	21.80	21.76	6.3 - 11.4	2.35	9.00	**1.14**	**1.14**	0.00
		1	Dmin	19.50	19.386	6.7 - 13.5	2.35	10.00	**1.15**	**1.15**	0.00
		1	Oval. Ratio	1.12	1.12	2.4 - 5.0	1.36	19.39	0.98	0.98	0.13
		2.5	Dmax	42.30	42.17	3.3 - 10.0	2.61	8.00	**1.14**	**1.16**	0.00
	BEG	2.5	Dmin	33.90	33.42	8.8 - 27.1	13.65	15.90	**1.12**	**1.13**	0.037
		2.5	Oval. Ratio	1.28	1.26	2.6 - 29.5	16.00	19.40	1.03	1.02	0.138
		4	Dmax	67.30	67.11	5.2 - 7.8	3.85	7.00	**1.16**	**1.18**	0.00
		4	Dmin	49.60	48.57	12.1 - 25.5	6.41	19.20	**1.15**	**1.16**	0.011
TEST		4	Oval. Ratio	1.41	1.38	12.3 - 27.2	9.25	23.60	1.01	1.01	0.777

Spray Pattern Data - REF Product

PROD.	Sector	Distance	Plume Formation	Mean Arith (N=30)	Mean Geo (N=30)	Variability (%CV) Within-Lot (N=10)	Variability (%CV) Between-lot (N=3)	Variability (%CV) Total (N=30)
		1	Dmax	19.20	19.16	7.0 - 10.8	1.08	9.00
		1	Dmin	16.90	16.80	9.0 - 13.0	5.29	11.70
		1	Oval. Ratio	1.14	1.14	3.0 - 6.0	4.56	5.70
		2.5	Dmax	37.00	36.40	12.8 - 18.3	6.49	16.9
	BEG	2.5	Dmin	30.30	29.59	16.6 - 22.0	8.79	20.5
		2.5	Oval. Ratio	1.24	1.23	5.6 - 9.9	7.63	9.9
		4	Dmax	57.80	57.03	14.3 - 20.1	3.55	16.00
		4	Dmin	43.10	41.86	16.1 - 28.2	15.89	24.10
REF		4	Oval. Ratio	1.39	1.37	3.85 - 21.7	15.77	20.00

The reanalyzed spray pattern data show that more of the T/R geo ratios fall outside the acceptable 0.90 – 1.11 limits than in the original analysis.

Comment:

1. The expiration dates for the batches of the reference product used in the in-vitro studies could not be found. The sponsor should submit this information.

2. The sponsor should state the number of units in each sub-lot of their test product (lot size).

3. Spray pattern data, both original and reanalyzed data, show that the Test/Ref ratio (geometric) for some of the parameters are outside of acceptable limits [0.90 – 1.11]. The sponsor should redo the spray pattern tests using the image analysis software. If the test product has expired, the sponsor should manufacture 3 fresh batches of product. The sponsor should also employ 3 unexpired batches of the reference product in the spray pattern re-testing.

Recommendation:

1. The in-vitro performance studies conducted by ——— for Dey Laboratories on their ipratropium bromide nasal spray, 0.03%, is unacceptable per comment #3.

   All comments should be conveyed to the sponsor.

R. Lee 2/26/02
J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

3/4/2002

Concur: _____ Date: 3/18/02

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

JLee/jl/2-26-02

cc: NDA #75-552 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

CC: ANDA 75-552
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements:
HFD-655/ JLee E.S. 3/1/02
HFD-650/ Bio Team Leader
NFD-650/ GJPS GJPS - 3-1-02
HFD-617/ Nwaba
HFD-650/ Conner 3/18/02

3/4/02

Printed in draft on \ \
Printed in final on \ \
V:\firmsam\Dey\ltrs&rev\75552IVO401.doc

BIOEQUIVALENCY - DEFICIENCIES

1. **In-vitro STUDY** (STU) Strengths: 0.03%
Clinical:
Analytical:
✓ **Outcome:** **UN**

8. **DSI Inspection Report** (US Doc) Strengths: 0.03%
US Document
✓ **Outcome: UN**

OUTCOME DECISIONS:
UN - Unacceptable (fatal flaw) **IC** - Incomplete

WINBIO COMMENTS:
Spray pattern data needs redoing.

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-552 APPLICANT: Dey Laboratories

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.03%

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

1. The expiration dates for the batches of the reference product used in the in-vitro studies could not be found. Please submit this information.

2. Please state the number of units in each sub-lot of your test product (lot size).

3. Spray pattern data, both original and reanalyzed data, show that the Test/Ref ratio (geometric) for some of the parameters are outside of acceptable limits [0.90 - 1.11]. Please redo the spray pattern tests using the image analysis software. Please use 3 distances between 2 cm and 7 cm in the repeat analysis. If the test product has expired, please manufacture 3 fresh batches of product. Please also employ 3 unexpired batches of the reference product in the spray pattern re-testing.

Sincerely yours,

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

AUG 16 2002

Ipratropium Bromide
Nasal Spray, 0.03% (21 µg/spray)
ANDA #75-552
Reviewer: J. Lee
75552A402.doc

Dey Laboratories
Napa, Calif
Submission date:
April 2, 2002

Review of an Amendment

This amendment is in response to the deficiencies conveyed to the sponsor in the review of their in-vitro studies [rev 18 Mar 02; JLee].

1. The expiration date for the batches of the reference product used in the in-vitro studies could not be found. The sponsor was asked to submit this information.

☞ The expiration dates for Atrovent® Nasal Spray 0.03% used in the in-vitro studies were as follows:

lot #	Exp. Date
819012A	6/01
819014A	8/01
819015A	8/01

2. The number of units in each sub-lot of the test product (lot size) was requested.

☞ The number of units in each sub-lot of the test product are as follows:

lot #	Number of Units
W083	———
W084A	———
W084B	———

3. Spray pattern data, both original and reanalyzed data, showed that the Test/Ref ratio (geometric) for some of the parameters were outside of acceptable limits [0.90 – 1.11]. The sponsor was requested to redo the spray pattern tests using the image analysis software. If the test product had expired, the sponsor should manufacture 3 fresh batches of product. The sponsor was also requested to employ 3 unexpired batches of the reference product in the spray pattern re-testing.

☞ The sponsor states that on March 25, 2002, they had faxed to DBE information clarifying that the pump used for their product is the same as that used for Atrovent® and that the data produced are indicative of normal variance in device performance. Considering the means of the shortest and longest distances of the spray pattern, the percent CV for the three lots of Atrovent® range from 9.0 to 24.1. The corresponding range for the three Dey lots range from 7.0 to 23.6. Based on these ranges, there is no distinguishable difference in variability between the test and reference products.

☞ Because all other bioequivalence criteria have been met, the identical nature of the pumps, and the data demonstrating the variance in device performance, the sponsor feels that the nasal spray data which have been submitted to the Agency supports the bioequivalence of the products. The sponsor would appreciate comment and/or clarification on whether the Agency agrees that the bioequivalence criteria have been met.

Comment:

1. Deficiencies 1 and 2 have been satisfactorily addressed.
2. Re: deficiency 3

   The Division of Bioequivalence acknowledges that based on the spray pattern data, the test product demonstrated a similar range of variance (%CV) to the reference product. However, the ratios of geometric means are outside the range of 0.9 - 1.11, currently used by the Division of Bioequivalence for acceptance of in-vitro performance data on nasal sprays.

   The sponsor should note that demonstration of in-vitro equivalence of nasal spray products is based on all tests evaluated individually. Acceptable data on other tests does not assure equivalent spray patterns, if the spray pattern data fail to meet the acceptance criteria.

   As stated in the deficiency letter of 20 March 2002, the sponsor should redo the spray pattern tests using the image analysis software. If the test product has expired, the sponsor should manufacture 3 fresh batches of product. The sponsor should also employ 3 unexpired batches of the reference product in the spray pattern re-testing.

Recommendation:

1. The Division of Bioequivalence still finds the application unacceptable per comment #2.

   Comment #2 should be conveyed to the sponsor.

J. Lee 8/2/02
J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

8/7/2002

Concur: _____ Date: 8/16/2002

for Dale Conner, Pharm. D.

CC: ANDA 75-552
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements:
HFD-655/ JLee E.J. 8/2/02
HFD-650/ Bio Team Leader
HFD-658/ GJPSingh 8/14/02
HFD-617/ Nwaba 8/7/02
HFD-650/ Conner for Dwp 8/16/2002

Printed in draft on \ \
Printed in final on \ \
V:\firmsam\Dey\ltrs&rev\75552A402.doc

BIOEQUIVALENCY - DEFICIENCIES

5. **STUDY AMENDMENT** (STA) Strengths: 0.03%
Outcome: UN

OUTCOME DECISIONS:
UN - Unacceptable (fatal flaw) **IC** - Incomplete

WINBIO COMMENTS:
Sponsor's argument about not repeating the spray pattern testing not accepted.

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-552 APPLICANT: Dey Laboratories

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.03% (21μg/spray)

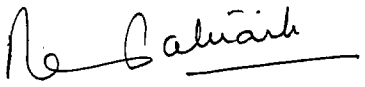
The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. The Division of Bioequivalence acknowledges that based on the spray pattern data, the test product demonstrated a similar range of variance (%CV) to the reference product. However, the ratios of the geometric means are outside the range of 0.9 - 1.11, currently used by the Division of Bioequivalence for acceptance of in-vitro performance data on nasal sprays.

   Please note that demonstration of in-vitro equivalence of nasal spray products is based on <u>all</u> tests evaluated individually. Acceptable data on other tests does not assure equivalent spray patterns, if the spray pattern data fail to meet the acceptance criteria.

   As stated in the deficiency letter of 20 March 2002, you should <u>redo</u> the spray pattern tests using the image analysis software. Please use 3 distances between 2 cm and 7 cm in the repeat analysis. If the test product has expired, please manufacture 3 fresh batches of product. Please also employ 3 unexpired batches of the reference product in the spray pattern re-testing.

Sincerely yours,



for

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

CC: ANDA 75-552
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements:
HFD-655/ JLee C.S. 8/2/02
HFD-650/ Bio Team Leader
HFD-658/ GJPSingh
HFD-617/ Nwaba
HFD-650/ Conner for Rwp 8/16/2002

8/7/02

Printed in draft on \ \
Printed in final on \ \
V:\firmsam\Dey\ltrs&rev\75552A402.doc

BIOEQUIVALENCY - DEFICIENCIES

5. **STUDY AMENDMENT** (STA) Strengths: 0.03%
Outcome: UN

OUTCOME DECISIONS:
UN - Unacceptable (fatal flaw) **IC** - Incomplete

WINBIO COMMENTS:
Sponsor's argument about not repeating the spray pattern testing not accepted.

FEB 13 2003

Ipratropium Bromide
Nasal Spray, 0.03% (21 µg/spray)
ANDA #75-552
Reviewer: J. Lee
75552AN02.doc

Dey Laboratories
Napa, Calif
Submission date:
November 18, 2002
December 27, 2002

Review of an Amendment

The original review of the in-vitro studies contained several deficiencies, one of which was conveyed to the sponsor twice - the repeat of the spray pattern test, since the original results of that test showed that the T/R geometric ratios for some of the parameters were outside the acceptance limits of [0.90 - 1.11]. In a teleconference with the sponsor (17 Sept 02) it was agreed that the sponsor could use ——— equipment for the re-test. The results of the spray pattern re-test are contained in this review.

Products used in spray pattern re-test:

Manufacturer	lot#	Mnfg date	expiry date
Dey	W141	8/02	N/A
Dey	W142	9/02	N/A
Dey	W143	9/02	N/A
Boehringer Ingelheim	156737A	N/A	6/03
Boehringer Ingelheim	157699A	N/A	8/03
Boehringer Ingelheim	158431A	N/A	11/03

Three newly manufactured lots of the Dey product were used in the re-test and new lots of the reference product were obtained as the old lots had expired.

All units were primed prior to obtaining the spray patterns. The firm conducted the spray pattern testing using Method ATM-782-01. Spray patterns were quantitated by (1) fitting an ellipse and (2) secondary pattern analysis. The latter traces the true shape of the spray pattern upon which D_{max}, D_{min} and ovality ratio are calculated. The spray pattern data presented in this review are based on the secondary pattern analysis method. The detailed description can be found on pages 42 - 56, vol 4.1. The complete validation can be found on pages 57 - 74, vol 4.1.

The firm submitted spray pattern data at three distances (2, 4 and 6 cm) from the laser sheet at beginning and end life sectors for the test and reference products. It provided individual results of spray pattern determination in terms of D_{max}, D_{min} and ovality ratio (D_{max}/D_{min}).

The results of the spray pattern re-test for 3 lots and 10 units each of the test and reference formulations are shown below:

Spray Pattern Data (Test Product) and Test/Ref Ratios

PROD.	Sector	Distance (cm)	Plume Formation	Mean Arith (N=30)	Mean Geo (N=30)	Variability (%CV) Within-Lot (N=10)	Variability (%CV) Between-lot (N=3)	Variability (%CV) Total (N=30)	TEST/REF Arith	TEST/REF Geo	p
TEST	BEG	2	Dmax	2.890	2.879	6.84 - 10.93	3.30	8.92	1.02	1.03	0.39
		2	Dmin	2.398	2.388	7.10 - 11.24	2.57	9.29	1.06	1.07	0.02
		2	Oval. Ratio	1.21	1.21	2.57 - 6.48	2.14	4.68	0.96	0.96	0.14
		4	Dmax	4.085	4.060	10.14 - 11.55	5.59	11.38	1.00	1.01	0.95
		4	Dmin	2.787	2.736	14.50 - 22.31	5.37	18.42	1.00	1.01	0.99
		4	Oval. Ratio	1.51	1.48	10.42 - 27.01	2.92	18.56	0.98	0.99	0.74
		6	Dmax	6.516	6.486	7.94 - 12.14	1.89	9.52	1.00	1.00	0.91
		6	Dmin	3.651	3.539	22.29 - 26.26	15.30	24.73	1.02	1.02	0.72
		6	Oval. Ratio	1.88	1.83	20.27 - 22.9	14.63	22.89	0.97	0.98	0.70
	END	2	Dmax	2.498	2.483	8.45 - 12.05	4.93	11.12	0.95	0.96	0.17
		2	Dmin	2.038	2.028	8.68 - 10.85	1.89	9.76	0.98	0.99	0.54
		2	Oval. Ratio	1.23	1.22	3.51 - 5.78	3.21	5.45	0.97	0.97	0.16
		4	Dmax	3.524	3.474	14.37 - 18.62	1.79	16.70	0.98	0.99	0.74
		4	Dmin	2.492	2.463	14.51 - 15.57	3.45	14.79	0.99	0.99	0.86
		4	Oval. Ratio	1.4	1.4	6.76 - 14.03	5.48	12.32	0.99	0.99	0.78
		6	Dmax	5.939	5.881	12.20 - 15.75	3.38	13.89	1.01	1.02	0.80
		6	Dmin	3.390	3.330	17.11 - 19.24	8.40	19.15	0.99	1.00	0.91
		6	Oval. Ratio	1.79	1.77	13.03 - 20.41	7.81	17.85	0.98	1.01	0.80

Spray Pattern Data (REF Product)

PROD.	Sector	Distance	Plume Formation	Mean Arith (N=30)	Mean Geo (N=30)	Variability (%CV) Within-Lot (N=10)	Variability (%CV) Between-lot (N=3)	Variability (%CV) Total (N=30)
REF	BEG	2	Dmax	2.823	2.801	10.27 - 15.43	3.25	12.92
		2	Dmin	2.254	2.241	8.95 - 12.15	2.58	10.45
		2	Oval. Ratio	1.26	1.25	6.02 - 19.57	2.80	13.17
		4	Dmax	4.094	4.039	14.43 - 18.65	6.27	17.10
		4	Dmin	2.788	2.713	19.71 - 26.47	6.14	22.67
		4	Oval. Ratio	1.54	1.49	15.73 - 38.48	3.88	29.06
		6	Dmax	6.536	6.482	9.25 - 15.72	4.53	12.43
		6	Dmin	3.573	3.458	21.12 - 25.22	5.65	23.61
		6	Oval. Ratio	1.93	1.87	21.54 - 30.49	5.94	25.92
	END	2	Dmax	2.617	2.585	10.07 - 22.14	4.75	16.77
		2	Dmin	2.072	2.055	8.70 - 16.93	2.84	12.49
		2	Oval. Ratio	1.27	1.26	8.19 - 18.38	1.60	12.67
		4	Dmax	3.578	3.524	10.65 - 23.60	3.80	19.20
		4	Dmin	2.509	2.484	12.00 - 17.02	2.91	14.59
		4	Oval. Ratio	1.4	1.4	12.31 - 16.23	0.78	14.14
		6	Dmax	5.880	5.776	8.62 - 26.47	2.58	16.80
		6	Dmin	3.409	3.317	16.37 - 27.38	12.53	22.02
		6	Oval. Ratio	1.83	1.74	16.92 - 54.18	15.35	39.98

The within-lot and between-lot variability of the reference product appear to be a little greater than that for the test product at both the beginning and end of life sectors. Total variability of the reference product was greater than that of the test product. With one exception (Dmin at 2 cm) the p-values show no significant differences. All T/R geometric ratios are within the acceptance range of 0.90 - 1.11.

Comment:

1. The spray pattern re-test data is acceptable.

2. All deficiencies have now been addressed.

3. From the bioequivalence perspective, final acceptance of the in-vitro studies for the 0.03% test product is contingent upon acceptance of all in-vitro studies in ANDA 75-553, the 0.06% strength test product from Dey Labs, since some of the in-vitro tests for the 0.03% test product were curtailed/omitted per draft Guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action".

Recommendation:

1. The in-vitro performance studies conducted by Dey Laboratories on its ipratropium bromide nasal spray, 0.03%, batch #W083, W084A, W084B, W141, W142 and W143, comparing it to Atrovent® Nasal Spray, 0.03% has been found acceptable to the Division of Bioequivalence.

2. All bioequivalence criteria have been met.

R. Lee 1/23/03

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 2/5/2003

Concur: Dale P. Conner Date: 2/13/03

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

JLee/jl/01-23-03

cc: NDA #75-552 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-552 APPLICANT: Dey Laboratories

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.03%

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

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

Sincerely yours,

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

CC: ANDA 75-552
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer

V:\FIRMSam\Dey\ltrs&rev\75552AN02.doc
Printed in final on / /

Endorsements: (Final with Dates)
HFD-655/ JLee R.J. 1/23/03
HFD-658/ GJPSingh GJPS 2-10-03
HFD-655/ Bio team Leader
HFD-650/ D. Conner NMR 2/13/03

1/27/03
2/28/03

BIOEQUIVALENCY - ACCEPTABLE submission date: Nov 18, 2002

5. **STUDY AMENDMENT** (STA) Strengths: 0.03%
Outcome: AC

8. **OTHER** (OTH) N/C diskette Strengths: 0.03%
Outcome: AC
Dec 27, 2002

Outcome Decisions: **AC** - Acceptable

WinBio Comments:
All in-vitro studies are now acceptable.

OFFICE OF GENERIC DRUGS
(7) DIVISION OF BIOEQUIVALENCE

ANDA #: 75-552 SPONSOR: Dey Laboratories

DRUG AND DOSAGE FORM: Ipratropium bromide Nasal Spray

STRENGTH(S): 0.03%

TYPES OF STUDIES: in-vitro

CLINICAL STUDY SITE(S): ——— and Dey

ANALYTICAL SITE(S): IL

STUDY SUMMARY: In-vitro studies now acceptable for 0.03% NS. Final acceptance is contingent upon acceptable in-vitro studies

DISSOLUTION: N/A for the 0.06% Nasal Spray. ☆

DSI INSPECTION STATUS

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

PRIMARY REVIEWER: J. Lee BRANCH: II

INITIAL: C.P. DATE: 1/23/03

TEAM LEADER: SG Nerurkar BRANCH: II

INITIAL: [signature] DATE: 2/5/2003

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

INITIAL: [signature] DATE: 2/13/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-552

CORRESPONDENCE

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL.(707) 224-3200 FAX (707) 224-1364

December 31, 1998

Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: Ipratropium Bromide Nasal Spray 0.03%
Original ANDA

Dear Mr. Sporn:

DEY hereby submits this abbreviated new drug application for Ipratropium Bromide Nasal Spray 0.03%.

In accordance with section 505(j)(2)(A) of the Federal Food, Drug and Cosmetic Act, DEY makes the following certifications:

(i) DEY certifies that this submission is for a drug product; the conditions of use prescribed, recommended, or suggested in the proposed labeling have been previously approved for a "listed drug" (i.e. Atrovent® (ipratropium bromide) Nasal Spray 0.03%, NDA 20-393 marketed by Boehringer Ingelheim Pharmaceuticals, Inc.). A copy of the appropriate page from the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") is enclosed in the labeling section.

(ii) The active ingredient in the "listed drug" and in the proposed product is Ipratropium Bromide Monohydrate.

(iii) The route of administration, dosage form and strength for the "listed drug" and the proposed product are topical (nasal), metered spray solution and 0.03%, respectively.

(iv) The proposed product is bioequivalent to the "listed drug". The proposed product and the "listed drug" are administered topically (nasal), contain the same active ingredient (ipratropium bromide) and are produced in the same dosage form (solution). For these reasons, DEY requests exemption from bioequivalence testing.

(v) The labeling for DEY's product is the same as the "listed drug" except for the exclusion of a pediatric (ages 6 to 11) indication for which the innovator has exclusive marketing rights until April 1, 2001, as well as changes that are necessary due to DEY being the manufacturer. Labeling for the "listed drug" and DEY's product is included within this application.

(vi) The items specified in section 505(b)(1)(B) through (F) of the Act are included within this application.

(vii) DEY certifies that one use-patent (4385048) exists for this product. This patent expires on May 24, 2000. There are no other patents claiming the product or use that is the subject of this application. DEY does not intend to market this product prior to expiration of the existing patent.

This ANDA has been organized in compliance with the Guidance for Industry--Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application. One archival copy and one review copy are submitted; each copy is comprised of six volumes. All original signature forms, certifications, and four copies of proposed draft labeling are included in the archival copy. Photocopies of all forms, certifications, and four sets of proposed draft labeling are included within the technical review copy.

A certified copy of this ANDA is being submitted to the field office, attention San Francisco District Director Patricia Ziobro at 1431 Harbor Bay Parkway, Alameda, CA 94502.

An electronic copy of this submission is being prepared and will be filed within 60 days of the date of this application.

Should there by any questions regarding this ANDA, please do not hesitate to contact me by phone (707-224-3200, ext. 475) or fax (707-224-1364).

Sincerely,

Peggy J. Berry

Peggy J. Berry
Regulatory Affairs Senior Manager

ANDA 75-552

Dey, L.P.
Attention: Peggy J. Berry
2751 Napa Valley Corporate Drive
Napa, CA 94558

FEB 4 1999

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated December 31, 1998, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Ipratropium Bromide Nasal Spray, 0.03%.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

We note that you have failed to provide a Field Copy Certification, Debarment Certification and Convictions Statement with an original signature. Please provide these certifications with an original signature.

Your application lacks a components/compositions statement reflecting a unit composition "per spray". In addition, we note you have utilized sodium hydroxide to adjust the pH of the solution and have not included this ingredient in your components/composition statement. Please submit a revised component/composition statement with all active and inactive ingredients utilized in the manufacturing of this drug product.

You have failed to provide the sources for your inactive ingredients. Please note that sources must be provided for all inactives listed.

You have failed to provide a Certificate of Analysis (COA) for sodium hydroxide. Provide a COA for this inactive ingredient.

You have failed to provide a Certificate of Analysis (COA) for the finished dosage form.

In addition, you have failed to provide three separately bound copies of your methods validation package. Please submit three copies in separate binders.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference

about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Carol Holquist
Project Manager
(301) 827-5862

Sincerely yours,

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-552
DUP/Jacket
Division File
HFD-92
Field Copy
HFD-600/Reading File
HFD-610/RWest
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, date 2/4/99
HFD-615/CHolquist, CSO, C. Holquist 1/27/99 date
HFD-625/MSmela/Sup. Chem, date
V:\FIRMSAM\DEY\LTRS&REV\75552.rtf.doc
F/T mjl/1/27/99
ANDA Refuse to File!

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL.(707) 224-3200 FAX (707) 224-1364

Ack for filing 3/8/99
5 month delay
505(j))

22 February 1999

NDA ORIG AMENDMENT
N/AC

Robert L. West, M.S., R. Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: ANDA 75-552
Ipratropium Bromide Nasal Spray 0.03%
Response to FDA letter dated February 4, 1999

Dear Mr. West:

Reference is made to ANDA 75-552 for Ipratropium Bromide Nasal Spray 0.03% and to the FDA letter dated February 4, 1999. This amendment responds to each of the points outlined in the letter. For your convenience in reviewing the information, the FDA's comments are printed in bold italics followed by Dey's responses.

We note that you have failed to provide a Field Copy Certification, Debarment Certification and Convictions Statement with an original signature.

New originals are provided at Tab 1 in the archival copy of this amendment.

Your application lacks a components/composition statement reflecting a unit composition "per spray". In addition, we note you have utilized sodium hydroxide to adjust the pH of the solution and have not included this ingredient in your components/composition statement. Please submit a revised component/composition statement with all active and inactive ingredients utilized in the manufacturing of this drug product.

Sodium hydroxide has been added to the components/composition table as have "per spray" unit composition. While not done for the batch in the original ANDA, Dey's

RECEIVED
FEB 25 1999
GENERIC DRUGS

procedures permit use of hydrochloric acid to adjust pH. Therefore, HCl has been added to the components/composition table at Tab 3.

You have failed to provide the sources for your inactive ingredients. Please note that sources must be provided for all inactives listed.

Sources of inactive ingredients are provided in the original ANDA in section VIII. For your convenience, a table listing sources of all inactives is included at Tab 4.

You have failed to provide a Certificate of Analysis (COA) for sodium hydroxide. Provide a COA for this inactive ingredient.

Certificates of Analysis for sodium hydroxide and Dey's —— approved suppliers of hydrochloric acid have been included in this amendment at Tab 5.

You have failed to provide a Certificate of Analysis (COA) for the finished dosage form

Dey has not typically prepared a COA for the finished dosage form as all of the data are provided and available for review. However, at the request of the FDA, a Certificate of Analysis for the finished dosage form is included in this amendment at Tab 6.

In addition, you have failed to provide three separately bound copies of your methods validation package. Please submit three copies in separate binders.

Three separate bound copies of the methods validation package are provided.

Please do not hesitate to call me at (707) 224-3200 ext. 4750 if you have any questions or require additional information.

Sincerely,

Peggy J. Berry

Peggy J. Berry
Regulatory Affairs Senior Manager

ANDA 75-552

MAR 16 1999

Dey, L.P.
Attention: Peggy J. Berry
2751 Napa Valley Corporate Drive
Napa, CA 94558

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.

Reference is also made to our "Refuse to File" letter dated February 4, 1999 and your amendment February 22, 1999.

NAME OF DRUG: Ipratropium Bromide Nasal Spray, 0.03%

DATE OF APPLICATION: December 31, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 25, 1999

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:

Denise Huie
Project Manager
(301) 827-5848

Sincerely yours,

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Suppo
Office of Generic Drugs
Center for Drug Evaluation and Researc

cc: ANDA 75-552
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-610/R. West
HFD-330
HFD-92
HFD-615/M.Bennett

Endorsements: HFD-615/PRickman, Chief, RSB — date 3/12/99
HFD-615/SMiddleton, CSO S. Middleton — date 3/11/99
HFD-625/MSmela, Sup. Chem. — date
V:\FIRMSAM\DEY\LTRS&REV\75552.ACK
F/T by mjl/3/9/99
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

JUN - 7 1999

ANDA 75-552

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

TO: APPLICANT: Dey Labs PHONE: 707-224-3200

ATTN: Peggy J. Berry FAX: 707-224-1364

FROM: Patty Nguyen PROJECT MANAGER (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on February 22, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Spray, 0.03%.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 4 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

Phone 6/4/99

X:\new\ogdadmin\glossary\biofax.frm

JUN - 7 1999

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-552 APPLICANT: Dey Labs

DRUG PRODUCT: Ipratropium bromide 0.03% nasal solution

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

The submitted in-vitro tests are deficient. All tests should be repeated as follows:

1. The requirements below apply to the following tests:

   A. Unit Spray/Content Uniformity.
   B. Priming, loss of prime and tail off
   C. Droplet size distribution by Malvern Mastersizer/Cascade Impaction
   D. Spray pattern.
   E. Plume geometry

   For all these comparative *in vitro* tests:

   - ☞ The bottles should be actuated using a validated automated actuation device to increase reproducibility. Validation data including the effect of actuation force, actuation velocity and other factors should be submitted.
   - ☞ No fewer than 10 units each of the test and reference products should be tested in a blinded manner.
   - ☞ Data from three batches each of the test and reference products should be submitted, including batch records for all batches of the test product.
   - ☞ SOPs for all tests effective at the time of testing should be submitted. SOPs should describe the automated actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s).
   - ☞ Raw data for <u>all tests</u> should be submitted in the form of paper copies (tables) as well as electronic files (Excel 5.0 spread sheets).
   - ☞ For tests performed at the beginning (B), middle (M), and end (E) or B and E of use life sectors, comparative performance of test and reference products will be assessed at each sector.

With regard to specific tests:

2. <u>Unit Spray/Content Uniformity</u>

   Consistent with the Potency Test described in the 27 June 1989 *Division of Bioequivalence Guidance for the in vitro portion of bioequivalence requirements for metaproterenol sulfate and*

albuterol inhalation aerosols (metered dose inhalers), this test should be performed at beginning, middle, and end of use life of the product after product priming.

The amount of drug per single spray should be determined using a validated analytical procedure (chemical/chromatographic). Assay validation data should be submitted. Determination of amount of drug per spray by weight difference of the bottles is an unacceptable procedure.

3. Spray Pattern

Spray patterns should be determined at three distances from the TLC plate at the beginning and end life sectors, based on single actuations. The spray pattern at end of use life is requested to assure comparative performance of the pump throughout the labeled use of the products. Visualization of the spray patterns should be accomplished using a drug-specific reagent (that will not develop color when tested with placebo). Photographs (not photocopies of photographs) of spray patterns, in color if appropriate, should be analyzed to measure the shortest (D_{min}) and widest (D_{max}) diameters. Reported data should include values of D_{min}, D_{max} and ovality ratio (D_{min}/D_{max}), along with photographs (with superimposed grid for quantitation) and markings indicating D_{min} and D_{max}.

4. Laser Diffraction

Testing should be done at beginning, middle, and end of use life of the product. Measurements should be made at three distances from the orifice to the laser beam. At each distance, measurements should be made at different delay times (minimum of 3) in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time(s). Data should be reported in the form of D_{10}, D_{50}, D_{90} and SPAN $[(D_{90}-D_{10}/D_{50})]$. Data should be reported based on mass (volume). All instrument/computer printouts should also be submitted, including cumulative percent undersize tables and histograms of particle size distribution. Obscuration should be reported for each run, along with the instrument manufacturer's recommended obscuration ranges. The sponsor's reported obscuration range of ——% (set in the SOP) is too low.

Please also explain how the equipment was calibrated for optimum droplet size.

5. Cascade Impactor

Cascade impactor data based on a validated assay should account for mass balance and be reported in the following groups:

1. Adaptor to throat or separator and stage 0,

2. Stage 1

3. Stage 2 to filter.

Because the purpose of the cascade impactor test for this product is to characterize fines only, and not to provide a particle size distribution, you may provide cascade impactor studies only at the beginning and end of canister through-life testing.

6. Plume Geometry

Plume geometry data should describe two side views, at a 90° angle to each other and relative to the axis of the plume, of the aerosol cloud when actuated into space. Plume geometry need only be performed at the beginning of use life. Plumes should be characterized at three or more different delay times after actuation. These times should be chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time(s). Photographs of spray plumes should be used to measure plume length, plume width, and plume (spray cone) angle. Please provide all photographs and data characterizing plume dimensions. Photographs should be overlaid with marked grids for quantitation.

7. Priming and Tail-off Data

Please submit data to support comparative priming characteristics (priming, loss of prime) of the test and reference products. In addition, evidence for comparable tail-off characteristics should be submitted. Data should be based on the amount of drug per actuation using a validated analytical procedure.

Loss of prime data should be submitted for the test and reference products after 24 hours and after 7 days. Prime retention properties of the Dey product should be comparable to Atrovent per labeling:

> *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.*

8. Since the device and formulation are integral components of a nasal spray, you should provide information to support sameness of test and reference devices. Please provide to the extent possible a side-by-side comparison of the pumps and actuators used in the test and reference products. This information should include the manufacturer, model numbers of the pumps, actuators,

actuator inserts and the overcaps. Technical drawings with dimensions should also be submitted, if available.

9. Please provide a quantitative formulation table of your test product in terms of amount/spray.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL.(707) 224-3200 FAX (707) 224-1364

9 August 1999

ND NEW CORRESP
NC Bio

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

RE: ANDA 75-552
Ipratropium Bromide Nasal Spray 0.03%
ANDA 75-553
Ipratropium Bromide Nasal Spray 0.06%

Dear Ms. Hu:

Reference is made to the facsimile dated June 7, 1999 regarding bioequivalency requirements for ANDA 75-552 and the facsimile dated June 29, 1999 regarding bioequivalency requirements for ANDA 75-553. Dey is seeking clarification of several items contained in the requirements.

The fourth bulleted item under Section 1 states, " SOPs should describe the automated actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s)." If mechanical actuations are being performed for all tests, is blinding of products necessary? And if so, to what extent? It seems there is no possibility of bias if the analysts have no role in the performance of the actuator.

The first paragraph of Section B, Priming and Tail-Off Data, states, " Data should be based on the amount of drug per actuation using a validated analytical procedure." Will spray weight calculations suffice since these tests are a measure of pump performance which is strictly a function of spray weight for solution products? Unit spray through bottle life and content uniformity analyses should provide sufficient data to show that the pump is delivering the required amount of drug per spray.

The first paragraph of Section D, Spray Pattern, states, "Spray patterns should be determined at three distances from the TLC plate..." Dey's spray pattern development efforts have shown that a third distance of scientific merit cannot be visualized given the staining techniques available. Will two distances be acceptable?

The first paragraph of Section A, Unit Dose and Uniformity of Unit Dose states, "...this test should be performed at beginning, middle, and end of use life of the product after

product priming." However, page 10 of the June 1999 Draft Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action states, " For BA and BE studies, dose or spray content uniformity data should be determined on primed units at the beginning of unit life, at the middle of unit life, and at the end of unit life[7] for nasal aerosols, and at beginning and end of unit life for nasal sprays." Is beginning and end testing acceptable?

The June 7 facsimile would require Dey to perform the full amount of bioequivalence testing on the 0.03% product whereas the table on page 29 of the Draft Guidance mentioned above outlines a reduced testing regime for low strength products. Can Dey follow the testing regimen outlined in the Draft Guidance?

Please contact me at (707) 224-3200, ext. 4750 if you have questions or need further information and to arrange a time to discuss answers to these questions.

Sincerely,

Peggy J. Berry

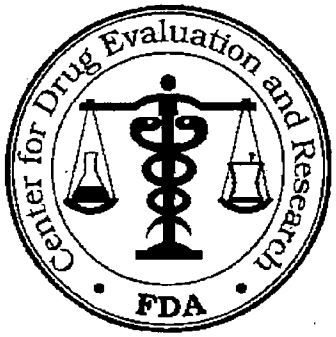
Peggy J. Berry
Regulatory Affairs Senior Manager

APPEARS THIS WAY
ON ORIGINAL

MAJOR AMENDMENT

ANDA 75-552
75-553

AUG 26 1999



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

TO: APPLICANT: Dey, L.P. PHONE: (707) 224-3200

ATTN: Peggy J. Berry FAX: (707) 224-1364

FROM: Michelle Dillahunt PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Spray, 0.03% and 0.06%.

Reference is also made to your amendment(s) dated February 22, 1999.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (10 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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

SPECIAL INSTRUCTIONS: CMC AND LABELING COMMENTS INCLUDED

X:\new\ogdadmin\macros\faxmaj.frm

MD

Redacted 3 page(s)

of trade secret and/or

confidential commercial

information from

8/26/1999 FDA LETTER

f.

g.

h.

i.

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

1. The cGMP compliance of all facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Please be advised that samples of the drug product for methods validation will be requested at a later date once the testing issues have been resolved.

3. Please submit the currently available stability data for both exhibit batches.

4. Labeling deficiencies will also need to be addressed in your reply.

5. We await your response to deficiency letters issued by the Division of Bioequivalence on June 7, 1999 and June 29, 1999 for these ANDAs.

6. Please submit revised drug substance specifications, drug product specifications and stability specifications and also submit copies of all current analytical methods in a separate section of your amendment to facilitate the method validation package.

Sincerely yours,

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

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

ANDA Number: 75-552 **Date of Submission: February 22, 1999**

Applicant's Name: Dey Labs

Established Name: Ipratropium Bromide Nasal Solution, 0.03%

Labeling Deficiencies:

1. GENERAL COMMENT

   a. The established name for this product is Ipratropium Bromide Nasal Solution. Revise all labels and labeling accordingly. Note: "Spray" may appear on labels and labeling separate and away from the established name.

2. CONTAINER (30 mL bottle)

   a. Revise "CAUTION: Federal law…" statement to read "Rx only".

   b. Include the following statement:

      This product may contain Sodium hydroxide and/or Hydrochloric acid.

   c. Revise your storage recommendation to read as follows:

      Store between 15°C to 30°C (59°F to 86°F).

   d. See comment (a) under GENERAL COMMENTS.

3. CARTON (1 X 30 mL)

   a. See comments under CONTAINER.

4. PHYSICIAN'S INSERT

   a. TITLE

      We encourage the inclusion of "Rx only" in this section.

b. Please note, the most recent labeling for the reference listed drug, ATROVENT® Nasal Spray, 0.03%, was approved April 1, 1998. Please revise your insert labeling to be in accord.

c. See comment (a) under GENERAL COMMENTS.

5. PATIENT PACKAGE INSERT

a. Revise your storage recommendation to read as follows:

Store between 15°C to 30°C (59°F to 86°F).

b. See comment (a) under GENERAL COMMENTS.

Please revise your container labels and carton, physician's insert and patient package insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of carton labeling. Submit 4 copies of draft physician's insert and patient package insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

John L. Grace for/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Copy of Reference Listed Drug labeling removed.

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL.(707) 224-3200 FAX (707) 224-1364

30 August 1999

NEW CORRESP
NC

Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place, HFD-600
Metro Park North II
Rockville, MD 20855

Not Needed 4/9/03

RE: ANDA 75-552 Amendment 002
Ipratropium Bromide Nasal Spray 0.03%
FDA Not Approvable facsimile dated 26 August 1999

Dear Mr. Sporn:

This letter is in response to the Not Approvable facsimile from the FDA dated 26 August 1999 for ANDA 75-552 (Ipratropium Bromide Nasal Spray 0.03%). In accordance with 21 CFR 314.120, Dey provides notification to the FDA of the intention to file an amendment to the ANDA which responds to said facsimile. Dey is reserving further comments on the facsimile pending FDA response to several issues applicable to the ANDA. Questions regarding bioequivalence requirements have already been submitted and additional questions regarding facsimile items will be submitted within the next two weeks.

Dey understands that this notice represents an agreement to extend the review period as stated under 21 CFR 314.60 and 314.96 when new information is submitted to the ANDA. The amendment to be submitted by Dey will contain a complete response to all of the FDA issues contained within the 26 August 1999 facsimile and will be indicated plainly as a MAJOR AMENDMENT.

If Dey determines at any time that this strategy will no longer be pursued or will change in any way, it will notify the FDA via letter to the ANDA. If the FDA requires additional information regarding this response, please do not hesitate to contact me at (707) 224-3200, ext. 4750.

Sincerely,

Peggy J. Berry

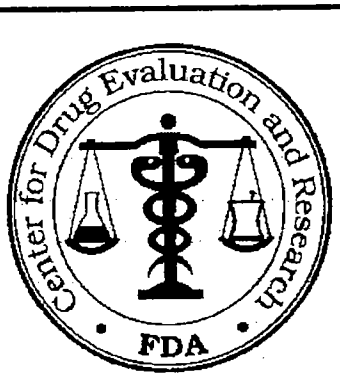
Peggy J. Berry
Regulatory Affairs Senior Manager

CENTER FOR DRUG
REC'D
SEP 0 1 1999
EVALUATION AND RESEARCH

BIOEQUIVALENCY AMENDMENT

ANDA 75-552 and 75-553

OCT - 7 1999



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

TO: APPLICANT: Dey, L.P. PHONE: 707-224-3200

ATTN: Peggy J. Berry FAX: 707-224-1364

FROM: Jennifer Fan PROJECT MANAGER (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on August 9, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Spray, 0.03% and 0.06%.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\glossary\biofax.frm

10/6/99

OCT -7 1999

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:75-552 and 75-553 APPLICANT: Dey Labs

DRUG PRODUCT: Ipratropium bromide, 0.03% and 0.06% Nasal Solution

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following responses are provided:

1. " 'SOPs should describe the automated actuation devices used for each experiment, and procedures used for blinding test and RLD products from the analyst(s).' If mechanical actuations are being performed for all tests, is blinding of products necessary?" etc.

Res: Blinding of products is necessary not only to remove potential bias in the actuations, but extends to postacutuation evaluations, where knowledge of the identity of the product could influence the interpretation of the results. You should describe in the SOPs for each in-vitro test the blinding measures taken (see p. 10 of Draft Guidance for Industry - Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action).

2. Priming and Tail-off Data: " 'Data should be based on the amount of <u>drug per actuation</u> using a validated analytical procedure.' Will spray weight calculations suffice since these tests are a measure of pump performance which is strictly a function of spray weight for solution products?" . . . etc.

Res: Spray weight calculations will not suffice. Amount of <u>drug per actuation</u> should be based on a validated chemical analysis.

3. " 'Spray patterns should be determined at <u>three</u> distances from the TLC plate…' Dey's spray pattern development efforts have shown that a third distance of scientific merit cannot be visualized given the staining techniques available. Will two distances be acceptable?"

Res: The Division of Bioequivalence requires that spray patterns be determined at <u>three</u> distances (e.g. 1, 2.5-3, 5 cm). Based on the Division's experience with aqueous nasal spray products, spray patterns can be measured at distances even greater than 5 cm. You should endeavor to find a staining technique that is <u>specific</u> and can differentiate spray patterns at three <u>different</u> distances.

4. . . " 'Unit Dose and Uniformity of Unit Dose states, . . .this test should be performed at beginning, middle, and end of use life of the product after product priming. However, page 10 of . . Draft Guidance . . beginning of unit life, at the middle of unit life, and at the end of unit life for nasal aerosols, and at

the beginning and end of unit life for nasal sprays.' Is beginning and end testing acceptable?"

Res: Beginning and end testing is acceptable for this drug product per Draft Guidance.

4. "The June 7 facsimile would require Dey to perform the full amount of bioequivalence testing on the 0.03% product whereas the table on page 29 of the Draft Guidance mentioned above outlines a reduced testing regime for low strength products. Can Dey follow the testing regime outlined in the Draft Guidance?"

Res: Dey may follow the reduced testing regime for the 0.03% product per Draft Guidance.

Sincerely yours,

Dale P. Conner

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

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL.(707) 224-3200 FAX (707) 224-1364

Questions 6f, 6g, 7e, and 7i would require pre-review to answer. This is not allowed per OGD procedure. Dey should be advised to respond in the MAJOR Amendment. Dey should be referred to John Grace for the labeling question
M Shmele 11/22/99

NEW CORRESP
NDC

15 November 1999

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

RE: ANDA 75-552
Ipratropium Bromide Nasal Spray 0.03%
ANDA 75-553
Ipratropium Bromide Nasal Spray 0.06%

Dear Ms. Dillahunt:

Reference is made to the facsimiles dated August 26, 1999 regarding the ANDAs noted above. Dey is seeking clarification of several items contained therein.

Items from the facsimiles are printed in bold, followed by Dey's question or comment. To avoid misinterpretation, the items listed under the second #5 on page 3 of the facsimiles will be referred to here as #6. Subsequently, the items listed under #6 will be referred to here as #7.

The following items pertain to the drug product controls:

6f.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 16 1999
OGD

11-17

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

11/15/1999 DEY LETTER

ANDA 75-552

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

Dey Laboratories
Attention: Peggy J. Berry
2751 Napa Valley Corporate Drive
Napa, CA 94558

APR 12 2000

Dear Madam:

This letter is in reference to your Abbreviated New Drug Application (ANDA) dated December 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Spray, 0.03%.

We refer you to our "Not Approvable" letter dated August 26, 1999, which detailed the deficiencies identified during our review of your ANDA. We acknowledge your correspondence dated November 5, 1999, stating your intent to amend the application. The Agency may consider an ANDA applicant's failure to respond to a "Not Approvable" letter within 180 days to be a request by the applicant to withdraw the ANDA under 314.120(b). Your amendment to the application is overdue. You must amend your application within 10 days of receipt of this letter. Otherwise, an action to withdraw the application will be initiated per 21 CFR 314.99.

If you do not wish to pursue approval of this application at this time, you should request withdrawal in accord with 21 CFR 314.65. A decision to withdraw the application would be without prejudice to refiling.

APPEARS THIS WAY
ON ORIGINAL

Please send all correspondence to the following address:

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

Sincerely yours,

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

cc: ANDA # 75-552
DUP/Division File
HFD-610/PRickman
Endorsement:
HFD-617/NMahmud, Chief, RSB, _____ date 4/12/00
HFD-617SMiddleton, CSO, _____ date 4/12/00
Word File
V:\FIRMSAM/DEY/LTRS&REV/75552.OTH
F/T by mjl/4/10/00
10 DAY LETTER!

DEY

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL.(707) 224-3200 FAX (707) 224-1364

Will respond by 6/30/00 / check status then. S. Middleton 5/3/00

18 April 2000

NEW CORRESP
NC

Peter Rickman
Acting Director, Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-552 Amendment 003
Ipratropium Bromide Nasal Spray 0.03%
FDA Request for Amendment dated April 12, 2000

Dear Mr. Rickman:

This letter is in response to the FDA correspondence dated April 12, 2000 requesting amendment to ANDA 75-552. As stated in Amendment 002 to the application dated August 30, 1999, Dey intends to submit a complete response to all of the FDA issues contained in the August 26, 1999 Not Approvable facsimile.

In addition, the amendment will include a complete response to the bioequivalence issues contained in the June 7, 1999 facsimile. Dey is currently conducting the required in vitro bioequivalence testing and expects to have analyzed results available for submission within 60 days.

In order to accommodate the additional time needed for in vitro bioequivalence testing and analysis, Dey requests an extension of the review period as stated in 21 CFR 314.120 (5).

If the FDA prefers that Dey submit an amendment responding to the August 26 facsimile at this time, followed by a subsequent amendment addressing the bioequivalence issues,

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 19 2000
OGD

RW 5/1/00

from the June 7 facsimile, Dey will act on the request.

Please call me at (707) 224-3200, ext. 4750 if you would like to discuss the timing of these responses.

Sincerely,

Peggy J. Berry

Peggy J. Berry
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL.(707) 224-3200 FAX (707) 224-1364

Film will amend NDA by Oct. 31, 2000, then. Check Status 5 Middleton 8/24/00

18 August 2000

NEW CORRESP
NC

Saundra Middleton
Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-552 Amendment 004
Ipratropium Bromide Nasal Spray 0.03%
FDA Request for Amendment

Dear Ms. Middleton:

This letter is in response to your phone call of 17 August 2000 requesting amendment to ANDA 75-552. Reference is also made to Amendment 003 dated 18 April 2000.

In Amendment 003 Dey stated that the in vitro bioequivalence testing needed to respond to the FDA's June 7, 1999 facsimile was then underway and results should be available within 60 days. Delays in completing the testing have pushed back Dey's expected date for filing the submission to October 2000.

In order to accommodate the additional time needed to complete the testing, Dey requests an extension of the review period as stated in 21 CFR 314.120 (5).

Please call me at (707) 224-3200, ext. 4750 if you have any questions.

Sincerely,

Peggy J. Berry
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 22 2000
OGD

1 000

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-1364

27 April 2001

Gary Buehler, Acting Director
Office of Generic Drugs, HFD-650
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

ORIG AMENDMENT
N1AC

RE: ANDA 75-552/A-005
Ipratropium Bromide Nasal Spray 0.03%
MAJOR Amendment/Bioequivalency Amendment

Dear Mr. Buehler:

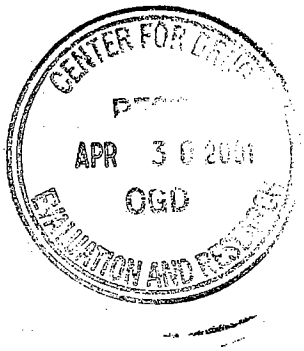
This submission to ANDA 75-552 provides full and complete responses to all deficiencies presented in the FDA's Major Amendment facsimile dated 26 August 1999 and in the FDA's Bioequivalency Amendment facsimile dated 7 June 1999.

Responses to items in both facsimiles are provided in volume 1 of this amendment. Volumes 2 through 6 provide data, analyses, and information pertaining to the *in vitro* bioequivalency testing. Volume 7 is a separate compilation of active raw material specifications, finished product specifications, and all associated test methods.

If you have questions or need additional information, please call me at 707-224-3200, x4750.

Sincerely,

Peggy J. Berry
Director, Regulatory Affairs



01 001

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-1364

10 May 2001

Gary Buehler, Acting Director
Office of Generic Drugs, HFD-650
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

ORIG AMENDMENT
N/AC

RE: ANDA 75-552/A-006
Ipratropium Bromide Nasal Spray 0.03%
MINOR Amendment

Dear Mr. Buehler:

This MINOR Amendment to ANDA 75-552 provides additional information related to the 27 April 2001 amendment.

The following information is included:

- A complete copy of Test Method TM-DY02-03, "Priming and Re-priming of 0.03% Ipratropium Bromide Nasal Sprays, Generated by Automated Actuation during a Bioequivalency Study." A partial copy of the method was included with Bioequivalency Response 1 (volume 1, page 01 364) of the 27 April 2001 amendment.

The CD-ROM labeled Data 0201, which is included in volume 1 of the 27 April 2001 amendment, contains SAS transport files of the data generated by _____ during in vitro bioequivalence testing. The files are password protected and can be accessed using the password '_____'.

If you have questions or need additional information, please call me at 707-224-3200, x4750.

Sincerely,

Peggy J. Berry

Peggy J. Berry
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 11 2001
OGD

01 001

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-1364

31 July 2001

N/AC

Gary Buehler, Acting Director
Office of Generic Drugs, HFD-650
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

ORIG AMENDMENT

RE: ANDA 75-552/A-007
Ipratropium Bromide Nasal Spray, 0.03%
Methods Validation Package

Dear Mr. Buehler:

Enclosed is the Methods Validation Package for Ipratropium Bromide Nasal Spray, 0.03%. This Methods Validation includes analytical methods and validation reports for both drug substance and drug product. Please note the following:

01 001

- [redacted]
- [redacted]
- [redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 02 2001
OGD

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

7/31/2001 DEY LETTER

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-1364

11 October 2001

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

NEW CORRESP
NC

RE: ANDA 75-552
Ipratropium Nasal Spray, 0.03%
General Correspondence: Contact Information

Dear Mr. Buehler:

This letter is to inform you of new contact information for this ANDA. Beginning as of the date of this letter all correspondence should be directed to:

Kim Carneal
Manager, Regulatory Affairs
Documentation and Submissions

707-224-3200, x6076
707-224-1364 (fax)

kim.carneal@deyinc.com

CENTER FOR DRUG EVALUATION AND RESEARCH
OCT 15 2001
OGD

Sincerely,

Peggy J. Berry
Director, Regulatory Affairs

01 001

MINOR AMENDMENT

ANDA's 75-552
75-553

NOV 14 2001

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

TO: APPLICANT: Dey, L.P.

TEL: 707-224-3200

ATTN: Kim Carneal

FAX: 707-224-1364

FROM: Michelle Dillahunt

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Spray, 0.03% and 0.06%.

Reference is also made to your amendment(s) dated: April 27, May 10 and July 31, 2001.

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

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

SPECIAL INSTRUCTIONS: Chemistry and Labeling comments included.

11/14/01

38. Chemistry Comments to be Provided to the Applicant NOV 14 2001

ANDA: 75-552 & 75-553 APPLICANT: Dey L.P.

DRUG PRODUCT: Ipratropium Bromide Nasal Solution, 0.03% and 0.06%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. [redacted]

2.

3.

4.

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

1. Please be advised that samples of the drug substance and drug product for methods validation are being requested concurrent to this letter.

2. Your response must also address the labeling deficiencies identified for ANDA 75-553.

3. Your response regarding bioequivalence of the drug products is pending review.

Sincerely yours,

Paul S Lee

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

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-1364

03 December 2001

Gary Buehler, Director
Office of Generic Drugs, HFD-650
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

ORIG AMENDMENT
N/AM

RE: ANDA 75-552/A-008
Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)
MINOR Amendment

Dear Mr. Buehler:

This MINOR Amendment responds to all deficiencies and comments stated in the FDA facsimile dated 14 November 2001.

Chemistry responses address both this ANDA and ANDA 75-553, Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray), as stated in the FDA comments. Labeling responses address only this ANDA.

If you have questions or need additional information, please call me at 707-224-3200, x6076.

Sincerely,

Kimberly S. Carneal

Kimberly S. Carneal
Manager, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 04 2001

01 001

MINOR AMENDMENT

ANDA's 75-552 (0.03%)
75-553 (0.06%)

FEB 12 2002

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

TO: APPLICANT: Dey , L.P.

TEL: 707-224-3200

ATTN: Kimberly S.Carneal

FAX: 707-224-1364

FROM: Michelle Dillahunt

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Solution.

Reference is also made to your amendment(s) dated: December 3, 2001.

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

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

SPECIAL INSTRUCTIONS: Chemistry comments included.

2/12/02

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

2/12/2002 FDA FAX

11. Please provide a copy of your revised drug product release and stability specifications for both strengths incorporating the changes requested in this communication.

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

1. Your response regarding bioequivalence of the drug products is under review. Deficiencies, if any, will be communicated separately.

2. The Method Validation study is currently in progress.

Sincerely yours,

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

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-1364

28 February 2002

ORIG AMENDMENT
N/AM

Gary Buehler, Director
Office of Generic Drugs, HFD-650
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

RE: ANDA 75-552/A-009
Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)
MINOR Amendment

Dear Mr. Buehler:

This MINOR Amendment responds to all deficiencies and comments stated in the FDA facsimile dated 12 February 2002.

Responses address both this ANDA and ANDA 75-553, Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray).

If you have questions or need additional information, please call me at 707-224-3200, x6076.

Sincerely,

Kimberly S. Carneal
Manager, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
MAR 01 2002

1 001

BIOEQUIVALENCY AMENDMENT

ANDA 75-552

MAR 20 2002

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

APPLICANT: Dey Laboratories TEL: 707-224-3200

ATTN: Peggy Berry FAX: 707-224-1364

FROM: Nina Nwaba PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on April 27, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Spray, 0.03%..

Reference is also made to your amendment(s) dated: December 6, 2001.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

MAR 20 2002 3.1

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-552 APPLICANT: Dey Laboratories

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.03%

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

1. The expiration dates for the batches of the reference product used in the in-vitro studies could not be found. Please submit this information.

2. Please state the number of units in each sub-lot of your test product (lot size).

3. Spray pattern data, both original and reanalyzed data, show that the Test/Ref ratio (geometric) for some of the parameters are outside of acceptable limits [0.90 - 1.11]. Please redo the spray pattern tests using the image analysis software. Please use 3 distances between 2 cm and 7 cm in the repeat analysis. If the test product has expired, please manufacture 3 fresh batches of product. Please also employ 3 unexpired batches of the reference product in the spray pattern re-testing.

Sincerely yours,

Dale P. Conner

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

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-1364

02 April 2002

Gary Buehler, Director
Office of Generic Drugs, HFD-650
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

N/AB

ORIG AMENDMENT

RE: ANDA 75-552/A-010
Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)
Bioequivalency Amendment

Dear Mr. Buehler:

Per my conversation with Ms. Nina Nwaba today, this amendment contains responses to the Agency questions received by Dey on 20 March 2002. As we discussed, shortly after this amendment is submitted I will contact the Agency to determine whether a teleconference should be arranged to discuss the spray pattern data.

For ease of review, the Agency questions are repeated in bold within this amendment, followed by Dey's responses.

1. **The expiration date for the batches of the reference product used in the in-vitro studies could not be found. Please submit this information.**

   Expiration dates for the batches of the reference product, Atrovent (ipratropium bromide) Nasal Spray .03%, used in the in-vitro studies are as follows:

Lot #	Expiration Date
819012A	6/01
819014A	8/01
819015A	8/01

RECEIVED
APR 0 3 2002
OGD / CDER
01.001

2. **Please state the number of units in each sub-lot of your test product (lot size).**

The number of units in each sub-lot of test product are as follows:

Lot #	Number of units
W083	
W084A	
W084B	

3. **Spray pattern data, both original and reanalyzed data, show that the Test/Ref ratio (geometric) for some of the parameters are outside of acceptable limits [0.90 – 1.11]. Please redo the spray pattern tests using the image analysis software. Please use 3 distances between 2 cm and 7 cm in the repeat analysis. If the test product has expired, please manufacture 3 fresh batches of product. Please also employ 3 unexpired batches of the reference product. Please also employ 3 unexpired batches of the reference product in the spray pattern re-testing.**

On 25 March 2002 Dey submitted facsimile information to the Agency clarifying that the pump used for Dey's product is the same as that used for Atrovent and that the data produced are indicative of normal variance in device performance. The last table of the facsimile (see attached) reformats the data provided in the bioequivalency amendment (A-005 dated 27 April 2001) to highlight the nasal spray pattern, especially as it relates to the Atrovent data. Considering the means of the shortest and longest distances of the spray pattern, the percent coefficient of variance for the three lots of Atrovent range from 9.0 to 24.1. The corresponding range for the three Dey lots range from 7.0 to 23.6. Based on these ranges, there is no distinguishable difference in variability between the test and reference articles.

Because all other bioequivalence criteria have been met, the identical nature of the pumps, and the data demonstrating the variance in device performance, we feel that the nasal spray data which have been submitted to the Agency supports the bioequivalence of the products. To facilitate launch, we would appreciate comment and/or clarification as soon as possible on whether the Agency agrees that the bioequivalence criteria have been met.

Thank you in advance for your consideration. I can be reached at 707-224-3200, x4750 and am looking forward to hearing from you.

Sincerely,

Michelle A. Carpenter

Michelle A. Carpenter
VP, Regulatory Affairs and Clinical Development

APPEARS THIS WAY
ON ORIGINAL

01.003

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-1364

26 April 2002

ORIG AMENDMENT
N/AM

Gary Buehler, Director
Office of Generic Drugs, HFD-650
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

RE: ANDA 75-552/A-011
Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)
Telephone Amendment

Dear Mr. Buehler:

This Telephone Amendment responds to FDA requests made in a 23 April 2002 teleconference with Mike Smela, Chemistry Team Leader, and Mujahid Shaikh, Chemistry Reviewer.

Comments stated by the Agency are printed in bold followed by Dey's responses.

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

4/26/2002 DEY LETTER

BIOEQUIVALENCY AMENDMENT

ANDA 75-552

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)

AUG 20 2002

APPLICANT: Dey Lab

TEL: 707-224-3200 ext 4750

ATTN: Michelle Carpenter

FAX: 707-224-1364

FROM: Nina Nwaba

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on April 2, 2002, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Solution 0.03 %.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1_ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

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

AUG 20 2002

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-552 APPLICANT: Dey Laboratories

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.03% (21μg/spray)

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

1. The Division of Bioequivalence acknowledges that based on the spray pattern data, the test product demonstrated a similar range of variance (%CV) to the reference product. However, the ratios of the geometric means are outside the range of 0.9 - 1.11, currently used by the Division of Bioequivalence for acceptance of in-vitro performance data on nasal sprays.

   Please note that demonstration of in-vitro equivalence of nasal spray products is based on all tests evaluated individually. Acceptable data on other tests does not assure equivalent spray patterns, if the spray pattern data fail to meet the acceptance criteria.

   As stated in the deficiency letter of 20 March 2002, you should redo the spray pattern tests using the image analysis software. Please use 3 distances between 2 cm and 7 cm in the repeat analysis. If the test product has expired, please manufacture 3 fresh batches of product. Please also employ 3 unexpired batches of the reference product in the spray pattern re-testing.

Sincerely yours,

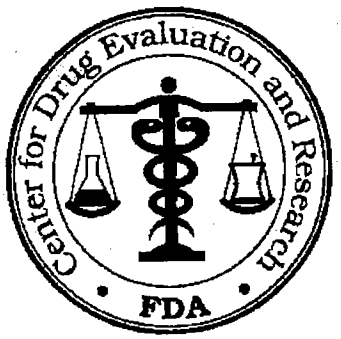
for Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

ANDA 75-552

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)

AUG 29 2002



TO: APPLICANT: Dey L.P.

TEL: 707-224-3200

ATTN: Michelle A. Carpenter

FAX: 707-224-1364

FROM: Peter Chen

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Nasal Solution, 0.03%.

Reference is also made to your amendment(s) dated: ~~April 2~~, April 26, 2002. PC 9/5/02

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

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

SPECIAL INSTRUCTIONS: Chemistry comment included.

PC 8/29/02

AUG 29 2002

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-552 APPLICANT: Dey L.P.

DRUG PRODUCT: Ipratropium Bromide Nasal Solution, 0.03%

The deficiencies presented below represent Minor deficiencies.

Bioequivalence for this product has not been demonstrated. Please submit your response to the deficiency letter dated August 20, 2002. If a new batch(es) of drug product is manufactured to address the bioequivalence deficiencies, please provide a Certificate of Analysis and confirmation that the process and controls currently provided in the ANDA were used to manufacture the batch(es).

Sincerely yours,

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

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-1364

11 September 2002

Gary Buehler, Director
Office of Generic Drugs, HFD-650
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

NEW CORRESP
NC

RE: ANDA 75-552
Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)
Response to Not Approvable Facsimile Dated 29 August 2002

Dear Mr. Buehler:

This letter is in response to the Not Approvable facsimile dated 29 August 2002 for ANDA 75-552. Dey hereby provides notification of the intention to file an amendment to the ANDA which will include a full response to all deficiencies listed in the facsimile. The amendment will be identified as a MINOR Amendment.

If you should have any questions or require additional information, please call me at 707-224-3200, x4750.

Sincerely,

Michelle A Carpenter

Michelle A. Carpenter, J.D.
Vice President, Regulatory and Clinical Affairs.

NAI
9/17/02

RECEIVED
SEP 13 2002
OGD / CDER

DEY, L.P.
2751 Napa Valley Corporate Drive
Napa, CA 94558
TEL. (707) 224-3200 FAX (707) 224-1364

18 November 2002

ORIG AMENDMENT

N/A

Gary Buehler, Director
Office of Generic Drugs, HFD-650
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20857

RE: ANDA 75-552/A-012
Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)
MINOR AMENDMENT/BIOEQUIVALENCYAMENDMENT
Response to FDA facsimiles dated 29 August 2002 and 20 August 2002

Dear Mr. Buehler:

This MINOR AMENDMENT/BIOEQUIVALENCY AMENDMENT responds to all deficiencies listed in the FDA facsimiles dated 29 August 2002 and 20 August 2002 (see attached) for ANDA 75-552, Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray). The content of this amendment was discussed during a teleconference conducted 17 September 2002 between Dey and the FDA.

As agreed during the teleconference, Dey has repeated spray pattern testing as a parameter for demonstrating bioequivalence between the Dey product and the reference listed drug. Test results show that the ratios of geometric means of test product, Dey's Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray), to reference product, Atrovent® (ipratropium bromide) Nasal Spray .03%, fall within the FDA required 0.90 to 1.11 range.

Samples from three recently manufactured batches of the Dey product were tested, along with samples from three unexpired batches of Atrovent. A table listing Dey lot numbers and manufacture dates is included in Appendix 1 along

RECEIVED
NOV 21 2002
OGD/CDER

with a table of Atrovent lot numbers and expiration dates. Certificates of Analysis for the three lots of Dey product are provided in Appendix 2.

As further agreed during the teleconference, testing was performed using ——— equipment manufactured by ———. Distances of 2, 4, and 6 cm from the actuator tip were utilized. A report, ATR 782-09, summarizing the results of the testing, along with raw data listings, is included in Appendix 3.

The test method, ATM 782-01, is included in Appendix 4. The validation report, ATR 782-08, for the method is included in Appendix 5. Representative photographs of how the data is quantitated are included in a CD found in Appendix 6. Photocopies of the photographs are included in the same appendix.

Dey certifies that the method of manufacture for the three batches of Dey product used in the conduct of the spray pattern testing is consistent with that submitted in the MAJOR AMENDMENT (A-005) dated 27 April 2001.

If you have any questions regarding the content of this submission, please contact me at 707-224-3200 x4750.

Sincerely,

Michelle A Carpenter

Michelle A. Carpenter, J.D.
VP, Regulatory and Clinical Affairs