CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-553

***Name*:** Ipratropium Bromide Nasal Solution, 0.06%, (Nasal Spray), 0.042 mg/spray

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-553

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-553

APPROVAL LETTER

ANDA 75-553

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, 0.06%, (Nasal Spray), 0.042 mg/spray, packaged in a 15 mL bottle fitted with a metered nasal spray pump.

Reference is also made to your amendments dated April 30, and December 27, 2002. We also acknowledge your correspondence dated December 27, 2002, addressing the I-327 exclusivity listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the Orange Book.

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, 0.06%, (Nasal Spray) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Atrovent® Nasal Spray, 0.06%, 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 75-553
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

3/28/2003

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F/T by

APPROVAL

3/14/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-553

LABELING

DEY

00356101

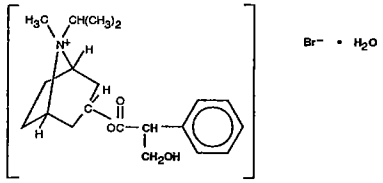
Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray)

Rx only

Prescribing Information

APPROVED MAR 31 2003

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:



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 0.06% (Nasal Spray) is a metered-dose, manual pump spray unit which delivers 42 mcg ipratropium bromide (on an anhydrous basis) per spray (70 µL) 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 165 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 adult volunteers, naturally-acquired common cold pediatric patients, or perennial rhinitis adult 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 84 mcg of ipratropium bromide per nostril three times a day in patients 5-18 years old (n=42) with a naturally-acquired common cold, the mean amount of the total dose excreted unchanged in the urine of 7.8% was comparable to 84 mcg per nostril four times a day in an adult induced common cold population (n=22) of 7.3 to 8.1%. Plasma ipratropium concentrations were relatively low (ranging from undetectable up to 0.62 ng/mL). No correlation of the amount of the total dose excreted unchanged in the urine (Ae) with age or gender was observed in the pediatric population.

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

Drug-Drug 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, Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) in adult patients (n=22) with induced colds, (84 mcg/nostril four times a day) and in pediatric patients (n=45) with naturally acquired common colds (84 mcg/nostril three times a day) had no significant effects on pupillary diameter, heart rate, or systolic/diastolic blood pressure.

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 0.06% (Nasal Spray) were conducted in patients with rhinorrhea associated with naturally occurring common colds. In two controlled four day comparisons of Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) (84 mcg per nostril, administered three or four times daily; n=352) with its vehicle (n=351), there was a statistically significant reduction of rhinorrhea, as measured by both nasal discharge weight and the patients' subjective assessment of severity of rhinorrhea using a visual analog scale. These significant differences were evident within one hour following dosing. There was no effect of Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) on degree of nasal congestion or sneezing. The response to Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) did not appear to be affected by age or gender. No controlled clinical trials directly compared the efficacy of three times daily versus four times daily treatment.

INDICATIONS AND USAGE Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) is indicated for the symptomatic relief of rhinorrhea associated with the common cold for adults and children age 5 years and older. Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) does not relieve nasal congestion or sneezing associated with the common cold.

The safety and effectiveness of the use of Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) beyond four days in patients with the common cold has not been established.

CONTRAINDICATIONS Ipratropium Bromide Nasal Solution 0.06% (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 0.06% (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 0.06% (Nasal Spray) comes into direct contact with the eyes. Patients should be instructed to avoid spraying Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) in or around the 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 0.06% (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 70 and 35 times the maximum recommended daily intranasal dose in adults, respectively,and approximately 45 and 25 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 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

ATTENTION PHARMACIST – DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

DEY

Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray)

APPROVED MAR 31 2003

Patient's Instructions for Use

Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) is indicated for the symptomatic relief of rhinorrhea (runny nose) associated with the common cold for adults and children age 5 years and older. Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) does not relieve nasal congestion or sneezing associated with the common cold. Do not use Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) for longer than four days unless instructed by your physician. Read complete instructions carefully and use only as directed.

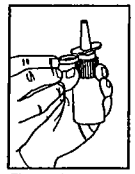


Figure 1

To Use:

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

Figure 2

2. The nasal spray pump must be primed before Ipratropium Bromide Nasal Solution 0.06% (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.

3. Before using Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray), blow your nose gently to clear your nostrils if necessary.

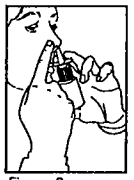


Figure 3

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.

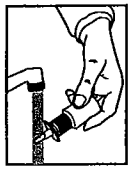
6. After spraying the nostril and removing the unit, tilt your head backwards for a few seconds to let the spray spread over the back of the nose.

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. You should not take extra doses or stop using Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) without consulting your physician.



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.

Figure 4

Caution:
Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) is intended to relieve your rhinorrhea (runny nose) with regular use. It is therefore important that you use Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) as prescribed by your physician. For most patients, some improvement in runny nose is usually apparent following the first dose of treatment with Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray). Do not use Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) for longer than four days unless instructed by your physician.

Do not spray Ipratropium Bromide Nasal Solution 0.06% (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 0.06% (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 0.06% (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

03-561-01 November 2001

125 mg/kg in rabbits. These doses correspond, in each species respectively, to approximately 60, 12,000, and 3,000 times the maximum recommended daily intranasal dose in adults on a mg/m² basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg, respectively, (approximately 20 and 45 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 1,100 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 0.06% (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 0.06% (Nasal Spray) is administered to a nursing woman.

Pediatric Use The safety of Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) at a dose of two sprays (84 mcg) per nostril three times a day (total dose 504 mcg/day) for two to four days has been demonstrated in two clinical trials involving 362 pediatric patients 5-11 years of age with naturally acquired common colds. In this pediatric population, Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) had an adverse event profile similar to that observed in adolescent and adult patients.

When ipratropium bromide was concomitantly administered with an oral decongestant (pseudoephedrine HCl) in 122 children ages 5-12 years, and concomitantly administered with an oral decongestant/antihistamine combination (pseudoephedrine HCl/chlorpheniramine maleate) in 123 children ages 5-12 years, adverse event profiles were similar to ipratropium bromide alone. The effectiveness of Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) for the treatment of rhinorrhea associated with the common cold in this pediatric age group is based on extrapolation of the demonstrated efficacy of Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) in adolescents and adults with this condition and the likelihood that the disease course, pathophysiology, and the drug's effect are substantially similar to that of adults. The recommended dose for the pediatric population is based on cross-study comparisons of the efficacy of Ipratropium Bromide Nasal Solution 0.06% (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 0.06% (Nasal Spray) in pediatric patients under 5 years of age have not been established.

ADVERSE REACTIONS Adverse reaction information on Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) in patients with the common cold was derived from two multicenter, vehicle-controlled clinical trials involving 1,276 patients (195 patients on Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray), 352 patients on Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray), 189 patients on ipratropium bromide nasal spray 0.12%, 351 patients on vehicle and 189 patients receiving no treatment).

The following table shows adverse events reported for patients who received Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) at the recommended dose of 84 mcg per nostril, or vehicle, administered three or four times daily, where the incidence is 1% or greater in the ipratropium bromide group and higher in the ipratropium bromide group than in the vehicle group.

	% of Patients Reporting Events[1]	
	Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) (N=352)	Vehicle Control (N=351)
Epistaxis[2]	8.2%	2.3%
Dry Mouth/Throat	1.4%	0.3%
Nasal Congestion	1.1%	0.0%
Nasal Dryness	4.8%	2.8%

[1] This table includes adverse events for which the incidence was 1% or greater in the ipratropium bromide group and higher in the ipratropium bromide group than in the vehicle group.
[2] Epistaxis reported by 5.4% of ipratropium bromide patients and 1.4% of vehicle patients, blood tinged nasal mucus by 2.8% of ipratropium bromide patients and 0.9% of vehicle patients.

Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) was well tolerated by most patients. The most frequently reported adverse events were transient episodes of nasal dryness or epistaxis. The majority of these adverse events (96%) were mild or moderate in nature, none was considered serious, and none resulted in hospitalization. No patient required treatment for nasal dryness, and only three patients (<1%) required treatment for epistaxis, which consisted of local application of pressure or a moisturizing agent (e.g., petroleum jelly). No patient receiving Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) was discontinued from the trial due to either nasal dryness or bleeding.

Adverse events reported by less than 1% of the patients receiving Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) during the controlled clinical trials which are potentially related to ipratropium bromide's local effects or systemic anticholinergic effects include: taste perversion, nasal burning, conjunctivitis, coughing, dizziness, hoarseness, palpitation, pharyngitis, tachycardia, thirst, tinnitus and blurred vision. Additional anticholinergic effects noted with other ipratropium bromide dosage forms (ipratropium bromide inhalation solution, ipratropium bromide inhalation aerosol and Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)) include: precipitation or worsening of narrow-angle glaucoma, urinary retention, prostate disorders, constipation and bowel obstruction.

There were no reports of allergic-type reactions in the controlled clinical trials. Allergic-type reactions such as skin rash, angioedema of the 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 for three times daily versus four times daily.

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 two bottles of Ipratropium Bromide Nasal Solution 0.06% (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 mm Hg 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 6,000 and 3,800 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m² basis) 1,700 mg/kg in rats (approximately 21,000 and 13,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m² basis) and 400 mg/kg in dogs (approximately 16,000 and 10,000 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 0.06% (Nasal Spray) is two sprays (84 mcg) per nostril three or four times daily (total dose 504 to 672 mcg/day) for symptomatic relief of rhinorrhea associated with the common cold in adults and children age 5 years and older. Optimum dosage varies with response of the individual patient. The recommended dose of Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) for children age 5-11 years is two sprays (84 mcg) per nostril three times daily (total dose of 504 mcg/day).

The safety and effectiveness of the use of Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) beyond four days in patients with the common cold have not been established.

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 0.06% (Nasal Spray) is supplied in a white high density polyethylene (HDPE) bottle fitted with a metered nasal spray pump, a purple safety clip to prevent accidental discharge of the spray, and a clear plastic dust cap. It contains 16.6g of product formulation, 165 sprays, each delivering 42 mcg (70 µL) of ipratropium per spray, or 10 days of therapy at the maximum recommended dose (two sprays per nostril four 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

03-561-01 Printed: November 2001

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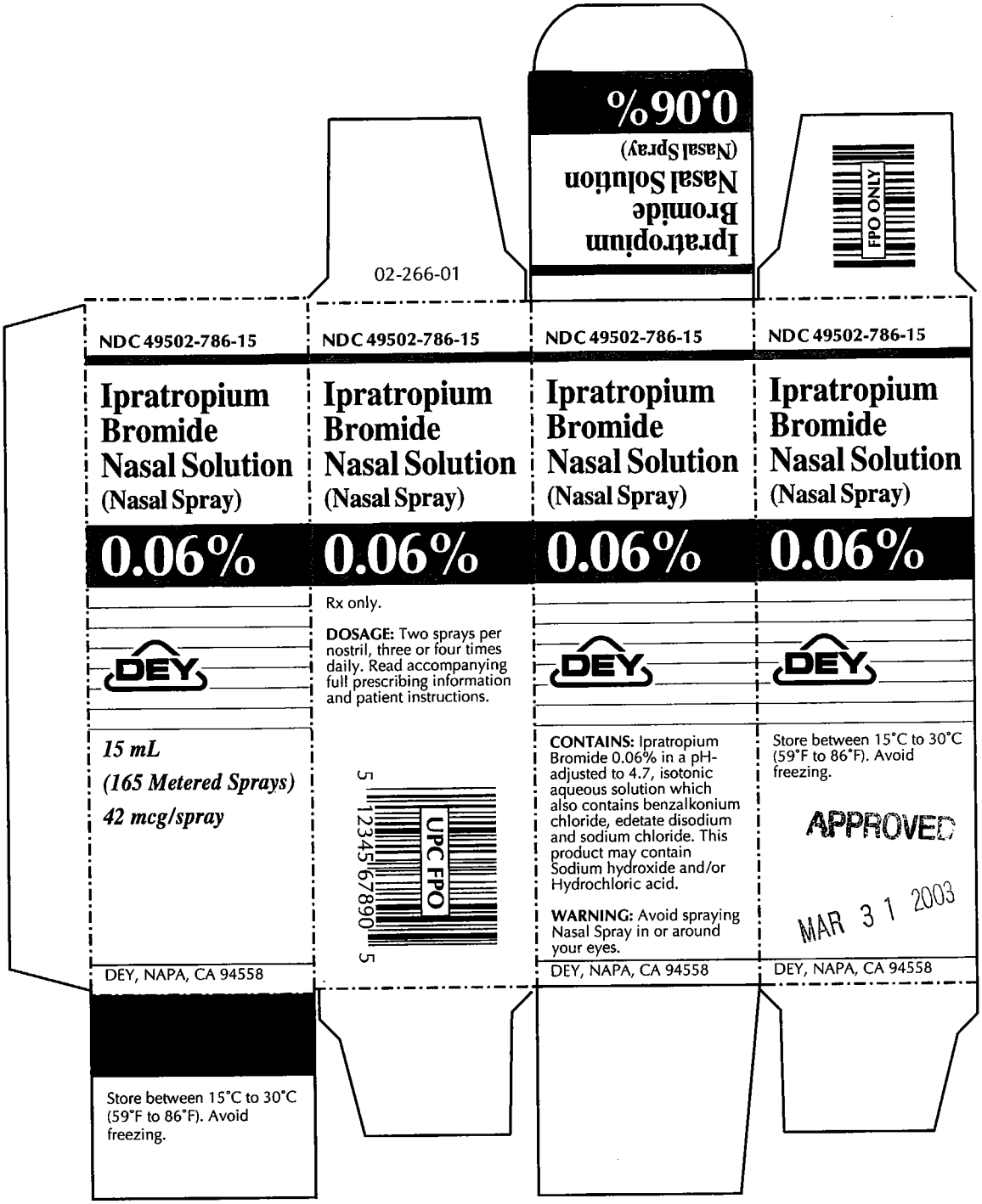
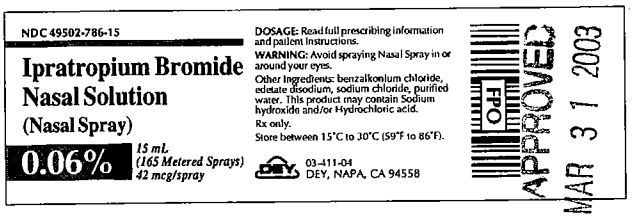




CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-553

LABELING REVIEWS

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

ANDA Number: 75-553 Date of Submission: February 22, 1999

Applicant's Name: Dey Labs

Established Name: Ipratropium Bromide Nasal Solution, 0.06%

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

   a. See comment (a) under GENERAL COMMENTS.

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

   c. Include the following statement:

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

   d. Revise your storage recommendation to read as follows:

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

3. CARTON

   a. See comment (a) under GENERAL COMMENTS.

   b. See comments under CONTAINER.

4. PHYSICIAN'S INSERT

a. See comment (a) under GENERAL COMMENTS.

b. Please note the most recent labeling for the reference listed drug, ATROVENT® Nasal Spray, was approved November 9, 1998. Please revise your insert labeling to be in accord with the enclosed copy of this labeling.

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).

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 final printed 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?

Container Labels: (15 mL)

Carton Labeling: (1 x 15 mL)

Professional Package Insert Labeling:

Patient Package insert:

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, 0.06%

NDA Number: 20-394/S-001
NDA Drug Name: Ipratropium Bromide Nasal Spray, 0.06%
NDA Firm: Boerhinger Ingelheim

Date of Approval of NDA Insert and supplement #: November 9, 1998

Has this been verified by the MIS system for the NDA? Yes.

Was this approval based upon an OGD labeling guidance? NO

Basis of Approval for the Container Labels: 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, 0.06% (Boerhinger Ingelheim; NDA#20-394; Approved November 9, 1998).

2. Patents/Exclusivities

   Patent#4385048- U-119 (Treatment of Nasal Hypersecretion)
   Expires: May 24, 2000.
   Exclusivity - NDF
   Expired October 28, 1998.
   Exclusivity - I-243 (Use in the symptomatic relief of rhinorrhea associated with the common cold in children age 5 to 11 years.)
   Expires: November 9, 2001

   The applicant states it will not market until the expiration of the exclusivity. See Vol. 1.1, page 6.

3. The product is manufactured by Dey, 2751 Napa Valley Corporate Drive, Napa, CA 94558. See Vol. 1.1, page 100250.

4. Outside firms are utilized for testing purposes only. See Vol. 1.2, page 100261.

5. Container/Closure

   The container/closure system is 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 100397 and 100399.

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 100025A.

7. Product Line

   Supplied as 15 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 15 mL bottle is designed to deliver 165 sprays (42 mcg each). See Vol. 1.1, page 100025A.

8. Components/Composition

Innovator:
Active: Ipratropium Bromide, 0.06%
Inactive: benzalkonium chloride
Edetate disodium
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Purified water

Applicant:
Active: Ipratropium Bromide, 0.06%
Inactive: benzalkonium chloride
Edetate disodium
Sodium chloride
Purified water
Sodium hydroxide
Hydrochloric acid

See Vol. 1.1, page 7 and 100039.

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 the 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 100025A.

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

Reviewer: J. Watkins **Date:** 4/14/99

Team Leader: John Grace **Date:** 4/15/1999

cc:
ANDA: 75-553
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
V:\FIRMSAM\DEY\LTRS&REV\75553na1.1
Review

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

ANDA Number: 75-553 **Date of Submission: April 27, 2001 and May 10, 2001**

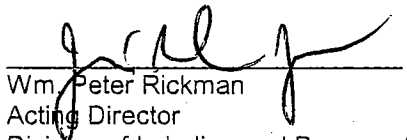
Applicant's Name: Dey Labs
Established Name: Ipratropium Bromide Nasal Solution, 0.06% (Nasal Spray)
Labeling Deficiencies:

1. GENERAL COMMENT
   a. Please update your exclusivity statement.
   b. We note your comment on revising the product name. However, "Nasal Spray" could be used as indicated below. The established name for this product is Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray). Revise all labels and labeling accordingly.
2. CONTAINER 15 mL - See comment under GENERAL COMMENTS.
3. CARTON 15 mL - See comment under GENERAL COMMENTS.
4. PHYSICIAN'S INSERT-
   a. See comment (a) under GENERAL COMMENTS.
   b. Please comment on the layout of your insert. The text appears in different directions. The front side of the insert and backside are printed in different directions. Please revise and /or comment.
   c. Several paragraphs breaks are needed in your insert. Please insert a paragraph break at the following locations:
      i. Adverse Reactions – current 3rd paragraph at "Adverse events reported by less than 1%...
      ii. Adverse Reactions – current 4th paragraph at" No controlled trial was conducted...
      iii. OVERDOSAGE – At "oral median lethal doses of...".
      iv. DOSAGE AND ADMINSTRATION – Current 2nd paragraph at "Initial pump priming requires...
   d. PRECAUTIONS. Pediatric Use
      i. 2nd second sentence - ...pediatric population ipratropium Bromide... (combined sentences).
      ii. Create a paragraph break at "When Ipratropium bromide was concomitantly administered...
   e. Revise your storage recommendation to read as follows: Store between 15°C to 30°C (59°F to 86°F).
5. PATIENT PACKAGE INSERT – The layout of your insert makes it impossible for the patient to receive the full text. Perforations appear on opposite sides of the insert. The text should be positioned so that the patient gets the full running text.

Please revise your labels and labeling, as instructed above, and submit 12 final print labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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



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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling?
Container Labels: (15 mL)
Carton Labeling: (1 x 15 mL)
Professional Package Insert Labeling:
Patient Package insert:
Revisions needed post-approval:
BASIS OF APPROVAL:

Patent Data For NDA – 20-394: no unexpired patents. Paragraph II filed.

Exclusivity Data/

supplement No	Expiration	Use Code	Description	Labeling Impact
s-001/app. Nov. 9. 98	Nov 09, 01	I-243	Use in the symptomatic relief of rhinorrhea associated with the common cold in children age 5 to 11 years	Has in insert
s-004/app 10/27/00	*	*	Use in the symptomatic relief of rhinorrhea associated with seasonal allergic rhinitis in patients 5 years of age and older	No impact firms needs to update statment

***consulted Ms Holovac on whether they will get exclusivity she said they will but it will take a couple of weeks. Firms will need to update exclusivity statement once it is available publicly.**
Was this approval based upon a petition? No.
What is the RLD on the 356(h) form: atrovent
NDA Number: 20-394
NDA Drug Name: Ipratropium bromide Nasal spray 0.06%
NDA Firm: Boehringer Ingel
Date of Approval of NDA Insert and supplement #: s-001 approved in FPL Jan. 22, 99.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: 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.
Other comments: S-004 is protected by exclusivity

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			X

unacceptable, has the firm been notified?			
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	

APPEARS THIS WAY
ON ORIGINAL

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, 0.06% (Boerhinger Ingelheim; NDA#20-394; Approved November 9, 1998).
2. Patents/Exclusivities

   Patent#4385048- U-119 (Treatment of Nasal Hypersecretion)
   Expires: May 24, 2000.

   Exclusivity – NDF
   Expired October 28, 1998.

   Exclusivity - I-243 (Use in the symptomatic relief of rhinorrhea associated with the common cold in children age 5 to 11 years.)
   Expires: November 9, 2001

   The applicant states it will not market until the expiration of the exclusivity. See Vol. 1.1, page 6.
3. The product is manufactured by Dey, 2751 Napa Valley Corporate Drive, Napa, CA 94558. See Vol. 1.1, page 100250.
4. Outside firms are utilized for testing purposes only. See Vol. 1.2, page 100261.
5. Container/Closure
   The container/closure system is 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 100397 and 100399.
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 100025A.
7. Product Line
   Supplied as 15 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 15 mL bottle is designed to deliver 165 sprays (42 mcg each). See Vol. 1.1, page 100025A.
8. Components/Composition
   Innovator:
   Active: Ipratropium Bromide, 0.06%
   Inactive: benzalkonium chloride
   Edetate disodium
   Sodium chloride
   Sodium hydroxide
   Hydrochloric acid
   Purified water

   Applicant:
   Active: Ipratropium Bromide, 0.06%
   Inactive: benzalkonium chloride
   Edetate disodium
   Sodium chloride
   Purified water

Sodium hydroxide
Hydrochloric acid

See Vol. 1.1, page 7 and 100039.

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 the 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 100025A.

Date of Review: June 20, 2001 **Date of Submission: May 10,**

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cc:

ANDA: 75-553
DUP/DIVISION FILE
HFD-613/APayne/Jbarlow for JGrace (no cc)
V:\FIRMSAM\DEY\LTRS&REV\75553na2.I
Review

APayne 6/21/01
J 6/22/01

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 75-553 **Date of Submission: December 3, 2001**
Applicant's Name: Dey Labs
Established Name: Ipratropium Bromide Nasal Solution, 0.06% (Nasal Spray)

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling?
Container Labels: (15 mL) submitted Dec. 3, 2001 vol.
Carton Labeling:(1 x 15 mL) submitted Dec 3, 2001 vol.
Professional Package Insert Labeling: #03-561-01 rev. Nov. 2001. Submitted December 3, 2001 vol.
Patient Package insert: Attached to Professional Package insert labeling.
Revisions needed post-approval:
BASIS OF APPROVAL:

Patent Data For NDA – 20-394: no unexpired patents. Paragraph II filed.

Exclusivity Data/

supplement No	Expiration	Use Code	Description	Labeling Impact
s-001/app. Nov. 9. 98	Nov 09, 01	I-243	Use in the symptomatic relief of rhinorrhea associated with the common cold in children age 5 to 11 years	Same As
s-004/app 10/27/00	Oct. 27, 2003	I-327	Use in the symptomatic relief of rhinorrhea associated with seasonal allergic rhinitis in patients 5 years of age and older	No impact firms needs to update statment Not used.

***consulted Ms Holovac on whether they will get exclusivity she said they will but it will take a couple of weeks. Firms will need to update exclusivity statement once it is available publicly.**
Was this approval based upon a petition? No.
What is the RLD on the 356(h) form: atrovent
NDA Number: 20-394
NDA Drug Name: Ipratropium bromide Nasal spray 0.06%
NDA Firm: Boehringer Ingel
Date of Approval of NDA Insert and supplement #: S-001 approved 11/09/98, approved in FPL Jan. 22, 99.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: 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.
Other comments: S-004 is protected by exclusivity

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, 0.06% (Boerhinger Ingelheim; NDA#20-394; Approved November 9, 1998).
2. Patents/Exclusivities

   Patent#4385048- U-119 (Treatment of Nasal Hypersecretion)
   Expires: May 24, 2000.

   Exclusivity – NDF
   Expired October 28, 1998.

   Exclusivity - I-243 (Use in the symptomatic relief of rhinorrhea associated with the common cold in children age 5 to 11 years.)
   Expires: November 9, 2001

   The applicant states it will not market until the expiration of the exclusivity. See Vol. 1.1, page 6.
3. The product is manufactured by Dey, 2751 Napa Valley Corporate Drive, Napa, CA 94558. See Vol. 1.1, page 100250.
4. Outside firms are utilized for testing purposes only. See Vol. 1.2, page 100261.
5. Container/Closure
   The container/closure system is a high density polyethylene bottle and nasal pump assembly. The bottle has a pre-printed pressure sensitive label that will be [redacted] stamped with lot number and expiration date. See Vol. 1.2, page 100397 and 100399.
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 100025A.
7. Product Line
   Supplied as 15 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 15 mL bottle is designed to deliver 165 sprays (42 mcg each). See Vol. 1.1, page 100025A.
8. Components/Composition
   Innovator:
   Active: Ipratropium Bromide, 0.06%
   Inactive: benzalkonium chloride
   Edetate disodium
   Sodium chloride
   Sodium hydroxide
   Hydrochloric acid
   Purified water

   Applicant:
   Active: Ipratropium Bromide, 0.06%
   Inactive: benzalkonium chloride
   Edetate disodium
   Sodium chloride
   Purified water

Sodium hydroxide
Hydrochloric acid

See Vol. 1.1, page 7 and 100039.

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 the 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 100025A.

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

---

cc:

ANDA: 75-553
DUP/DIVISION FILE
HFD-613/APayne/~~Jbarlowfor~~JGrace (no cc)
V:\FIRMSAM\DEY\LTRS&REV\75553.apL
Review

Date 12/10/01
12/10/2001

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-553

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

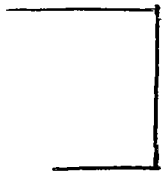
9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-31-98 (Both ANDAs)
Amendment: 2-22-99 (Both ANDAs) [Response to 2-4-99 letter]
NC: 5-19-99 (ANDA 75-553)

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)



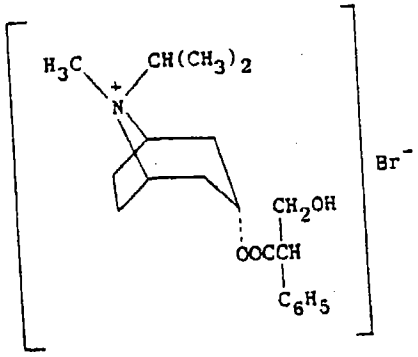
13. DOSAGE FORM
Solution

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.

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CHEMISTRY REVIEW #1

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,

/S/

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 Mufeed Shaikh 8/20/99
HFD-625/M.Smela/8/13/99 B Ci for M. Smela 8/20/99

Project Manager:

HFD-617/M.Dillahunt/8/17/99 M Dillahunt 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)

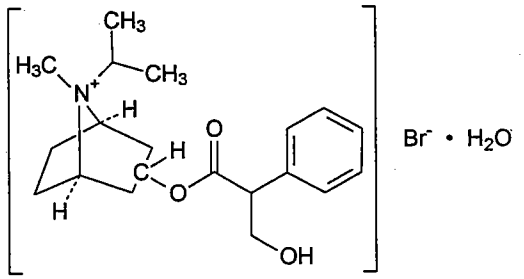
[redacted]

3. 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

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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 11/7/01
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,

Paul Schwartz for 11/19/98

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 M Shaikh 11/7/01
HFD-625/K.Furnkranz for M.Smela/11/6/01 for M.Smela 11/7/01

Project Manager:

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

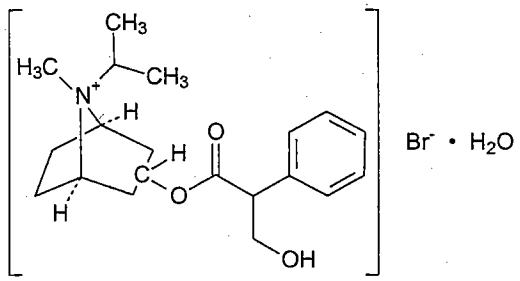
[redacted]

3. 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 [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

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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 Shrewsbury 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 Mujeeb 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 MDillahunt 2/12/02

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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]

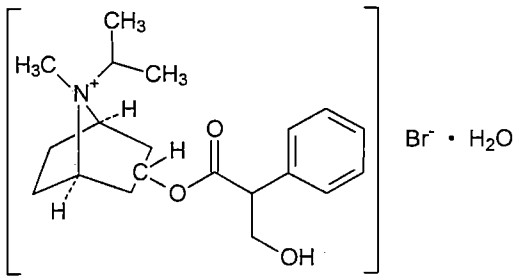
13. DOSAGE FORM
Solution

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 [redacted] for [redacted] - the manufacturer of [redacted] 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

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F/T by:

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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
[redacted]	II/ [redacted]	3	Adequate	6-21-01
	Comments: NO new information is submitted.			
[redacted]	III/ [redacted]	4	-	-
	Comments: None			
[redacted]	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 75-553

Ipratropium Bromide Nasal Spray, 0.06%

This addendum is being written to issue a MINOR amendment action based on the bioequivalence deficiencies identified in the bioequivalence review completed by Sikta Pardhan on 9-6-02. Item # 38 is written to request a Minor amendment from the firm.

Following items are also checked:

Status of DMF ——: After review of annual report submitted on August 6, 2002, the DMF remains adequate per review (CR # 8) completed by this reviewer on August 27, 2002.

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

38. Chemistry Comments to be Provided to the Applicant

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

DRUG PRODUCT: Ipratropium Bromide Nasal Solution, 0.06%

The deficiencies presented below represent Minor deficiencies.

Bioequivalence for this product has not been demonstrated. Please submit your response to the attached bioequivalence deficiencies. 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 9/10/02

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

cc: AND 75-553
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/9/10/02 mujahid shaikh 9/10/02
HFD-625/M.Smela/9/10/02 M Smela 9/10/02

Project Manager:
HFD-617/P.Chen/9/10/02 Peter Chen 9/10/02

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F/T by: gp/9/10/02

1. CHEMISTRY REVIEW NO. 5

2. ANDA # **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, 0.06% (Boehringer Ingelheim)

Patent Expiration date: 5-24-2000

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
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
Minor Amendment: 2-28-02 [Response to 2-12-02 NA letter]
Telephone Amendment: 4-26-02 [CMC issues]
Bio Amendment: 4-30-02
- NC: 9-26-02 (Intent to file amendment to NA letter 9-11-02)
- Amendment (Labeling): 12-27-02
- Minor Amendment (Bio): 12-27-02 (Response to 9-11-02 NA letter)

10. PHARMACOLOGICAL CATEGORY
Anticholinergic Agent

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

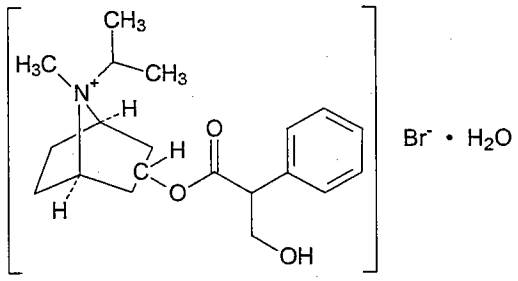
[redacted]

13. DOSAGE FORM
Solution

14. POTENCY
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 8-27-02. No new information is submitted.
2. EER is acceptable as of 6-26-02.
3. MV is completed on 4-18-02 for ANDA 75-552 (Ipratropium Bromide Nasal Spray 0.03%). It is acceptable.
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: Acceptable as of 2-13-03
6. Labeling: Acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: March 4, 2003

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

Endorsements:

HFD-625/M.Shaikh/3/4/03 Mujahid Shaikh 3/10/03
HFD-625/M.Smela/3/5/03 M Smela 3/10/03

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CHEMISTRY REVIEW #5

37. **DMF CHECKLIST FOR ANDA # 75-553 REVIEW # 5**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
[redacted]	II/ [redacted]	3	Adequate	8-27-02
	Comment: None			
[redacted]	III/ [redacted]	4	-	-
	Comments: None			
[redacted]	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 3/10/03
Reviewer Signature Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-553

BIOEQUIVALENCE REVIEWS

Ipratropium Bromide
Nasal Spray, 0.06% (42mcg/spray)
ANDA # 75-553
Reviewer: Sikta Pardhan
File #75553VTS.299

Dey, L.P.
Napa, CA
Submission Date:
February 22, 1999

REVIEW OF IN VITRO BIOEQUIVALENCE STUDY DATA

BACKGROUND

Ipratropium Bromide Nasal Spray 0.06% is indicated for the relief of rhinorrhea associated with the common cold for adults and children age 12 years and older. It is a Quaternary amine that is poorly absorbed into the systemic circulation from the nasal mucosa. The reference listed drug (RLD) is Atrovent[R] Nasal Spray, 0.06% (42 mcg/spray) manufactured by Boehringer Ingelheim.

For Ipratropium Bromide Nasal Spray 0.06%, the recommended dose is two sprays (84 mcg) per nostril three or four times daily. The drug is supplied as 15 mL of solution in a high density polyethylene bottle fitted with a ***metered nasal spray pump***. The 15 mL bottle is designed to deliver 165 metered sprays of 0.07 mL each (42 mcg/spray ipratropium bromide).

The firm has submitted an application for ipratropium bromide 0.06% nasal solution and has requested a waiver of in-vivo bioavailability requirements under 21 CFR 320.22 (b)(3). To support their request, the firm has provided comparative formulation data of its proposed test product and Atrovent[R] Nasal Spray, 0.06% manufactured by Boerhinger Ingelheim (see **Table 1** below).

TABLE 1. FORMULATION COMPARISON (not for release under FOI)

Ingredient	Test Product		RLD[a]		Allowed Range (mg/mL)
	Per Spray	mg/mL	Per Spray	mg/mL	
Ipratropium bromide*	42 mcg	0.600	42 mcg	0.600	------
Edetate disodium USP					
Sodium chloride USP					
Benzalkonium chloride NF					
Sodium hydroxide NF	pH adjustment to 4.7		pH adjustment to 4.7		
Hydrochoric acid NF	pH adjustment to 4.7		pH adjustment to 4.7		
Purified water USP	q.s.		q.s.		
Spray Volume	70 mcl		70 mcl		

a. The information was taken from Comis Main Menu/Drug Product Reference File.
b. Benzalkonium Chloride NF calculated as 100% solution
* Ipratropium bromide nasal spray 0.06% in an anhydrous basis is equivalent to 42 mcg of ipratropium bromide (each actuation delivers 0.07 mL of the product).
The drug is an isotonic aqueous solution with pH adjusted to 4.7

The sponsor has also conducted several in vitro tests to demonstrate comparable performance of the delivery system for the proposed drug product vs the reference product.

IN-VITRO TESTS:

Test Product: Ipratropium Bromide Nasal Spray 0.06% (Dey Labs), lot #W009 EOL

Reference Product: Atrovent[R] Nasal Spray, 0.06% (Boehringer Ingelheim), lot #866012B

Unit Spray Content:

Unit spray content through bottle life was obtained according to the procedure on page 100303 (vol. 1.2) of this submission. Three bottles of the nasal spray were sampled at the beginning (actuations 11 & 12), middle (actuations 82 & 83) and end (actuations 164 & 165) of each bottle to determine (by weight difference) the concentration of ipratropium bromide per unit spray. The results are shown below:

Test Product			
Spray	Bottle #1 % Label Claim	Bottle #1 % Label Claim	Bottle #3 % Label Claim
11	103	104	104
12	102	103	105
82	104	104	104
81	104	99	101
164	103	104	103
165	104	102	102

The firm did not provide any data for unit spray content for the reference product.

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 100301 (vol. 1.2).

Results showed an average of 103.37% of label claim (n=20; %CV=1.2). The firm did not provide content uniformity information for Atrovent[R].

Spray Pattern:

This test method is for the determination of the spray pattern of the test and the innovator formulations on the target TLC plate at specific distances of 1.0, and 2.5 cm from the tip of the nasal device. Measurement of spray pattern employed the use of hard manual actuation ("quick and firm", see validation on pages 100574-606 in

Vol. 1.3). Four spray patterns (for 3 bottles) were prepared at each distance (at 0°, 90°, 180° and 270°). 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 unit was also actuated in three orientations at each distance selected. For details, please see validation report on pages 100574-606 in Vol. 1.3. 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. Results are presented in attachment 1.

Particle Size Distribution

Particle size distribution was evaluated using two methods, i) ——————— and ii) 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 = $[d_{90} - d_{10}]/d_{50}$ (see validation on pp. 100665-83, vol. 1.3).

Cascade Impactor

Particle size distribution was also measured using the ——— cascade impactor. The nasal spray test unit was primed 7 times and the tip was cleaned and dried before weighing. The unit was then inserted into the intake of the 1L chamber. An air - flow rate was set to 28.3$\pm$0.3 L/min. The nasal sprays were manually actuated (10 times) and the deposition of ipratropium bromide on the various components of the impactor was measured using an HPLC method (see method validation on pp. 100638 - 664, vol. 1.3).

Results are shown in Attachment #2. The manual actuation (soft and hard) produced variability. However, in comparison with soft actuation, hard actuation force provided the better results with respect to reproducibility.

Plume Geometry

The intent of the plume geometry test procedure was to provide the means by which a visual record of the features of an aerosol cloud (plume) can be used to demonstrate the comparability or potential differences between the test and reference products. Plume geometry was measured using manual actuation and high-speed photography. The number of priming actuations was not reported for this test. Photocopies of the scanned photographs were submitted.

Validation data for plume geometry are insufficient. The validation protocol 6730-02FS outlined an analysis method based on three images per sequence, and three sequences per test (spray) assay per test article. However, due to the inherent variability in using a manual actuation method determined during method development, only the first image captured per sequence could be analyzed (Validation on pp. 100695-709, Vol. 1.3]

Results are presented in attachment #3.

Priming and Tail-off Data

No information was provided.

COMMENTS

1. The concentrations of the inactive ingredients for the test product fall in the acceptable range ($\pm$5%) of the Agency's Inactive Ingredient Guide. Therefore, based on the data submitted by the sponsor, composition of the proposed test product is qualitatively (Q_1) and quantitatively (Q_2) the same as in the reference product.

2. However, the *in vitro* testings conducted by the firm on unit dose, spray pattern, plume geometry, droplet size distribution (using cascade impactor and laser diffraction), and priming and tail off sprays are all deficient. Therefore, all *in vitro* tests should be repeated as follows:

   Comparative performance of drug delivery devices of the test and reference products should be based on the following tests:

   A. Unit Dose/Content Uniformity.
   B. Priming, loss of prime and tail off
   C. Droplet size distribution by at least two methods.

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 should be assessed at each sector.

With regard to specific tests:

A. Unit Dose and Uniformity of Unit Dose

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 procedure, of determination of the amount of drug per spray by weight difference of the bottles, is not acceptable. The amount of drug per single spray should be determined using a validated analytical

(chemical/chromatographic) procedure. Assay validation data should be submitted.

B. 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 each test for both 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.*

C. Droplet size distribution

1. *Laser Diffraction*: Droplet size distribution by laser diffraction (e.g. ———————) should be determined 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 in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time. 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.

2. *Cascade impaction:* The cascade impactor characterizes particles in a smaller size range than the expected range for this product. However, it is useful to assure that there is not an excess mass of "fines" in the test

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

Group-1: From valve stem and actuator up to top stage (stage zero)
Group-2: One stage below the top stage
Group-3: Everything from 2nd stage through the filter

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

D. Spray Pattern

Spray patterns should be determined at three distances from the TLC plate at the beginning and end life sectors, based on single actuation. 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}.

E. 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.

3. As 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. Information regarding the manufacturer, model numbers of the pumps, actuators, actuator inserts and overcaps should also be provided. Technical drawings with dimensions should be submitted, if available.

RECOMMENDATION

The in vitro bioequivalence study application submitted by Dey Lab Pharmaceutical for its Ipratropium Bromide Nasal Spray, 0.06%, is incomplete due to reasons cited in Comments #2 and #3.

Sikta Pradhan

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---------- 6/14/99

Concur: ---------- Date: 6/21/99

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

cc: ANDA # 75-553 (original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File

Draft:SP/5-24-99/ V:\firmsam\Dey\75553VTS.299

Attachment 1

SPRAY PATTERN TEST FOR IPRATROPIUM BROMIDE NASAL SPRAY UNITS

Product: Dey Nasal Spray 0.06%
Timepoint: T = 0
Lot #: W009

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

Distance (cm)	Orientation	Unit #2 Vertical (mm)	Unit #2 Horizontal (mm)	Unit #2 Ratio	Unit #5 Vertical (mm)	Unit #5 Horizontal (mm)	Unit #5 Ratio	Unit #10 Vertical (mm)	Unit #10 Horizontal (mm)	Unit #10 Ratio	Mean Vertical (mm)	Mean Vertical % RSD	Mean Horizontal (mm)	Mean Horizontal % RSD	Mean ± Std. Dev. Ratio	Mean ± Std. Dev. % RSD
1.0	0°										26.5	10.0	25.7	11.1	1.03 ± 0.012	1.1
	90°										28.3	3.7	28.5	3.0	1.00 ± 0.04	4.1
	180°										28.2	1.0	27.2	2.8	1.04 ± 0.02	1.9
	270°										26.3	10.8	27.0	4.9	0.98 ± 0.065	6.7
	Mean	26.8	27.3	0.99	27.8	27.0	1.03	27.5	27.0	1.02	27.3		27.1		1.02 ± 0.024	
	% RSD	6.9	4.4	6.7	10.4	11.2	1.1	4.9	3.4	3.2	3.9		4.3		2.35%	
2.5	Orientation															
	0°										41.3	0.7	38.8	0.7	1.06 ± 0.000	0.0
	90°										39.0	3.8	40.5	1.2	0.96 ± 0.032	3.3
	180°										42.0	1.2	40.0	1.3	1.05 ± 0.023	2.2
	270°										38.8	3.9	41.5	2.4	0.93 ± 0.029	3.1
	Mean	39.6	39.9	1.00	41.0	40.6	1.01	40.3	40.3	1.00	40.3		40.2		1.03 ± 0.018	
	% RSD	6.4	3.1	8.9	1.4	3.6	4.8	4.4	2.2	5.8	4.0		2.8		1.75%	

100829

SPRAY PATTERN TEST FOR IPRATROPIUM BROMIDE NASAL SPRAY UNITS

Product: Atrovent® Nasal Spray 0.06%
Timepoint: T = 0
Lot #: 866012B

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

Distance (cm)	Orientation	Unit #6 Vertical (mm)	Unit #6 Horizontal (mm)	Unit #6 Ratio	Unit #9 Vertical (mm)	Unit #9 Horizontal (mm)	Unit #9 Ratio	Unit #23 Vertical (mm)	Unit #23 Horizontal (mm)	Unit #23 Ratio	Mean Vertical (mm)	Mean Vertical % RSD	Mean Horizontal (mm)	Mean Horizontal % RSD	Mean ± Std. Dev. Ratio	Mean ± Std. Dev. % RSD
1.0	0°										25.2	9.8	26.2	8.0	0.96 ± 0.035	3.6
	90°										26.5	5.0	26.5	6.8	1 ± 0.04	4.0
	180°										27.5	13.7	28.2	12.6	0.98 ± 0.04	4.1
	270°										27.2	12.9	27.5	8.3	0.99 ± 0.058	5.9
	Mean	29.3	29.6	0.98	26.5	26.5	1.00	24.0	25.0	0.96	26.6		27.1		0.98 ± 0.038	
	% RSD	6.0	5.6	2.7	7.7	3.4	5.4	3.0	1.6	3.8	3.9		3.4		3.88%	
2.5	Orientation															
	0°										43.3	8.2	43.2	8.1	1.01 ± 0.060	6.0
	90°										43.0	7.3	42.5	10.3	1.01 ± 0.04	4.0
	180°										43.3	11.0	43.2	9.6	1.01 ± 0.07	7.0
	270°										42.8	7.8	43.5	7.0	0.98 ± 0.057	5.8
	Mean	44.9	45.6	0.99	39.4	38.9	1.01	45.1	44.8	1.01	43.1		43.1		1.01 ± 0.057	
	% RSD	3.1	2.3	4.7	1.6	2.9	2.5	5.9	2.1	7.7	0.6		1.0		5.64%	

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BIOEQUIVALENCE REVIEW - ATTACHMENT 1

Attachment #2

Table 2

CASCADE IMPACTION
FOR IPRATROPIUM BROMIDE NASAL SPRAY UNITS

Timepoint: T = 0

Product	Dey Nasal Spray Units 0.06%				
Test Method	TM 6730-04				
Lot #	W009				
Bottle #	2	5	10	Mean	%RSD
%Material Balance:				96.8	6.51
% of drug with Particle Size > 9 µm	100.0%	100.0%	100.0%	100.0%	0.00
Amount of drug per spray (µg)				40.33	7.61
Shot Weight (mg)				69.4	1.63

Table 3

CASCADE IMPACTION
FOR IPRATROPIUM BROMIDE NASAL SPRAY UNITS

Timepoint: T = 0

Product	Atrovent® Nasal Spray Units 0.06%				
Test Method	TM 6730-04				
Lot #	866012B				
Bottle #	6	9	23	Mean	%RSD
%Material Balance:				92.7	2.83
% of drug with Particle Size > 9 µm				99.1%	1.63
Amount of drug per spray (µg)				38.18	2.17
Shot Weight (mg)				68.7	0.68

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Table 4. Particle Sizing by ——— Laser Diffraction

August 13, 1997

Drug: **Ipratropium Bromide**
Product: **0.06% Dey Nasal Spray**
Lot# : **W009**
Stability Study Time Point: **Time = 0**

Storage Condition: N/A

Spray Bottle Unit # 2

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	27.09	47.28	148.17
StdDev	3.23	7.23	92.15
% RSD	11.9%	15.3%	62.2%

Spray Bottle Unit # 5

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	28.39	49.17	226.66
StdDev	2.02	3.66	111.57
% RSD	7.1%	7.4%	49.2%

Spray Bottle Unit # 10

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	27.33	45.10	158.11
StdDev	1.28	1.06	75.61
% RSD	4.7%	2.4%	47.8%

Mean Data for Units# 2, 5, 10

	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
mean	27.60	47.18	177.65
StdDev	2.1	4.45	89.63
% RSD	7.6%	9.4%	50.5%

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I:\6730\timezero\ ——— \LS\0.06% Dey
8/13/97 15:50

Table 5, Particle Sizing by ——— Laser Diffraction
August 13, 1997

Drug: **Ipratropium Bromide**
Product: **0.06% Atrovent Nasal Spray**
Lot# : **866012B**
Stability Study Time Point: **Time = 1**

Storage Condition: N/A

Spray Bottle Unit # 6

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	33.98	50.8	128.63
StdDev	3.4	3.17	54.01
% RSD	10.0%	6.2%	42.0%

Spray Bottle Unit # 9

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	33.66	52.58	207.94
StdDev	0.5	1.06	174.73
% RSD	1.5%	2.0%	84.0%

Spray Bottle Unit # 23

Assay #	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
1			
2			
3			
mean	34.35	54.9	154.69
StdDev	3.84	10.14	87.76
% RSD	11.2%	18.5%	56.7%

Mean Data for Units# 6, 9, 23

	Particle Diameter, µm D (v,0.1)	D (v,0.5)	D (v,0.9)
mean	34.00	52.76	163.75
StdDev	2.59	5.63	107.3
% RSD	7.6%	10.7%	65.5%

101429

866730\timezero\ ——— .S\0.06% Atrovent
8/13/97 15:50

Attachment #3

Test Method: TM 6730-05
Test Name: 2D Still Image Plume Geometry
Product: Atrovent® (ipratropium bromide) Nasal Spray 0.06%
Company: Dey Laboratories

Time Point: T = 0
Condition: NA
Orientation: NA
Lot Number: 8660128

Sample Unit ID	Image Number	Initial Angle °
Bottle 6	1	\
	2	
	3	
	mean	*76.2*
	% RSD	*2.8%*
Bottle 9	1	\
	2	
	3	
	mean	*78.9*
	% RSD	*1.6%*
Bottle 23	1	\
	2	
	3	
	mean	*74.8*
	% RSD	*8.7%*

Mean Statistics	
Overall Mean	*76.6 °*
% RSD	*5.1%*
Mean of Means	*76.6 °*
% RSD	*2.7%*

101756

Redacted 6 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW - ATTACHMENT 3

BIOEQUIVALENCY DEFICIENCIES

ANDA: #75-553 APPLICANT: Dey Lab Pharmaceutical

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.06%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has the following comments:

1. The *in vitro* testings conducted by you on unit dose, spray pattern, plume geometry, droplet size distribution (using cascade impactor and laser diffraction), and priming and tail off sprays are all deficient. Therefore, all *in vitro* tests should be repeated as follows:

   Comparative performance of drug delivery devices of the test and reference products should be based on the following tests:

   A. Unit Dose/Content Uniformity.
   B. Priming, loss of prime and tail off
   C. Droplet size distribution by at least two methods.
   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 should be assessed at each sector.

With regard to specific tests:

A. Unit Dose and Uniformity of Unit Dose

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 procedure, of determination of the amount of drug per spray by weight difference of the bottles, is not acceptable. The amount of drug per single spray should be determined using a validated analytical (chemical/chromatographic) procedure. Assay validation data should be submitted.

B. Priming and Tail-off Data

You 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 each test for both 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.*

C. Droplet Size Distribution

(i). *Laser Diffraction*: Droplet size distribution by laser diffraction (e.g. , should be determined 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 in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time. 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.

(ii). *Cascade impaction:* The cascade impactor characterizes particles in a smaller size range than the expected range for this product. However, it is useful to assure that there is not an excess mass of "fines" in the test product relative to the RLD. Cascade impactor data based on a validated assay should account for mass balance and be reported in the following groups:

Group-1: From valve stem and actuator up to top stage (stage zero)
Group-2: One stage below the top stage
Group-3: Everything from 2nd stage through the filter

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

D. Spray Pattern

Spray patterns should be determined at three distances from the TLC plate at the beginning and end life sectors, based on single actuation. 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}.

E. 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. You are requested to provide all photographs and data characterizing plume dimensions. Photographs should be overlaid with marked grids for quantitation.

2. As the device and formulation are integral components of a nasal spray, you are required to provide information to support sameness of test and reference devices. You should provide to the extent possible a side-by-side comparison of the pumps and actuators used in the test and reference products. Information regarding the manufacturer, model numbers of the pumps, actuators, actuator inserts and overcaps should also be provide. Technical drawings with dimensions should be submitted, if available.

Sincerely yours,

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

CC: ANDA #75-553
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

Endorsements: (Final with Dates)
HFD-652/ S. Pradhan SP
HFD-650/ Y. Huang YH 6/14/99
HFD-617/ E. Hu EH 6/21/99
HFD-650/ D. Conner WPC 6/21/99

Printed in draft on \\
Printed in final on ~~5\24~~\99
6/14

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1. IN VITRO BIOEQUIVALENCY STUDIES Submission date: 02-22-99
Nasal Spray, 0.06% Outcome ~~IN~~ IC
Study (ST~~W~~)
U
OIC

OUTCOME DECISIONS: IC
~~IN~~ - Incomplete

WINBIO COMMENTS: Incomplete InVitro Biostudy

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

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

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Printed in final on \ \
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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, 0.06% (42mcg/spray)
ANDA # 75-553
Reviewer: Sikta Pardhan
V:\Firmsam\Dey\ltrs&rev\75553A0401

Dey, L.P.
Napa, CA
Submission Date:
April 27, 2001
May 10, 2001

REVIEW OF AN AMENDMENT TO THE IN VITRO BIOEQUIVALENCE STUDY DATA

BACKGROUND

Ipratropium Bromide Nasal Spray 0.06% is indicated for the relief of rhinorrhea associated with the common cold for adults and children age 12 years and older. It is a quaternary amine that is poorly absorbed into the systemic circulation from the nasal mucosa. The reference listed drug (RLD) is Atrovent^{R} Nasal Spray, 0.06% (42 mcg/spray) manufactured by Boehringer Ingelheim.

For Ipratropium Bromide Nasal Spray 0.06%, the recommended dose is two sprays (84 mcg) per nostril three or four times daily. The drug is supplied as 15 mL of solution in a high density polyethylene bottle fitted with a ***metered nasal spray pump***. The 15 mL bottle is designed to deliver 165 metered sprays of 0.07 mL each (42 mcg/spray ipratropium bromide).

OBJECTIVE

The firm had previously submitted an application for Ipratropium Bromide Nasal Spray, 0.06% and requested a waiver of *in vivo* bioequivalency testing requirements under 21 CFR 320.22 (b)(3). The application was found incomplete due to

insufficient data analyses. In the current amendment, the firm had provided additional analytical data requested by the Agency.

Formulation:

The firm had previously (February 22, 1999) provided acceptable comparative formulation data of its proposed test product and Atrovent[R] Nasal Spray, 0.06% manufactured by Boerhinger Ingelheim (see **Table 1** below).

TABLE 1. FORMULATION COMPARISON (not for release under FOI)

Ingredient	Test Product		RLD[a]		Allowed Range (mg/mL)
	Per Spray	Mg/mL	Per Spray	mg/mL	
Ipratropium bromide*	42 mcg	0.600	42 mcg	0.600	------
Edetate disodium USP	[redacted]				
Sodium chloride USP					
Benzalkonium chloride NF					
Sodium hydroxide NF	pH adjustment to 4.7		pH adjustment to 4.7		
Hydrochoric acid NF	pH adjustment to 4.7		pH adjustment to 4.7		
Purified water USP	q.s.		q.s.		
Spray Volume	70 mcl		70 mcl		

a. The information was taken from Comis Main Menu/Drug Product Reference File.
b. Benzalkonium Chloride NF calculated as 100% solution
* Ipratropium bromide nasal spray 0.06% in an anhydrous basis is equivalent to 42 mcg of ipratropium bromide (each actuation delivers 0.07 mL of the product).
The drug is an isotonic aqueous solution with pH adjusted to 4.7

Drug Products:

Test Product: Ipratropium Bromide Nasal Spray 0.06% (Dey Labs), lot #W085, #W086A and #W086B
Lot size: [redacted]
(information on number of units in each lot has not been provided.)

Reference Product: Atrovent[R] Nasal Spray, 0.06% (Boehringer Ingelheim), lot #869004A (Exp. 6/01), #869005A (Exp. 6/01) and #869006A (Exp. 7/01)

Comments:

1. The firm had previously (February 22, 1999) provided acceptable composition of its test product, Ipratropium Bromide Nasal Spray 0.06%. The firm is advised to provide a statement indicating that there is no change in compositions between the current lots and the lot used in 1999, whose composition was acceptable to the Agency.

2. The firm is requested to provide the lot size and number of spray units present in each lot (#W085, #W086A and #W086B).

The sponsor has repeated the following in vitro tests to demonstrate comparable performance of the delivery system for the proposed drug product vs the reference product:
(1) Spray Content Uniformity through Container Life (2) Priming and Repriming (3) Tail Off Profile (4) Droplet Size Distribution – [redacted] (5) Droplet Size Distribution – Cascade Impaction (6) Plume Geometry (7) Spray Pattern.

Comparability of Spray Devices:

The pump supplier, [redacted], indicated that the metered dose pump supplied for Dey's Ipratropium Bromide Nasal Spray, 0.06% is identical to that used in Atrovent^{R} Nasal Spray (also supplied by [redacted]). Technical drawings (page 383 of Vol. 3.1) of the device are attached, along with a letter from the device manufacturer, [redacted], which offers a side-by-side comparison of the test and reference product devices.

The in vitro equivalence studies were conducted at [redacted].

Procedures and Information Applicable to All Tests:

All actuations of the nasal spray products were done using an automated mechanical actuator to actuate the nasal sprays in a reproducible manner. The mechanical actuator used was a proprietary unit designed by [redacted], for nasal spray actuation. The actuator operating conditions were as follows:

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

Unit spray content and uniformity of unit dose

For each test, ten (10) units from each of the three sub-lots of the test product and each of the three lots of the reference product were tested. Therefore, for each test a total of 30 units of the test product and 30 units of the reference product were tested.

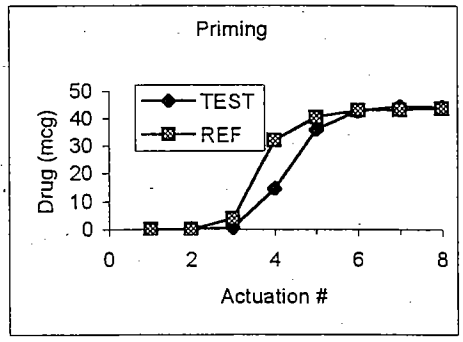
The weight of individual sprays was determined by weighing bottles before and after each spray collection, and the amount of drug per spray was determined by a validated HPLC analysis (LOQ= [redacted]).

Table 1. Unit Dose (Unit Spray Content) Data

Prod	Sec.	Mean Arith.	Mean Geo	Variability (%CV) Within-lot (N=10)	Bet-lot (N=3)	Total N=30	Test/Ref Arith. (N=30)	Test/Ref Geo N=30)	P-value
TEST	BEG	43.77	43.21	1.95-5.45	2.71	4.49	1.03	1.02	0.058
	END	44.28	44.21	2.24-4.63	1.23	4.68	1.03	1.04	0.043
REF	BEG	42.46	42.43	2.31-3.01	1.66	2.85			
	END	42.92	42.68	5.43-9.73	2.23	8.45			

Priming

Act. #	TEST Mean	TEST %CV	REF Mean	REF %CV
1	0	-	0.00	-
2	0	-	0.00	-
3	0.58	547.72	3.98	153.73
4	14.55	69.07	32.06	11.89
5	35.93	17.46	40.52	7.13
6	42.72	5.39	43.08	4.65
7	44.53	3.17	43.20	4.50
8	44.18	2.59	43.60	2.54



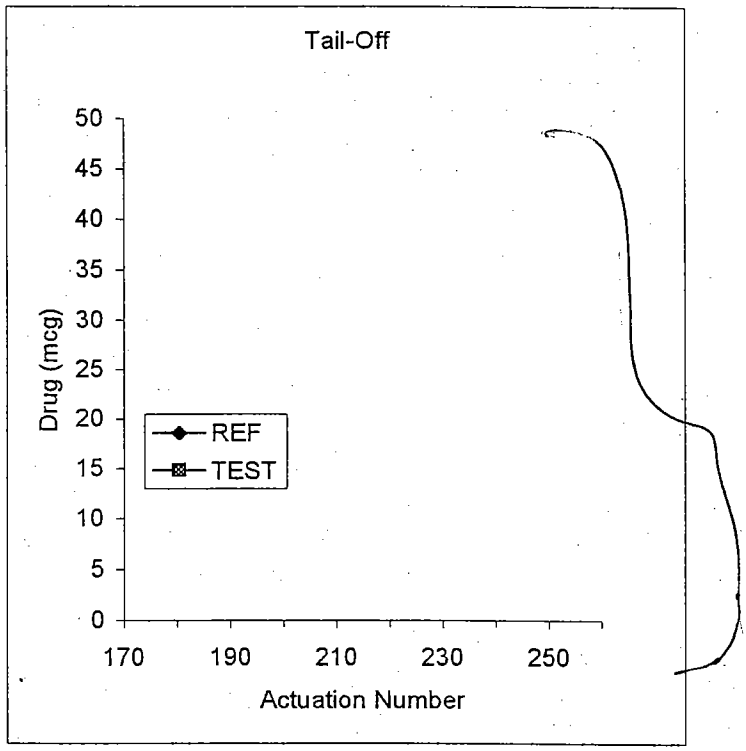
Priming and Re-priming

Priming and repriming data provided information to ensure delivery of the labeled dose of drug. Information given in the package insert of the Atrovent[R] Nasal Spray suggests a re-priming of the nasal spray pump with 2 sprays following inactivity of 24 hours, and a re-priming of the nasal spray pump with 7 sprays following inactivity of 7 days.

The number of sprays required to prime the pump was determined by assaying the first ten sprays of each unit. The sponsor has reported the prime retention characteristics of its product after 24-hour and 7-day of non-use. For the 24-hour re-priming test, the sponsor primed products by wasting 7 sprays. Then the units were not used for 24 hours. The 24-hour re-priming was based on sprays 8-10. The same units were then kept for 7 days without use. At the end of the 7-day period the units were re-primed by wasting sprays 11-17, and the prime retention was determined based on spray #18.

Tail-Off

Act. #	REF	TEST
172		
176		
182		
187		
190		
193		
196		
199		
202		
205		
208		
211		
214		
217		
220		
223		
226		
229		
232		
235		
238		
241		
247		
250		
253		



Tail off profile characterizes the decrease in emitted dose following delivery of the labeled number of actuations. The tail off was characterized by measuring the drug concentration from spray No. 166 to product exhaustion. Data given above indicate that the test product delivers the labeled numbers of doses and it's tail off is no more erratic than that of the reference product. Tail off profiles of test and reference products are comparable.

Comments on the Unit Dose Priming and Repriming Data

1. The test product variability (%CV) was comparable to that the reference product with regard to the unit spray content data. For the unit spray content, the test/ref ratios are within the 90-111% limits used by DBE for acceptance of nasal spray.

2. The quantity of the drug assayed is based on each single spray. A bottle delivers 165 sprays. The minimum and maximum values for the test product show that the delivered doses fall within 90-111% of the labeled dose.

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

4. Based on the data obtained, the test product is fully primed at the 6th spray. Based on the data submitted, the test and reference products have similar prime retention characteristics.

Particle Size Distribution

Particle size distribution was evaluated using two methods, i) [redacted] and ii) Cascade Impaction.

Droplet size distribution

a. Laser Diffraction:

Droplet size determination was performed on 10 units from each of the 3 lots of the test and reference products. Each unit was tested at beginning, middle, and end sectors of unit life. At each sector of unit life, each unit was actuated at three distances relative to the [redacted] laser beam (1 cm, 2.5 cm, and 5 cm).

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

Bioequivalence evaluation is based on D50 and SPAN data provided by the firm. A summary of these data based on the reviewer's calculations is given in Table 2.

Table 2
Droplet Size Distribution - D50 Data (Test Product) and Test/Ref Ratios

PROD.	stage	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	Initial	260.17	243.86	27.9-39.5	1.07	31.89	1.02	1.03	0.645
		1	Intermediate	89.58	71.63	76.6-89.5	18.26	87.33	0.86	0.91	0.241
		1	Dissip.	314.14	305.77	19.2-22.6	8.66	22.01	1.11	1.14	0.015
		2.5	Initial	154.97	134.27	51.9-59.6	12.91	55.97	0.92	0.92	0.317
	BEG	2.5	Intermediate	32.57	29.24	5.4-132.9	26.64	102.22	0.94	0.97	0.721
		2.5	Dissip.	114.01	109.2	32.7-39.4	1.11	37.16	1.12	1.13	0.035
		5	Initial	76.29	66.1	56.1-78.8	19.35	76.26	1.05	1.04	0.695
		5	Intermediate	31.97	31.94	3.5-5.5	0.77	4.51	1.00	1.00	0.761
		5	Dissip.	61.12	49.58	72.3-105.4	19.35	76.26	0.95	0.99	0.710
		1	Initial	222.13	199.2	35.6-47.4	11.28	39.56	1.20	1.21	0.001
		1	Intermediate	90.56	60.55	99.4-100.4	26.85	104.33	1.44	1.29	0.038
		1	Dissip.	121.73	115.28	23.3-42.8	13.61	37.16	1.07	1.07	0.206
		2.5	Initial	180.7	157.99	44.3-54.6	9.04	49.8	0.96	0.95	0.595
TEST	MIDDLE	2.5	Intermediate	31.81	29.26	5.7-133.2	19.39	95.02	1.13	1.04	0.266
		2.5	Dissip.	104.37	101.47	18.0-26.7	7.86	23.49	1.04	1.04	0.219
		5	Initial	113.49	90.61	68.0-84.1	16.55	76.01	1.21	1.15	0.087
		5	Intermediate	32	31.98	3.2-3.6	0.63	3.39	0.97	0.97	0.000
		5	Dissip.	80.14	57.52	87.8-124.6	11.83	105.31	1.65	1.34	0.002
		1	Initial	227.74	212.68	28.5-38.0	10.12	33.37	1.18	1.27	0.010
		1	Intermediate	65.57	48.54	67.1-109.4	37.03	112.48	1.01	1.02	0.955
		1	Dissip.	124.67	119.13	25.0-41.3	10.71	33.13	1.14	1.13	0.003
		2.5	Initial	180.25	157.72	49.5-53.6	2.37	49.78	1.07	1.08	0.448
	END	2.5	Intermediate	29.45	28.86	4.9-43.8	9.55	27.46	1.02	1.01	0.474
		2.5	Dissip.	93.92	92.37	15.2-39.3	4.68	18.64	0.99	1.00	0.833
		5	Initial	132.92	104.99	72.2-79.9	12.53	74.05	1.64	1.52	0.000
		5	Intermediate	32.65	32.63	2.8-91.9	1.01	3	0.99	0.99	0.185
		5	Dissip.	44.65	39.74	12.2-99.4	18.29	77.56	0.95	0.99	0.675

Droplet Size Distribution – D50 Data (REF Product)

PROD.	Stage	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	Initial	255.16	237.06	32.0-37.0	7.97	33.81
		1	Intermediate	103.9	78.45	85.3-90.6	17.3	89.6
		1	dissip.	283.53	268.73	26.6-34.4	5.97	30.93
		2.5	Initial	169.11	146.17	35.5-61.2	19.75	50.54
	BEG	2.5	Intermediate	34.53	30.12	5.4-138.3	16.31	115.17
		2.5	dissip.	101.88	96.97	30.0-43.3	3.45	35.22
		5	Initial	72.36	63.44	66.7-71.1	14.05	71.12
		5	Intermediate	32.02	31.99	4.3-5.1	1.54	4.88
		5	dissip.	64.53	50.31	104.0-104.6	21.95	103.05
		1	Initial	185.09	165.16	38.2-49.4	7.52	43.56
		1	Intermediate	62.95	46.88	110.5-121.5	4.08	115.85
		1	dissip.	113.89	107.88	27.6-39.4	14.61	33.87
		2.5	Initial	188.53	165.51	48.6-49.9	6.14	48.73
TEST	MIDDLE	2.5	Intermediate	28.26	28.21	5.3-6.6	0.16	5.88
		2.5	dissip.	100.2	97.55	14.1-38.1	4.64	24.54
		5	Initial	93.74	79.09	73.1-95.5	6.7	78.15
		5	Intermediate	32.95	32.92	9.3-5.3	1.12	4.28
		5	dissip.	48.44	43	18.2-100.0	17.95	78.99
		1	Initial	192.31	167.22	46.5-51.4	16.84	49.47
		1	Intermediate	64.9	47.66	110.4-117.5	24.59	118.7
		1	dissip.	109.06	105.3	23.0-35.6	6.45	29.83
		2.5	Initial	169.14	145.9	51.2-55.8	8.62	53.17
	END	2.5	Intermediate	28.8	28.63	6.0-35.2	1.4	12.88
		2.5	dissip.	94.56	92.2	15.0-27.9	6.12	23.53
		5	Initial	80.98	69.3	52.0-90.4	7.2	75.26
		5	Intermediate	32.83	32.8	4.1-49.7	1.4	4.24
		5	dissip.	47.14	39.95	89.6-119.1	8.19	108.32

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

PROD.	Stage	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	Initial	1.48	1.33	41.5-67.4	6.59	56.92	0.92	0.91	0.280
		1	Intermediate	5.7	5.06	29.1-44.1	9.7	36	1.06	1.12	0.253
		1	Dissip.	0.96	0.93	22.5-26.8	6.22	25.49	0.83	0.85	0.0005
		2.5	Initial	2.13	1.98	32.8-40.7	13.19	38.31	0.94	0.97	0.257
	BEG	2.5	Intermediate	1.75	1.71	4.3-55.6	9.4	36.19	1.06	1.04	0.158
		2.5	Dissip.	1.75	1.74	10.3-15.8	2.33	12.96	0.97	0.97	0.170
		5	Initial	3.16	2.53	52.7-69.0	10.09	58.43	1.24	1.32	0.032
		5	Intermediate	1.12	1.12	7.7-10.0	0.33	9.06	1.01	1.01	0.611
		5	Dissip.	5.02	4.1	42.6-55.1	6.98	49.91	1.08	1.14	0.314
		1	Initial	1.71	1.55	43.9-51.7	2.28	47.93	0.84	0.84	0.017
		1	Intermediate	2.16	2.05	31.5-46.0	5.2	37.51	1.00	0.99	0.992
		1	Dissip.	1.78	1.72	23.9-29.3	2.34	27.25	0.90	0.91	0.013
		2.5	Initial	1.92	1.77	37.3-56.4	11.87	47.97	0.96	0.97	0.481
TEST	MIDDLE	2.5	Intermediate	1.76	1.7	6.2-53.2	8.19	41.29	1.07	1.04	0.160
		2.5	Dissip.	1.83	1.83	7.9-10.4	3.26	9.83	0.98	0.99	0.324
		5	Initial	2.87	2.37	50.9-63.2	22.6	58.51	0.93	0.95	0.317
		5	Intermediate	1.16	1.15	5.8-8.5	2.49	7.3	1.02	1.01	0.257
		5	Dissip.	4.84	3.79	54.5-61.3	6.73	58.09	0.95	1.00	0.665
		1	Initial	1.62	1.49	29.6-57.3	7.83	47.59	0.79	0.81	0.002
		1	Intermediate	2.65	2.5	28.7-43.6	1.1	36.56	0.91	0.94	0.176
		1	Dissip.	2.03	1.96	25.3-30.7	5.47	27.87	1.00	1.00	0.946
		2.5	Initial	1.93	1.79	42.0-44.3	5.82	43.24	0.92	0.93	0.253
	END	2.5	Intermediate	1.95	1.77	6.3-85.1	27.11	69.14	1.13	1.07	0.155
		2.5	Dissip.	1.94	1.92	7.6-12.7	8.1	12.39	0.96	0.95	0.015
		5	Initial	2.66	2.24	50.8-58.5	21.06	57.9	1.08	1.19	0.437
		5	Intermediate	1.14	1.14	5.4-8.0	2.51	7.26	1.01	1.02	0.212
		5	Dissip.	3.43	2.18	85.2-104.1	9.11	91.07	0.85	0.91	0.235

Droplet Size Distribution - SPAN Data (REF Product)

PROD.	Stage	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	BEG	1	Initial	1.61	1.46	45.7-60.9	11.59	54.45
		1	Intermediate	5.36	4.53	32.1-50.5	6.99	43.04
		1	Dissip.	1.16	1.09	28.5-45.0	10.51	36.46
		2.5	Initial	2.27	2.05	36.3-61.8	17.49	51.2
		2.5	Intermediate	1.65	1.65	4.8-7.7	1.47	6.1
		2.5	Dissip.	1.8	1.79	10.2-23.4	0.24	15.82
		5	Initial	2.55	1.92	61.9	8.15	75.25
		5	Intermediate	1.11	1.11	8.1-9.7	1.44	9.21
		5	Dissip.	4.64	3.61	54.1-63.7	5.93	57.34
	MIDDLE	1	Initial	2.03	1.85	42.7-52.0	8.49	49.1
		1	Intermediate	2.16	2.07	18.4-52.7	5.86	37.78
		1	Dissip.	1.97	1.89	30.0-33.9	3.07	32.04
		2.5	Initial	2	1.83	43.7-48.8	5.86	46.71
		2.5	Intermediate	1.65	1.64	4.8-6.7	0.8	5.55
		2.5	Dissip.	1.86	1.85	9.4-12.9	2.49	11.27
		5	Initial	3.08	2.5	50.8-67.5	14.96	57.83
		5	Intermediate	1.14	1.14	5.5-9.3	2.41	7.2
		5	Dissip.	5.07	3.78	50.2-66.4	4.17	59.1
	END	1	Initial	2.04	1.83	41.9-59.7	14.44	52.72
		1	Intermediate	2.92	2.65	33.4-52.1	12.12	46.82
		1	Dissip.	2.04	1.96	28.4-33.9	8.42	31.44
		2.5	Initial	2.09	1.93	38.2-46.5	3.87	43.36
		2.5	Intermediate	1.72	1.66	4.7-65.3	9.5	42.53
		2.5	Dissip.	2.03	2.02	9.9-17.4	3.03	13.57
		5	Initial	2.47	1.88	61.0-90.4	19.41	75.17
		5	Intermediate	1.13	1.12	6.1-8.9	2.24	7.63
		5	Dissip.	4.04	2.4	81.3-98.2	15.78	88.67

Comments on Droplet Size Distribution

1. Evaluation of the comparative droplet size distributions by laser diffraction is based on data pertaining to the fully formed plume, which is represented by the intermediate plume stage, characterized by stable % transmission. Based on the D50 data for the intermediate portion, T/R ratio were within the 0.9 – 1.11, with the exception of the 1cm data. The 1cm data may not be included in determination of equivalence because at that distance from the nozzle, the spray is mainly in the form of a jet stream, rather than a plume. Therefore, the evaluation of equivalence of the D50 and span data in this application is based on the 2.5 cm and 5 cm data. Based on these two distances, test/ref ratios for the D50 data were within the range of 0.9 – 1.11.

2. The ratios of the test geometric means to the reference geometric means for SPAN at 2.5 cm and 5 cm distances for the fully primed plumes are within 0.9-1.11.

3. For D50 and SPAN, the variability for the test product is comparable to that of the reference product in majority of the cases.

4. Based on the geometric mean data for the intermediate portion of the plume, the T/R ratios for D50 and SPAN are within the 0.9-1.11 range, used hitherto by DBE for acceptance of solution nasal spray products.

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

Cascade Impactor Analysis

Droplet size distribution was also measured using the ——— cascade impactor. The nasal spray test unit was primed 7 times and the tip was cleaned and dried before weighing. The unit was then inserted into the intake of the 1L chamber. An air - flow rate was set to 28.3±0.3 L/min. The nasal sprays were manually actuated (10 times) and the deposition of ipratropium bromide on the various components of the impactor was measured using an HPLC method (see method validation on pp. 11045 – 11066, Vol. 3.11).

Table 3. **Cascade Impaction Data**

PROD.	SECTOR	Mean		Variability (%CV)			TEST/REF		p
		Arith (N=30)	Geo (N=30)	Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)	Arith	Geo	
TEST	BEG	411.78	411.17	1.62-8.38	2.31	5.23	1.02	1.00	0.113
	END	412.24	409.12	7.21-15.00	2.7	12.38	1.03	1.00	0.251
REF	BEG	402.32	401.9	2.38-5.7	2.56	4.55			
	END	400.67	400.01	2.13-8.41	2.73	5.49			

Comment on Cascade Impaction Data:

1. The Cascade Impaction results indicated that the amount of drug deposited in droplets >9 um is similar between test and reference products (geometric mean ratio of Test and Ref is 1.00).

Plume Geometery

The intent of the plume geometry test procedure was to provide the means by which a visual record of the features of an aerosol cloud (plume) can be used to demonstrate the comparability or potential differences between the test and reference products.

Plume geometry was studied by capturing plume images using a high-speed video camera. Plume angle, plume height and plume width were determined for images taken at three delay times (2.4, 105 and 208 msec).

Table 4
Plume Geometery - Data (Test Product) and Test/Ref Ratios

PROD.	View	Delay Time	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	0-Degree	2.4	Height	14.7	14.11	24.85-29.85	7.27	27.26	0.93	0.90	0.18
		2.4	Width	47.39	13.39	24.1-27.19	3.83	7.37	0.99	0.88	0.08
		2.4	Angle	80.91	80.53	9.30-10.11	3.75	9.93	1.00	1.00	0.85
		105	Height	28.08	27.96	8.48-10.62	2.4	9.41	1.06	1.06	0.01
		105	Width	18.66	18.55	8.10-11.93	4.47	10.69	0.99	0.99	0.73
		105	Angle								
		208	Height	36.97	36.73	10.93-12.86	1.62	11.27	1.05	1.05	0.04
		208	Width	19.05	18.86	10.07-16.55	6.58	14.31	0.99	0.99	0.66
		208	Angle								
	90-Degree	2.4	Height	14.73	14.33	19.79-26.83	5.59	22.5	0.89	0.88	0.02
		2.4	Width	47.27	13.97	19.13-24.36	3.83	6.69	0.97	0.89	0.05
		2.4	Angle	80.19	79.81	9.69-10.06	3.65	10.03	0.99	0.99	0.59
		105	Height	27.56	27.44	8.03-12.36	2.72	9.63	1.06	1.06	0.03
		105	Width	19.22	19.18	6.67-7.42	2.42	7	1.00	1.00	0.98
		105	Angle								
		208	Height	36.08	35.96	7.05-8.45	2.33	8.42	1.06	1.07	0.03
		208	Width	20.09	20.01	5.19-11.37	5.61	9.26	1.02	1.02	0.46
		208	Angle								

Plume Geometery - Data (REF Product)

PROD.	View	Delay Time	Plume Formation	Mean Arith (N=30)	Mean Geo (N=30)	Variability (%CV) Within-Lot (N=10)	Variability (%CV) Betwee n-lot (N=3)	Variability (%CV) Total (N=30)
REF	0-Degree	2.4	Height	15.89	15.73	7.64-16.59	4.93	13.86
		2.4	Width	48.02	15.18	13.59-25.35	7.67	6.32
		2.4	Angle	80.53	80.13	8.10-10.28	4.82	10.14
		105	Height	26.5	26.4	6.00-11.37	0.49	8.5
		105	Width	18.8	18.67	9.33-15.78	3.27	11.83
		105	Angle					
		208	Height	35.12	34.97	7.68-12.44	1.19	9.47
		208	Width	19.27	19.09	5.64-18.63	4.59	13.69
		208	Angle					
	90-Degree	2.4	Height	16.48	16.29	10.25-18.68	0.79	15.21
		2.4	Width	48.58	15.73	13.12-20.48	5	5.26
		2.4	Angle	81.21	80.81	9.03-11.97	0.49	9.91
		105	Height	25.99	25.78	10.62-15.64	4.74	12.9
		105	Width	19.23	19.1	8.42-13.10	5.23	11.33
		105	Angle					
		208	Height	34.02	33.68	10.17-17.65	6.05	13.91
		208	Width	19.75	19.64	9.15-11.98	4.28	10.6
		208	Angle					

Comments on Plume Geometry Data:

1. The firm should be requested to provide the detailed procedure for plume geometry test along with the sample quantification.

2. Plume Geometry measurements were taken at delay times of 2.4, 105 and 208 msec. These delay- times are not appropriate. Based on the Agency's experience, a delay time of 2.4 msec. is too short to reflect meaningful plume formation. Furthermore, at delay-times of 105 and 208 msec, the plume is no longer in contact with the actuator orifice.

3. The sponsor should repeat plume geometry analysis using appropriate delay times. Selection of delay times should permit measurements of plume angle, plume height and plume width when the plume is still in contact with the actuator's orifice. Plume angle measurements should be made at a delayed time between 10-50 msec.

4. The sponsor's measurement of plume height was not appropriate. Plume height should be measured as the distance between the actuator orifice and tip of the plume.

Spray Pattern

Spray pattern provides information about the shape and density of the plume following actuation. Spray patterns were determined on single actuations at 1 cm, 2.5 cm and 4 cm from the actuator to the target at the beginning and end of bottle life. Minimum diameter (D_{min}), maximum diameter (D_{max}), and the ovality ratio (D_{max}/D_{min}) of spray patterns were analyzed for each of the three distances.

A summary of the spray pattern data based on the reviewer's calculations is presented in Table 5.

Table 5

Spray Pattern (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	2.05	2.04	7.59-9.45	0.78	0.85	1.02	1.03	0.09
		1	Dmin	1.91	1.91	7.47-9.18	1.45	8.5	1.04	1.06	3E-04
		1	Oval. Ratio	1.07	1.07	6.34-6.5	1.42	5.64	0.97	0.97	0.004
		2.5	Dmax	4.4	4.39	5.91-8.28	2.48	7.3	1.01	1.01	0.515
	BEG	2.5	Dmin	4.03	4.02	7.02-7.66	4.45	7.83	1.01	1.02	0.299
		2.5	Oval. Ratio	1.09	1.09	5.06-7.64	1.49	6.19	0.99	0.99	0.571
		4	Dmax	6.56	6.54	6.77-8.10	4.07	8.13	1.02	1.03	0.223
		4	Dmin	5.97	5.94	7.58-8.45	7.33	9.4	1.03	1.05	0.093
TEST		4	Oval. Ratio	1.1	1.1	4.93-6.01	1.47	5.84	0.98	0.98	0.089
		1	Dmax	2.04	2.04	7.85-9.88	2.34	8.95	1.03	1.03	0.059
		1	Dmin	1.9	1.89	7.55-10.14	4.97	1.89	1.03	1.03	0.093
		1	Oval. Ratio	1.08	1.08	4.44-7.09	1.92	5.98	1.00	1.00	0.872
		2.5	Dmax	4.11	4.07	9.65-14.05	6.15	12.54	1.06	1.05	0.002
	END	2.5	Dmin	3.71	3.66	7.35-18.56	8.34	14.4	1.03	1.03	0.179
		2.5	Oval. Ratio	1.12	1.11	6.53-9.62	2.22	7.33	1.04	1.03	0
		4	Dmax	5.84	5.76	10.87-13.01	3.46	15.11	1.01	1.02	0.507
		4	Dmin	5.2	5.09	11.01-25.09	6.54	18.6	1.00	0.99	0.862
		4	Oval. Ratio	1.14	1.13	6.15-8.59	4.42	7.93	1.03	1.02	0.021

Spray Pattern - (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	1	Dmax	2.01	1.99	9.29-14.30	2.51	12.23
		1	Dmin	1.83	1.81	9.65-13.91	3.66	12.79
		1	Oval. Ratio	1.1	1.1	6.97-7.16	0.72	6.46
		2.5	Dmax	4.37	4.34	9.60-13.02	1.64	11.13
		2.5	Dmin	3.98	3.96	10.65-12.03	0.74	11.49
		2.5	Oval. Ratio	1.1	1.1	5.81-7.65	0.33	6.89
		4	Dmax	6.42	6.34	14.55-16.30	2.7	15.27
		4	Dmin	5.77	5.68	16.60-18.33	3.27	5.68
		4	Oval. Ratio	1.12	1.12	6.16-6.34	1.4	1.12
	END	1	Dmax	1.99	1.98	7.47-12.87	2.9	10.52
		1	Dmin	1.85	1.83	8.75-15.37	3.71	12.13
		1	Oval. Ratio	1.08	1.08	5.19-6.48	5.53	1.63
		2.5	Dmax	3.89	3.86	11.52-13.94	3.21	13.89
		2.5	Dmin	3.61	3.57	12.38-13.62	1.76	13.43
		2.5	Oval. Ratio	1.08	1.08	5.33-7.12	1.34	6.01
		4	Dmax	5.76	5.67	9.24-19.80	1.78	16.35
		4	Dmin	5.22	5.13	11.77-19.63	1.99	17.43
		4	Oval. Ratio	1.11	1.11	5.73-8.82	1.16	7.33

Based on a pre-approval inspection, the firm was advised to reanalyze the spray patterns. The reanalyzed data are presented below in Table 6.

Table 6
Revised Spray Pattern (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	21.8	21.77	6.8-9.6	1.61	8.4	0.99	1.00	0.75
		1	Dmin	19.5	19.45	6.7-11.2	0.89	3.4	0.99	1.01	0.97
		1	Oval. Ratio	1.12	1.12	2.08-4.22	2.36	3.4	0.99	0.99	0.21
		2.5	Dmax	43.4	43.38	4.8-5.3	3.11	5.6	0.99	1.00	0.66
	BEG	2.5	Dmin	36.3	36.11	4.9-9.3	8.84	10.1	0.98	0.99	0.59
		2.5	Oval. Ratio	1.21	1.2	2.48-10.76	7.07	9	1.02	1.01	0.5
		4	Dmax	66.7	66.59	3.8-4.1	4.45	5.3	1.01	1.02	0.77
		4	Dmin	52	51.53	5.9-11.9	11.13	1.3	1.07	1.08	0.13
TEST		4	Oval. Ratio	1.3	1.3	3.38-13.25	7.72	12.7	0.93	0.95	0.11
		1	Dmax	21.5	21.46	5.9-8.8	4.05	8	1.02	1.02	0.39
		1	Dmin	19.1	19.02	6.3-9.3	5.64	9.2	1.02	1.02	0.55
		1	Oval. Ratio	1.13	1.13	1.71-4.72	1.77	4	1.01	1.00	0.47
		2.5	Dmax	41.3	41.08	5.5-14.2	5.25	10.2	1.05	1.04	0.15
	END	2.5	Dmin	33.6	33.2	6.7-18.5	10.57	15.1	1.02	1.02	0.38
		2.5	Oval. Ratio	1.24	1.24	2.56-10.3	6.04	9.2	1.02	1.02	0.57
		4	Dmax	62	61.67	4.8-13.6	5.6	9.8	1.02	1.02	0.7
		4	Dmin	46.8	45.81	7.6-23.1	12.87	19.4	1.11	1.11	0.06
		4	Oval. Ratio	1.36	1.35	4.44-20,01	8.6	16	0.92	0.92	0.07

Revised Spray Pattern (REF Product)

PROD.	Sector	Distance	Plume Formation	Mean Arith (N=30)	Variability (%CV) Geo (N=30)	Within-Lot (N=10)	Between-lot (N=3)	Total (N=30)
		1	Dmax	22.1	21.81	12.0-22.5	5.5	17.3
		1	Dmin	19.6	19.29	12.0-22.5	6.81	18
		1	Oval. Ratio	1.13	1.13	1.72-3.93	1.02	3.2
		2.5	Dmax	44	43.56	12.8-17.7	4.65	15.6
	BEG	2.5	Dmin	36.9	36.55	12.4-15.5	4.22	13.7
		2.5	Oval. Ratio	1.19	1.19	4.0-9.5	2.1	6.8
		4	Dmax	66	65.47	8.0-15.7	2.67	12.5
		4	Dmin	48.8	47.9	13.1-21.2	3.84	18.6
REF		4	Oval. Ratio	1.4	1.37	10.62-26.32	4.72	22.9
		1	Dmax	21.00	20.96	6.9-15.1	2.97	10.6
		1	Dmin	18.7	18.64	7.1-16.2	3.63	11.2
		1	Oval. Ratio	1.12	1.12	1.48-4.02	0.51	2.9
		2.5	Dmax	39.58	39.58	4.9-15.0	3.73	11.9
	END	2.5	Dmin	32.64	32.64	5.0-18.2	2.71	14.1
		2.5	Oval. Ratio	1.21	1.21	4.35-7.02	0.83	5.6
		4	Dmax	60.6	60.38	9.1-17.6	1.62	14
		4	Dmin	42.2	41.45	10.7-23.7	3.19	19.3
		4	Oval. Ratio	1.48	1.46	15.43-23.89	2.03	20.7

Comments on Spray Pattern Analysis:

1. The ratios of the test geometric means to the reference geometric means for Ovality were within the acceptable 0.90-1.11 range.

2. The ratio of the test geometric mean to the reference geometric mean for Dmin and Dmax was also within the acceptable 0.90-1.11 at both life sectors.

3. The overall variability of the test product was less than that of the reference product.

4. The sponsor did not identify the reagent used for visualization of spray patterns on TLC plates. Without identification of the spray reagent, spray pattern testing is incomplete.

OVERALL DEFICIENCY COMMENTS

1. The firm had previously (February 22, 1999) provided acceptable composition of its test product, Ipratropium Bromide Nasal Spray 0.06%. The firm is advised to provide a statement indicating that there is no change in composition between the current lots and the lot used in 1999, whose composition was acceptable to the Agency.

2. The firm is requested to provide the lot size and number of spray units present in each lot (#W085, #W086A and #W086B).

3. The firm should be requested to provide a detailed analytical procedure for plume geometry along with the sample quantification.

4. Plume Geometry measurements were taken at delay times of 2.4, 105 and 208 msec. These delay- times are not appropriate. Based on the Agency's experience, a delay time of 2.4 msec. is too short to reflect meaningful plume formation. Furthermore, at delay-times of 105 and 208 msec, the plumes are no longer in contact with the actuator orifice.

5. The sponsor should repeat plume geometry analysis using appropriate delay times. Selection of delay times should permit measurements when the plume is still in contact with the actuator's orifice. Plume angle measurements should be made at a delayed time between 10-50 msec.

6. The sponsor's measurement of plume height was not appropriate. Plume height should be measured as the distance between the actuator orifice and tip of the plume.

7. The sponsor should clarify which reagents were used for visualization of the spray

patterns on TLC plates. If the submitted data are based on spot visualization without a reagent, spray pattern testing should be repeated.

RECOMMENDATION

The in vitro performance data submitted by Dey, L. P. for its Ipratropium Bromide Nasal Spray, 0.06% is incomplete due to the deficiencies in plume geometry testing.

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---------- 3/5/2002

Concur: ---------- Date: 4/15/02
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-553 (original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File

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Draft: 2-6-02
Final: 3-4-02

Redacted 6 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW OF 4/27/01 and 5/10/01 SUBMISSIONS
ATTACHMENT

BIOEQUIVALENCY DEFICIENCIES

ANDA: #75-553 APPLICANT: Dey Lab Pharmaceutical
DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.06%

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 *in vitro* testing conducted by you on plume geometry is deficient. You are requested to provide a detailed analytical procedure for plume geometry along with the sample quantification.
2. Plume Geometry measurements were taken at delay times of 2.4, 105 and 208 msec. These delay- times are not appropriate. Based on the Agency's experience, a delay time of 2.4 msec. is too short to reflect meaningful plume formation. Furthermore, at delay-times of 105 and 208 msec, the plumes are no longer intact with the actuator orifice. Furthermore, the measurement of plume height was not appropriate. Plume height should be measured as the distance between the actuator orifice and tip of the plume.
   Hence, You are advised to repeat plume geometry analysis using appropriate delay times. Selection of delay times should permit measurements when the plume is still in contact with the actuator's orifice. Plume angle measurements should be made at a delayed time between 10-50 msec.
3. You are advised to clarify the reagents used for visualization of the spray patterns on TLC plates. If the submitted data are based on spot visualization without a reagent, spray pattern testing should be repeated.
4. You had previously (February 22, 1999) provided acceptable composition of your test product, Ipratropium Bromide Nasal Spray 0.06%. You are advised to provide a statement indicating that there is no change in composition between the current lots and the lot used in 1999, whose composition was acceptable to the Agency.
5. You are requested to provide the lot size and number of spray units present in each lot (#W085, #W086A and #W086B).

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 #75-553
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

Endorsements: (Final with Dates)
HFD-652/ S. Pradhan
HFD-655/ G. Singh
HFD-650/ Y. Huang 3/5/02
HFD-617/ K. Scardina
HFD-650/ D. Conner 4/15/02

Printed in draft on
Printed in final on 3-4-02

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1. IN VITRO BIOEQUIVALENCY STUDIES Submission date: 04-27-01
Nasal Spray, 0.06% Outcome IN
Study Amendment (STA) 01

OUTCOME DECISIONS: IN - Incomplete

2- Study Amendment (STA) Submission Date acw.
05-10-01

SEP 6 2002

Ipratropium Bromide
Nasal Spray, 0.06% (42mcg/spray)
ANDA # 75-553
Reviewer: Sikta Pardhan
V:\Firmsam\Dey\ltrs&rev\75553A0402

Dey, L.P.
Napa, CA
Submission Date:
April 30, 2002

REVIEW OF AN AMENDMENT TO THE IN VITRO BIOEQUIVALENCE STUDY DATA

OBJECTIVE

The firm had previously submitted an application for Ipratropium Bromide Nasal Spray, 0.06% and requested a waiver of *in vivo* bioequivalency testing requirements under 21 CFR 320.22 (b)(3). The application was found incomplete due to insufficient data analyses.

The firm had submitted an amendment (dated April 27, 2001) for the above application, and requested a waiver of *in vivo* bioequivalency testing requirements under 21 CFR 320.22 (b)(3). The application was found incomplete, and the Agency comments are presented below.

1. The *in vitro* testing conducted by you on plume geometry is deficient. You are requested to provide a detailed analytical procedure for plume geometry along with the sample quantification.
2. Plume Geometry measurements were taken at delay times of 2.4, 105 and 208 msec. These delay- times are not appropriate. Based on the Agency's experience, a delay time of 2.4 msec. is too short to reflect meaningful plume formation. Furthermore, at delay-times of 105 and 208 msec, the plumes are no longer intact with the actuator orifice. Furthermore, the measurement of

plume height was not appropriate. Plume height should be measured as the distance between the actuator orifice and tip of the plume.
Hence, You are advised to repeat plume geometry analysis using appropriate delay times. Selection of delay times should permit measurements when the plume is still in contact with the actuator's orifice. Plume angle measurements should be made at a delayed time between 10-50 msec.

3. You are advised to clarify the reagents used for visualization of the spray patterns on TLC plates. If the submitted data are based on spot visualization without a reagent, spray pattern testing should be repeated.

4. You had previously (February 22, 1999) provided acceptable composition of your test product, Ipratropium Bromide Nasal Spray 0.06%. You are advised to provide a statement indicating that there is no change in composition between the current lots and the lot used in 1999, whose composition was acceptable to the Agency.

5. You are requested to provide the lot size and number of spray units present in each lot (#W085, #W086A and #W086B).

In the current amendment dated April 30, 2002, the firm has provided additional information requested by the Agency.

1. The firm has provided the analytical procedure for recording of Images, measurement and calculations of Plume Angles.

2. The firm has informed the Division of Bioequivalence that the delay times were selected based on an Agency request for delay times that would characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time (29 June 1999 FDA Bioequivalency facsimile).

   Dey has further mentioned that the pumps used in this study are the same between the Dey product and the reference product. As such they provide the same dose of drug product per spray, have the same stroke length, and provide the same spray velocity. Measuring the plume height from the top of the orifice as opposed to the bottom of the plume will not effect the overall comparability of the test and reference products.

3. The firm has stated that the reagent used in the visualization of the TLC plates was [redacted]

4. The firm has confirmed that there was no change in composition between the current lots of Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray) and the lot used in 1999, whose composition was acceptable to the Agency.

5. Dey has stated that the lot size for W085 is ——— The lot size for W086 is ———. During filling, W086 was sub-lotted into W086A and W086B to accommodate the requirement for use of different manufacturers lots of pumps and bottles.

   The number of spray units filled for the three lots are as follows:

Lot #	Spray Units Filled
W085	
W086A	
W086B	

OVERALL DEFICIENCY:

The firm's response regarding plume geometry testing is not acceptable. Selection of delay times should permit measurements when the plume is still in contact with the actuator's orifice. Plume angle measurements should be made at a delayed time between 10-50 msec. Plume height should be measured as the distance between the actuator orifice and tip of the plume. The firm should repeat the plume geometry testing. The repeat testing may be performed on a single side view of the spray, instead of the two 0^0 and 90^0 views requested previously.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION

The in vitro performance data submitted by Dey, L. P. for its Ipratropium Bromide Nasal Spray, 0.06% is incomplete due to the deficiencies in plume geometry testing.

Sikta Pradhan

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---------- Y L Huang 9/4/2002

Concur: Dale P. Conner Date: 9/6/02
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-553 (original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File

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Draft: 8-26-02
Final: 9-3-02

BIOEQUIVALENCY DEFICIENCIES

ANDA: #75-553 APPLICANT: Dey Lab Pharmaceutical
DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.06%

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

Your response regarding plume geometry testing is not acceptable. Selection of delay times should permit measurements when the plume is still in contact with the actuator's orifice. Plume angle measurements should be made at a delayed time between 10-50 msec. Plume height should be measured as the distance between the actuator orifice and tip of the plume. You are advised to repeat the plume geometry testing. The repeat testing may be performed on a single side view of the spray, instead of the two 0^0 and 90^0 views requested previously.

Sincerely yours,

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

CC: ANDA #75-553
ANDA DUPLICATE
DIVISION FILE
FIELD COPY

Endorsements: (Final with Dates)
HFD-652/ S. Pradhan
HFD-655/ G. Singh 9/3/02
HFD-650/ Y. Huang 9/4/2002
HFD-617/ K. Scardina 9/5/02
HFD-650/ D. Conner 9/6/02

Printed in draft on
Printed in final on 9-4-02

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IN VITRO BIOEQUIVALENCY STUDIES
Nasal Spray, 0.06%

1. Study Amendment (STA) 01C Submission date: 04-30-02
Outcome ~~IN~~ LC

OUTCOME DECISIONS: **IN** - Incomplete

FEB 13 2003

Ipratropium Bromide
Nasal Spray, 0.06% (42mcg/spray)
ANDA # 75-553
Reviewer: Sikta Pardhan
V:\Firmsam\Dey\ltrs&rev\75553A1202

Dey, L.P.
Napa, CA
Submission Date:
December 27, 2002

REVIEW OF AN AMENDMENT TO THE IN VITRO BIOEQUIVALENCE STUDY

OBJECTIVE

The firm had previously submitted an application for Ipratropium Bromide Nasal Spray, 0.06% and requested a waiver of *in vivo* bioequivalency testing requirements under 21 CFR 320.22 (b)(3). The application was found incomplete due to insufficient data analyses only on Plume Geometry (Amendment dated April 30, 2002).

As requested by the Agency, Dey, L.P. has repeated plume geometry testing and the results have been reported in the current amendment dated December 27, 2002.

Dey, L.P. has repeated plume geometry testing as one of the tests demonstrating bioequivalence between the Dey product and the reference listed drug. Samples from three recently manufactured batches of the Dey product were tested, along with three unexpired batches of Atrovent.

Plume Geometry:

The plume geometry testing was performed using [redacted] equipment manufactured by [redacted] Plume angle, plume width, and plume height for test and reference samples were obtained at 13 and 32 milliseconds from start of spray. It was recommended by the Agency to use two delay times: one early (at about 10 msec.), and then (around 40-50 msec.) when the height and width can be fully determined.

The firm has provided an acceptable validation report (ATR 783-03 in Appendix 4). DEY has also stated that the method of manufacture for the three batches of Dey product used in the conduct of the plume geometry testing is consistent with that submitted in the MAJOR AMENDMENT (A-006) dated 27 April 2001.

The plume geometry for samples from three batches of the Dey product was compared to the plume geometry for the three batches of Atrovent. All units were primed prior to recovering the entire spray event following actuation at a single orientation. The entire spray event was then played back to determine the delay preceding the start of the spray event, the time taken to achieve steady state (constant plume angle), the time the plume front was within the recordable image frame and the lifetime of the plume. All times recorded were corrected for the delay between actuation and the start of the spray event. The results generated were used to determine appropriate time point characterizing the plumes for all units examined. The frames for the individual spray events at two time points, as recorded on the ———— were analyzed to obtain the plume angle and plume height. The plume width at maximum height was then calculated from the component angles reported, furthering determination of plume height and plume angle.

Results of the plume geometry testing at early stage of plume (t=13 ms. from start of spray) have been summarized below.

	Test Product				Reference Product			
	Lot#	Angle	Height	Width	Lot#	Angle	Height	width
	W138				1586-10A			
Mean		62.2	68.1	82.3		66.0	70.9	91.7
CV%		8.4	10.3	10.4		8.8	18.2	15.1
Geometric Mean		62.0	67.7	81.9		65.8	69.8	90.8
	PD4-021262-139				2561-80B			
Mean		66.6	63.5	83.4		63.9	68.2	85.4
CV%		13.1	10.0	11.4		8.3	6.9	9.6
Geometric Mean		66.1	63.2	82.9		63.7	68.1	85.0
	PD4-021263-140				2566-44A			
Mean		68.3	64.6	87.8		69.7	64.4	89.6
CV%		9.1	10.6	13.3		10.5	11.7	8.0
Geometric Mean		68.0	64.2	87.2		69.4	64.0	89.4
Overall mean (n=3)		65.7	65.4	84.5		66.6	67.8	88.9
Overall (geomt.) mean (n=3)		65.3	65.0	84.0		66.3	67.3	88.4
Ratio (T/R) of means		0.99	0.96	0.95				
Ratio (T/R) of Geomt. Means		0.99	0.97	0.95				
P value		0.60	0.11	0.09				
Bet-lot %CV		4.74	3.69	3.45		4.44	4.81	3.61
Overal Variabillity		10.83	10.40	11.77		9.73	13.46	11.41

Results of the plume geometry testing at early stage of plume (t=13 ms. from start of spray) show that the ratios of geometric means of the test product and reference products, Ipratropium bromide Nasal Spray 0.06% fall within the 0.90 to 1.11 range, currently used by the DBE for acceptance of *in vivo* studies on solution nasal sprays.

Results of the plume geometry testing at the fully formed stage of plume (t=32 ms. from start of spray) have been summarized below.

	Test Product				Reference Product			
	Lot#	Angle	Height	Width	Lot#	Angle	Height	width
	W138				1586-10A			
Mean		61.9	107.9	129.5		64.4	13.4	130.3
CV%		6.4	14.5	14.8		9.5	9.5	9.1
Geometric Mean		61.7	106.9	128.2		64.2	103.0	129.8
	PD4-021262-139				2561-80B			
Mean		65.6	103.8	134.0		62.1	110.8	133.7
CV%		13.4	9.0	13.8		9.3	12.7	14.9
Geometric Mean		65.0	103.4	132.8		61.8	110.1	132.4
	PD4-021263-140				2566-44A			
Mean		69.8	94.7	132.5		65.4	108.7	139.3
CV%		8.6	9.8	11.3		9.5	11.4	8.6
Geometric Mean		69.5	94.3	131.7		65.2	108.0	138.8
Overall mean (n=3)		65.7	102.1	132.0		64.0	107.7	134.4
Overall (geomt.) mean (n=3)		65.4	101.4	130.9		63.7	107.0	133.6
Ratio (T/R) of means		1.03	0.95	0.98				
Ratio (T/R) of Geomt. Means		1.03	0.95	0.98				
P value		0.21	0.05	0.45				
Bet-lot %CV		6.02	6.57	1.76		2.69	3.56	3.37
Overal Variabillity		10.84	12.42	12.97		9.37	11.35	11.15

Results of the plume geometry testing at the fully formed stage of plume (t=32 ms. from start of spray) show that the ratios of geometric means of the test product and reference products, Ipratropium bromide Nasal Spray 0.06% fall within the acceptable range of 0.90 to 1.11.

OVERALL COMMENTS:

1. The in vitro performance data on plume geometry testing submitted by Dey, L. P. for its Ipratropium Bromide Nasal Spray, 0.06%, have been found acceptable.

2. The sponsor had previously (February 22, 1999) provided acceptable compositions on its test product.

3. The sponsor has successfully conducted (submission dated April 27, 2001, and April 30, 2002) the following *in vitro* tests to demonstrate comparable performance of the delivery system for the proposed drug product *vs* the reference product: (i) Spray Content Uniformity through Container Life (ii) Priming and Repriming (iii) Tail Off Profile (iv) Droplet Size Distribution – [redacted] (v) Droplet Size Distribution – Cascade Impaction (vi) Spray Pattern.

RECOMMENDATIONS

1. The in vitro performance data on plume geometry testing submitted by Dey, L. P. for its Ipratropium Bromide Nasal Spray, 0.06%, have been found acceptable to the Division of Bioequivalences.
2. From the bioequivalence point of view, the application is acceptable.
3. The firm should be informed of the recommendation.

Sikta Pradhan

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---------- Y Huang 2/12/2003

Concur: Dale P. Conner Date: 2/13/03
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-553 (original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File

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Draft: 01-31-03; Final: 02-11-03

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75-553 APPLICANT: Dey, L.P.
DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.06%

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

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

Sincerely yours,

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

CC: ANDA #75-553
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Endorsements: (Final with Dates)
HFD-652/ S. Pradhan SP
HFD-655/ G. Singh GSPS -2-12-03
HFD-650/ Y. Huang YH 2/12/2003
HFD-617/ A. Sigler
HFD-650/ D. Conner DRC 2/13/03

Printed in draft on 01/31/03
Printed in final on 02/11/03

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IN VITRO BIOEQUIVALENCY STUDIES ACCEPTABLE
Nasal Spray, 0.06%

1. Study Amendment (STA) OK Submission date: 12-27-02

AC – Acceptable

OUTCOME DECISIONS: **AC** - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #75-553 APPLICANT: Dey ~~Lab Pharmaceutical~~ Labs
DRUG AND DOSAGE FORM: Ipratropium Bromide Nasal Spray
STRENGTH: 0.06%
TYPES OF STUDIES : Waiver In vitro testing
CINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic _No_ New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Sikta Pradhan, Ph.D. BRANCH : I
INITIAL : Sikta Pradhan DATE : 2/11/03

TEAM LEADER : Yih-Chain Huang, Ph.D. BRANCH : I
INITIAL : YCH DATE : 2/12/2003

DIRECTOR: DALE P. CONNER, Pharm.D.
DIVISION OF BIOEQUIVALENCE:
INITIAL : DPC DATE : 2/13/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-553

ADMINISTRATIVE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # **75-553** Applicant **Dey, L.P.**
Drug **Ipratropium Bromide Solution (Nasal Spray)** Strength **42 mcg/spray (0.06%)**

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

REVIEWER:

1. Project Manager, Team PETER CHEN — **DRAFT Package** Date 3/3/03 Initials P. — **FINAL Package** Date 3/6/03 Initials PC
   Review Support Br 2

Application Summary:

Original Rec'd date 2/25/99
Date Acceptable for Filing 2/25/99
Patent Certification (type) III
Date Patent/Exclus.expires EXPIRED
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD = ATROVENT 0.06%
Date checked 3/3/03 NDA# 20-394
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 6/26/02
Date of Office Bio Review 2/13/03
Date of Labeling Approv. Sum 12/10/01
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

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

2. Gregg Davis **PPIV ANDAs Only** Date 3/28/03 Initials AW — Date _____ Initials _____
   Supv., Reg. Support Branch

Contains GDEA certification: Yes ☐ No ☐ (required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☐ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Comments: At the time of filing the ANDA, Dey made a "paragraph 3" certification and addressed the exclusivity but was in effect at that time. Currently there are no unexpired patents listed in the Orange Book for this drug product. Dey has addressed the I-327 exclusivity and it has been "carved-out" of the final printed labeling.

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
Date Checked 3/28/03
Nothing Submitted ☒ NDA 20-394
Written request issued ☐
Study Submitted ☐
RLD = Atrovent Nasal Spray 0.06% (0.042 mg/spray) Boehringer Ingelheim Pharmaceuticals, Inc.

3. Div. Dir./Deputy Dir. Date 3/4/03
   Chemistry Div. I or II Initials PS
   Comments: specs OK

Note. This is the "sister" ANDA to 75-552 (0.03%).

REVIEWER:

FINAL ACTION

4. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review) SATISFACTORY

Date 3/27/03
Initials FH

5. Peter Rickman
~~Acting~~ Director, DLPS
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable CES dated 6/26/02 (Verified 3/28/03) No OAI alerts noted. Bioequivalency studies (in-vitro tests including unit spray content, content uniformity, spray pattern, particle size distribution, plume geometry, etc.) found acceptable 2/12/03. Formulation determined to be "QR" to the RLD. OSI inspection of _____ completed. office-level bio endorsed 2/13/03.
FR found acceptable 12/10/01 (as endorsed 3/5/03). E-327 exclusivity is "carved-out" - See Keys 12/27/02 amendment. CMC found acceptable 3/10/03. Methods validation was completed on "sister" ANDA 75-552 and found acceptable.

Date 3/28/03
Initials PR for RLD

5. Robert L. West
~~Acting~~ Deputy Director, OGD
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒ Petition: Yes☐ No☒
Comments:

Date 3/28/2003
Initials Robert West

This ANDA is recommended for approval.

6. Gary Buehler
Director, OGD
Comments:

Date 3/31/03
Initials GB

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

7. Project Manager, Team Peter Chen
Review Support Branch

Date 3/31/03
Initials PC

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

Applicant notification:
9:17A Time notified of approval by phone 9:22A Time approval letter faxed

FDA Notification:
3/31/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
3/31/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-553

CORRESPONDENCE

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

December 31, 1998

RTF
C. Holquist
1-26-99

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 0.06%
Original ANDA

Dear Mr. Sporn:

DEY hereby submits this abbreviated new drug application for Ipratropium Bromide Nasal Spray 0.06%.

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 0.06%, NDA 20-394 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 0.06%, 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.

A Lipha Americas Company
An Associate of Merck KGaA, Darmstadt, Germany

(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 75-553

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, 0.06%.

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 exclusivity statement is incorrect. It references "an indication for children ages 6 to 11" expiring on April 1, 2001. This exclusivity does not exist for NDA 20-394. Please provide a revised exclusivity statement referencing "I-243 - expiring on November 9, 2001". We refer you to the 18th edition of Approved Drug Products with Therapeutic Equivalence Evaluations, Cumulative Supplement 9 for further guidance.

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.

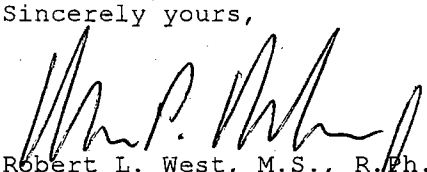
Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

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 75-553
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, date 1/29/99
HFD-625/MSmela/Sup. Chem, date
V:\firmsam\dey\ltrs&rev\75553.rtf.doc
F/T mjl/1/27/99
ANDA Refuse to File!

APPEARS THIS WAY
ON ORIGINAL

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

Ack for Chris S. Middleton 3/8/99 505(j)

MDA ORIG AMENDMENT
AC

22 February 1999

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 75-553
Ipratropium Bromide Nasal Spray 0.06%
Response to FDA letter dated February 4, 1999

Dear Mr. West:

Reference is made to ANDA 75-553 for Ipratropium Bromide Nasal Spray 0.06% 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 exclusivity statement is incorrect. It references "an indication for children ages 6 to 11" expiring on April 1, 2001. this exclusivity does not exist for NDA 20-394. Please provide a revised exclusivity statement referencing "I-243 - expiring on November 9, 2001". We refer you to the 18th edition of Approved Drug Products with Therapeutic Equivalence Evaluations, Cumulative Supplement 9 for further guidance.

Supplement 9 was not available to DEY at the time of filing. The exclusivity statement has been revised and a copy is included in this amendment at Tab 2.

RECEIVED
FEB 25 1999
GENERIC DRUGS

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 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 75-553

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

MAR 16 1999

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, 0.06%

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 Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-553
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 3/15/99
HFD-615/SMiddleton, CSO date 3/11/99
HFD-625/MSmela, Sup. Chem. date
V:\FIRMSAM\DEY\LTRS&REV\75553.ACK
FT by/njg/3/9/99
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

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

19 May 1999

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

VIA UNITED PARCEL SERVICE
(301) 827-5845

NEW CORRESP
NC

RE: ANDA 75-553 Amendment 002
Ipratropium Bromide Nasal Spray 0.06%
Electronic Submission and CMC Amendment 002

Dear Mr. Sporn:

Reference is made to ANDA 75-553 Ipratropium Bromide Nasal Spray 0.06%, submitted on 31 December 1998 and filed on 28 February 1999.

Enclosed please find an electronic copy of CMC information from the ANDA initial submission and amendments 001 and 002. While completing the EVA 4.13 database, it was noted that:

(1) In-process test data were requested in EVA that had not already been provided in the ANDA. Therefore, the in-process data sheets containing the additional testing information are enclosed.

(2) The three months content uniformity results (pages 100762 and 100766 of Volume 3 in the original submission) contained an error on the stability reports, the horizontal raw data were inadvertently placed with the upright raw data and vice versa. The corrected reports are enclosed.

If you have any questions or require additional information, please contact me at (707) 224-3200 ext. 4750.

Sincerely,

Peggy J. Berry
Regulatory Affairs Senior Manager

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 20 1999
OGD

001

BIOEQUIVALENCY AMENDMENT

JUN 29 1999

ANDA 75-553

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: Elaine Hu PROJECT MANAGER (301) 827-5847

Dear Ms. Berry:

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, 0.06% (42 mcg/spray).

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:

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

JUN 29 1999

BIOEQUIVALENCY DEFICIENCIES

ANDA: #75-553 APPLICANT: Dey Lab Pharmaceutical

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.06%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has the following comments:

1. The *in vitro* testings conducted by you on unit dose, spray pattern, plume geometry, droplet size distribution (using cascade impactor and laser diffraction), and priming and tail off sprays are all deficient. Therefore, all *in vitro* tests should be repeated as follows:

   Comparative performance of drug delivery devices of the test and reference products should be based on the following tests:

   A. Unit Dose/Content Uniformity.
   B. Priming, loss of prime and tail off
   C. Droplet size distribution by at least two methods.
   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 should be assessed at each sector.

With regard to specific tests:

A. Unit Dose and Uniformity of Unit Dose

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 procedure, of determination of the amount of drug per spray by weight difference of the bottles, is not acceptable. The amount of drug per single spray should be determined using a validated analytical (chemical/chromatographic) procedure. Assay validation data should be submitted.

B. Priming and Tail-off Data

You 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 each test for both 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.*

C. Droplet Size Distribution

(i). *Laser Diffraction*: Droplet size distribution by laser diffraction (e.g.) should be determined 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 in order to characterize the plume upon formation, as the plume has started to dissipate, and at some intermediate time. 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.

(ii). *Cascade impaction:* The cascade impactor characterizes particles in a smaller size range than the expected range for this product. However, it is useful to assure that there is not an excess mass of "fines" in the test product relative to the RLD. Cascade impactor data based on a validated assay should account for mass balance and be reported in the following groups:

Group-1: From valve stem and actuator up to top stage (stage zero)
Group-2: One stage below the top stage
Group-3: Everything from 2nd stage through the filter

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

D. Spray Pattern

Spray patterns should be determined at three distances from the TLC plate at the beginning and end life sectors, based on single actuation. 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}.

E. 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. You are requested to provide all photographs and data characterizing plume dimensions. Photographs should be overlaid with marked grids for quantitation.

2. As the device and formulation are integral components of a nasal spray, you are required to provide information to support sameness of test and reference devices. You should provide to the extent possible a side-by-side comparison of the pumps and actuators used in the test and reference products. Information regarding the manufacturer, model numbers of the pumps, actuators, actuator inserts and overcaps should also be provide. Technical drawings with dimensions should be submitted, if available.

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

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

AUG 26 1999

ANDA 75-552
75-553

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

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8/26/1999 FDA FAX

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

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

ANDA Number: 75-553 Date of Submission: February 22, 1999

Applicant's Name: Dey Labs

Established Name: Ipratropium Bromide Nasal Solution, 0.06%

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

   a. See comment (a) under GENERAL COMMENTS.

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

   c. Include the following statement:

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

   d. Revise your storage recommendation to read as follows:

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

3. CARTON

   a. See comment (a) under GENERAL COMMENTS.

   b. See comments under CONTAINER.

4. PHYSICIAN'S INSERT

a. See comment (a) under GENERAL COMMENTS.

b. Please note the most recent labeling for the reference listed drug, ATROVENT® Nasal Spray, was approved November 9, 1998. Please revise your insert labeling to be in accord with the enclosed copy of this labeling.

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).

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 final printed 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 D. 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

RE: ANDA 75-553 Amendment 003
Ipratropium Bromide Nasal Spray 0.06%
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 75-553 (Ipratropium Bromide Nasal Spray 0.06%). 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 EVALUATION AND RESEARCH
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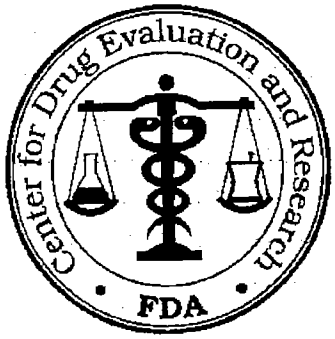
BIOEQUIVALENCY AMENDMENT

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:

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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

CMC questions would require pre-review to answer which is not allowed per OGD procedure. Dey should be advised to respond with their MAJOR Amendment. Dey should contact John Grace for the labeling question.
M Dillahunt 11/22/99

NEW CORRESP
NC

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

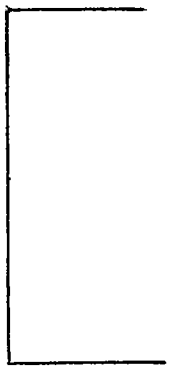
RE: ANDA 75-552
Ipratropium Bromide Nasal Spray 0.03%
ANDA 75-553
Ipratropium Bromide Nasal Spray 0.06%

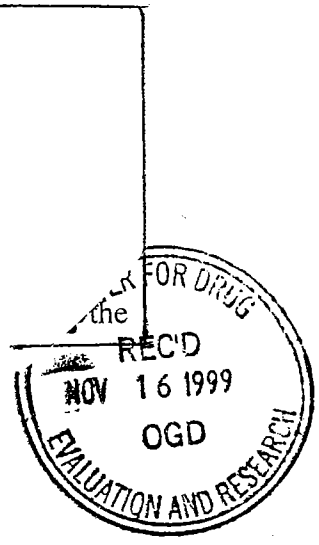
Dear Ms. Dillahunt:

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:





11-17-99

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11/15/1999 DEY LETTER

ANDA 75-553

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

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

JUN 1 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 Solution 0.03% and 0.06%.

We refer you to our "Not Approvable" letter dated August 26, 1999, which detailed the deficiencies identified during our review of your ANDA. Although we acknowledge your communication dated November 15, 1999, 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,

for Sandra J. Middleton

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

cc: ANDA # 75-553
DUP/Division File
HFD-610/PRickman

Endorsement:
HFD-617/NMahmud, Chief, RSB, for S. Middleton date 5/7/00
HFD-617SMiddleton, CSO, S. Middleton date 5/25/00
Word File
V:\FIRMSAM\DEY\LTRS&REV\75553.OTH
F/T by mjl/5/24/00
10 DAY LETTER!

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

Status will amend by 8/7/00 (Check their S. Mitchell letter 6/14/00

7 June 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 75-553 Amendment 004
Ipratropium Bromide Nasal Spray 0.06%
FDA Request for Amendment dated June 1, 2000

Dear Mr. Rickman:

This letter is in response to the FDA correspondence dated June 1, 2000 requesting amendment to ANDA 75-553. As stated in Amendment 003 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 29, 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).

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 08 2000
OGD

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

Fax will Amend ANDA by Oct 31, 2000! Cheers S. Middleton 8/22/00

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 75-553 Amendment 005
Ipratropium Bromide Nasal Spray 0.06%
FDA Request for Amendment

Dear Ms. Middleton:

This letter is in response to your phone call of 17 August 2000 requesting amendment to ANDA 75-553. Reference is also made to Amendment 004 dated 7 June 2000.

In Amendment 004 Dey stated that the in vitro bioequivalence testing needed to respond to the FDA's June 29, 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

Peggy J. Berry
Director, Regulatory Affairs

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
N/AC

RE: ANDA 75-553/A-006
Ipratropium bromide Nasal Spray 0.06%
MAJOR Amendment/Bioequivalency Amendment

Dear Mr. Buehler:

This submission to ANDA 75-553 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 29 June 1999.

Responses to items in both facsimiles are provided in volume 1 of this amendment. Volumes 2 through 12 provide data, analyses, and information pertaining to the *in vitro* bioequivalency testing. Volume 13 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

Peggy J. Berry
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
APR 30 2001
OGD

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 75-553/A-007
Ipratropium Bromide Nasal Spray 0.06%
MINOR Amendment

Dear Mr. Buehler:

This MINOR Amendment to ANDA 75-553 provides additional information related to the 27 April 2001 amendment.

The following information is included:

- Laboratory Method TM-DY01-03, "Content Uniformity and Tail off Characteristics of 0.06% Ipratropium Bromide Nasal Sprays Generated by Automated Actuation during a Bioequivalence Study." This method was inadvertently omitted from Bioequivalency Response 1 in volume 1 of the 27 April 2001 amendment.

- Twelve copies of color draft bottle label and shelf carton labeling. The text and placement are identical to that of the black and white bottle label and shelf carton labeling submitted (volume 1, page 01 307) in the 27 April 2001 amendment.

The CD-ROM labeled Data 0101, 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 ———

01 001

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

APPEARS THIS WAY
ON ORIGINAL

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

15 August 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

NEW CORRESP
NC

RE: ANDA 75-553/A-008
Ipratropium Bromide Nasal Spray 0.06%
Methods Validation Package

Dear Mr. Buehler:

Enclosed is the Methods Validation Package for Ipratropium Bromide Nasal Spray 0.06%. 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]

AUG 17 2001
OGD
EVALUATION AND RESEARCH

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8/15/2001 DEY LETTER

MINOR AMENDMENT

NOV 14

ANDA's 75-552
75-553

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 (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 and Labeling comments included.

11/14/01 M

NOV 14 2001

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,

Paul Schwagler

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: 75-553 **Date of Submission: April 27, 2001 and May 10, 2001**

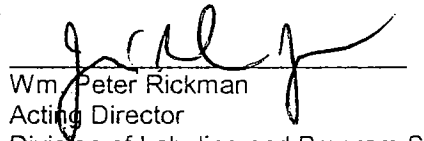
Applicant's Name: Dey Labs
Established Name: Ipratropium Bromide Nasal Solution, 0.06% (Nasal Spray)
Labeling Deficiencies:

1. GENERAL COMMENT
   a. Please update your exclusivity statement.
   b. We note your comment on revising the product name. However, "Nasal Spray" could be used as indicated below. The established name for this product is Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray). Revise all labels and labeling accordingly.
2. CONTAINER 15 mL - See comment under GENERAL COMMENTS.
3. CARTON 15 mL - See comment under GENERAL COMMENTS.
4. PHYSICIAN'S INSERT-
   a. See comment (a) under GENERAL COMMENTS.
   b. Please comment on the layout of your insert. The text appears in different directions. The front side of the insert and backside are printed in different directions. Please revise and /or comment.
   c. Several paragraphs breaks are needed in your insert. Please insert a paragraph break at the following locations:
      i. Adverse Reactions – current 3rd paragraph at "Adverse events reported by less than 1%...
      ii. Adverse Reactions – current 4th paragraph at" No controlled trial was conducted...
      iii. OVERDOSAGE – At "oral median lethal doses of...".
      iv. DOSAGE AND ADMINSTRATION – Current 2nd paragraph at "Initial pump priming requires...
   d. PRECAUTIONS. Pediatric Use
      i. 2nd second sentence - ...pediatric population ipratropium Bromide... (combined sentences).
      ii. Create a paragraph break at "When Ipratropium bromide was concomitantly administered...
   e. Revise your storage recommendation to read as follows: Store between 15°C to 30°C (59°F to 86°F).
5. PATIENT PACKAGE INSERT – The layout of your insert makes it impossible for the patient to receive the full text. Perforations appear on opposite sides of the insert. The text should be positioned so that the patient gets the full running text.

Please revise your labels and labeling, as instructed above, and submit 12 final print labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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



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

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 75-553/A-009
Ipratropium Bromide Nasal Solution 0.06% (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 75-552, Ipratropium Bromide Nasal Solution 0.03% (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
Manager, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 04 2001
OGD

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 MD

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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

APPEARS THIS WAY
ON ORIGINAL

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 75-553/A-011
Ipratropium Bromide Nasal Solution 0.06% (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.

[ ]

One product lot each of Atrovent Nasal Spray 0.03% and 0.06% were placed on stability at 25°C and tested concurrently with Dey's products for ———— ———— The table on the next page summarizes the available reference listed drug product data and proposes an upper limit using the same criteria as proposed for Dey's products. The reference product data shows a similar range of

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4/26/2002 DEY LETTER

As discussed in the teleconference, a copy of this amendment will be faxed to Dr. Shaikh.

Thank you for the opportunity to discuss these requests. Please call me at 707-224-3200, x4750 if you have any questions or comments.

Sincerely,

Michelle A Carpenter

Michelle A. Carpenter, J.D.
VP, Regulatory Affairs and Clinical Development

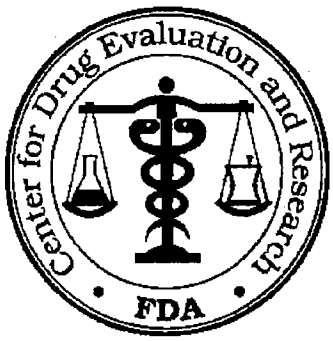
APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

ANDA 75-553

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)

APR 18 2002



APPLICANT: Dey L. P.

TEL: 707-224-3200 ext 4750

ATTN: Peggy J. 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, 0.06 %

Reference is also made to your amendment of May 10, 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: The following dissolution specification should be incorporated into you finished product release and stability specifications. Please revise and resubmit these specifications accordingly. The response should be noted as a "Telephone Amendment".

BIOEQUIVALENCY DEFICIENCIES APR 18 2002

ANDA: #75-553 APPLICANT: Dey Lab Pharmaceutical
DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.06%

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 *in vitro* testing conducted by you on plume geometry is deficient. You are requested to provide a detailed analytical procedure for plume geometry along with the sample quantification.
2. Plume Geometry measurements were taken at delay times of 2.4, 105 and 208 msec. These delay- times are not appropriate. Based on the Agency's experience, a delay time of 2.4 msec. is too short to reflect meaningful plume formation. Furthermore, at delay-times of 105 and 208 msec, the plumes are no longer intact with the actuator orifice. Furthermore, the measurement of plume height was not appropriate. Plume height should be measured as the distance between the actuator orifice and tip of the plume.
   Hence, You are advised to repeat plume geometry analysis using appropriate delay times. Selection of delay times should permit measurements when the plume is still in contact with the actuator's orifice. Plume angle measurements should be made at a delayed time between 10-50 msec.
3. You are advised to clarify the reagents used for visualization of the spray patterns on TLC plates. If the submitted data are based on spot visualization without a reagent, spray pattern testing should be repeated.
4. You had previously (February 22, 1999) provided acceptable composition of your test product, Ipratropium Bromide Nasal Spray 0.06%. You are advised to provide a statement indicating that there is no change in composition between the current lots and the lot used in 1999, whose composition was acceptable to the Agency.
5. You are requested to provide the lot size and number of spray units present in each lot (#W085, #W086A and #W086B).

Sincerely yours,

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

30 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

ORIG AMENDMENT
AB

RE: ANDA 75-553/A-012
Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray)
Bioequivalency Amendment

Dear Mr. Buehler:

This Bioequivalency Amendment responds to all deficiencies listed in the facsimile dated 18 April 2002. For ease of review, the Agency comments are repeated in bold within this amendment and are followed by Dey's responses along with pertinent documentation.

Please contact me at 707-224-3200, x4750 to clarify any comments or questions regarding this amendment. As launch preparation is underway, I will call later this week to confirm that this information was received and review status.

Sincerely,

Kimberle Carneal
FOR

Michelle A. Carpenter, J.D.
VP, Regulatory Affairs and Clinical Development

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MINOR AMENDMENT

ANDA 75-553

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)

SEP 11 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, 0.06%.

Reference is also made to your amendment(s) dated: April 26, 2002, and February 28, 2002

PC 9/11/02

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 and bioequivalency comments included.

PC 9/11/02

SEP 11 2002

38. Chemistry Comments to be Provided to the Applicant

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

DRUG PRODUCT: Ipratropium Bromide Nasal Solution, 0.06%

The deficiencies presented below represent Minor deficiencies.

Bioequivalence for this product has not been demonstrated. Please submit your response to the attached bioequivalence deficiencies. 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

SEP 11 2002

BIOEQUIVALENCY DEFICIENCIES

ANDA: #75-553 APPLICANT: Dey Lab Pharmaceutical
DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.06%

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

Your response regarding plume geometry testing is not acceptable. Selection of delay times should permit measurements when the plume is still in contact with the actuator's orifice. Plume angle measurements should be made at a delayed time between 10-50 msec. Plume height should be measured as the distance between the actuator orifice and tip of the plume. You are advised to repeat the plume geometry testing. The repeat testing may be performed on a single side view of the spray, instead of the two 0^0 and 90^0 views requested previously.

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

26 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 75-553
Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray)
Response to Not Approvable Facsimile Dated 11 September 2002

Dear Mr. Buehler:

This letter is in response to the Not Approvable facsimile dated 11 September 2002 for ANDA 75-553. 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,

JSummers for

Michelle A. Carpenter, J.D.
Vice President, Regulatory and Clinical Affairs.

NAI
TPC 10/16/02

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10/11/02

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

27 December 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

ORIGINAL
N/AF

RE: ANDA 75-553/A-014
Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray)
Labeling Amendment

Dear Mr. Buehler:

This Labeling Amendment responds to comments received in a 16 October 2002 teleconference with Dey and Angela Payne. During this call, we were informed that no more labeling comments were expected for our Ipratropium Nasal products and that we should, however, check for any changes to the innovator's labeling.

The listed drug referred to in this application, Atrovent® (ipratropium bromide) Nasal Spray 0.06%, has had a labeling update since our labeling submission of 03 December 2001 (A-009). Atrovent is the subject of an exclusivity for an indication of Seasonal Allergic Rhinitis. Dey will not seek approval of labeling that includes the exclusive indication and has prepared the attached Exclusivity Statement. Dey will commit to providing a side-by-side comparison showing the differences between the innovator's labeling (dated 3/01) and Dey's labeling (dated March 2001).

A copy of this amendment has been faxed to Angela Payne. If you have any questions, please contact me at 707-224-3200, x6076 or Michelle Carpenter, Vice President, Clinical and Regulatory Affairs at x4750. As launch preparation is underway, I will call next week to confirm that this information was received and to check on the review status.

Sincerely,

Kimberly S. Carneal, RAC
Manager, Regulatory Affairs

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

27 December 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

ORIG AMENDMENT
N/AM

RE: ANDA 75-553/A-013
Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray)
MINOR AMENDMENT/BIOEQUIVALENCY AMENDMENT
Response to FDA facsimile dated 11 September 2002

Dear Mr. Buehler:

This MINOR AMENDMENT/BIOEQUIVALENCY AMENDMENT responds to all deficiencies listed in the FDA facsimile dated 11 September 2002 (see attached) for ANDA 75-553, Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray). The content of this amendment was discussed during a teleconference conducted 30 September 2002 between Dey and the FDA.

As agreed during the teleconference, Dey has repeated plume geometry testing as a parameter for demonstrating bioequivalence between the Dey product and the reference listed drug. Samples from three recently manufactured batches of the Dey product were tested, along with three unexpired batches of Atrovent.

Test results show that the ratios of geometric means of test product, Dey's Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray), to reference product, Atrovent® (ipratropium bromide) Nasal Spray .06%, fall within the FDA required 0.90 to 1.11 range.

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As further agreed during the teleconference, testing was performed using ———— equipment manufactured by ————————————. Plume angle, plume width, and plume height for test and reference samples were obtained at 13 and 32 milliseconds from start of spray. A report, ATR 783-02, summarizing the results of the testing, along with raw data listings, is included in Appendix 1. The report also includes a table listing lot numbers and expiration dates for the test and reference product lots used.

Raw data listings in MS Excel 97 format are also included on the CD in Appendix 5. The CD in Appendix 5 also contains representative photographs showing how the data was quantitated. Photocopies of the photographs are included in the same appendix.

Analytical Results Summaries from the three tested batches of Dey product are included in Appendix 2.

The Test Method, ATM 783-01, is included in Appendix 3. The validation report, ATR 783-03, for the method is included in Appendix 4.

Dey certifies that the method of manufacture for the three batches of Dey product used in the conduct of the plume geometry testing is consistent with that submitted in the MAJOR AMENDMENT (A-006) 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