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RESEARCH**

APPLICATION NUMBER:

76-156

**BIOEQUIVALENCE
REVIEW(S)**

Ipratropium Bromide
Nasal Spray, 0.03% (21 µg/spray)
ANDA # 76-156
Reviewer: Gur J.P. Singh
W. 76156SW.301

Novex Pharma
Richmond Hill, Canada
Submission Date:
March 30, and July 6, 2001

*Review of Comparative Formulation
and In Vitro Performance Data*

Ipratropium Bromide Nasal Spray (IPBR NS) 0.03% is indicated for the relief of rhinorrhea associated with the common cold for adults and children age 12 years and older. The active drug is a quaternary amine that is poorly absorbed into the systemic circulation from the nasal mucosa. The reference listed drug (RLD) is Atrovent® Nasal Spray, 0.03% (21 µg/spray) manufactured by Boehringer Ingelheim.

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

Division of Bioequivalence (DBE) evaluates equivalence of solution nasal sprays based on Q1 and Q2 sameness of formulations and comparable in vitro performance in drug delivery. The firm submitted supporting data on March 30, 2001. Based on a preliminary review of this application, the firm was requested to provide additional supporting data. The sponsor submitted the requested information on July 6, 2001. The following review is based on the data submitted on March 30 and July 6, 2001.

FORMULATION COMPARISON (not for release under FOI)

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

pH = — (Test) and — (Ref)

IN VITRO TESTING RECOMMENDATIONS

This application contains in vitro performance data for the lower of the two marketed strengths (0.03% and 0.06%) of IPBR NS. Novex uses same models of pumps and actuators for its IPBR NS, 0.03% and 0.06%. The firm has submitted full in vitro testing on its IPBR NS 0.06% (ANDA #76-155) and abbreviated testing on the 0.03% product.

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

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

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

DRUG PRODUCTS

Test: Novex Pharma's Ipratropium Bromide Nasal Spray, 0.03%, consisted of one lot of the drug solution formulation (Lot #0X210, Lot size _____ divided into three sublots using three separate batches of pumps (Novex Pharma QC Nos. 5633, 5634 and 5635).

Reference: Boehringer Ingelheim's Atrovent® Nasal Spray, 0.03%; Lots 819013B, 819014A and 819014B. The expiry dates for all three batches was 8/01.

COMPARABILITY OF SPRAY DEVICES

The pump supplier _____ has confirmed that the metered dose pump supplied for Novex Pharma's Ipratropium Bromide Nasal Spray, 0.03% is identical to that used in Atrovent® Nasal Spray (also supplied by _____). Physical comparative data with the test and reference metering devices were provided. Based on the July 6 amendment, comparative dimension of the test and reference product actuators are as follows:

Parameter	Dimension	
	Test	REF
Height	34.44 mm	33.87 mm
Outer Width	8.25 mm	8.37 mm
Inner Width	4.27 mm	4.97 mm
Orifice Diameter	260 μ	264 μ

IN VITRO PERFORMANCE TESTING

Procedures and Information Applicable to All Tests

All actuations of the nasal spray products were made using an automated actuator to actuate the nasal sprays in a reproducible manner. The actuator used designed by _____ for nasal spray actuation. The procedure used for operation of the actuator is described in SOP# GM-143 (pp. 121, vol. 1.1). The actuator operating conditions were as follows:

Dose time:	20 msec
Return Time:	30 msec
Hold Time:	0.5 sec
Actuation Force:	6.0 kg

Unit dose (Unit spray content) and uniformity of unit dose

Novex Pharma submitted data for the above-mentioned testing. The firm performed the uniformity of unit dose test using a stability-indicating method [Test Method No. TM-1132, vol. 1.1, pp. 139]. Since the labeled number of full medication doses per bottle is 345 sprays, the unit dose test was carried out on the entire bottle to determine the priming, re-priming and tail-off characteristics. According to the *Patient's Instructions for Use leaflet* for reference listed drug, each unit is primed by wasting seven actuations, and the unit should be re-primed by actuating the pump twice after 24 hours of non-use and by 7 actuations after 7 days of non-use.

The number of sprays required to prime the pump was determined by assaying the first ten sprays of each unit. A re-priming study was performed by leaving the bottle for 24 hours in upright position, and drug content of the next spray (No. 177) was then analyzed immediately. Additional studies to evaluate the performance of the pump after 7 days of non-use were also performed. Repriming studies included units stored in both horizontal and vertical positions.

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 also determined by weighing bottles before and after each spray collection, and the amount of drug per spray was determined by a validated analysis (LOQ= _____)

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

Product	Sector	Mean		Variability (%CV)			T/R	p
		Arith.	Geo.	Intra-lot	Inter-lot	Total		
Test	Beg.	99.99		0.99-1.55	0.21	1.22	0.98	0.0004
			99.98				0.98	
	End	99.83		1.06-1.70	0.51	1.41	0.98	0.0008
			99.83				0.98	
Ref	Beg.	102.37		0.93-2.18	2.17	2.3		
			102.35					
	End	102.33		1.24-4.19	1.94	3.03		
			102.28					

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

Comments on the Unit Dose Data

1. For Novex's product, the geometric mean values at actuations 8 and 345 values are 2% lower than the corresponding reference product values. The test product exhibited slightly lower variability (%CV) than the reference product with regard to the unit dose data. The test/ref ratios are within the 90-111% limits employed hitherto by DBE for acceptance of nasal solution sprays.
2. The quantity of the drug assayed is based on each single spray. The minimum and maximum values for the test product show that the delivered doses fall within 95.5-106.3% of the labeled dose. The draft guidance recommends that based on the 'first tier' of testing (10 units), not more than one unit be outside 80-120% of the label claim, and none should be outside the 75-125%, and mean values should not outside 85-115%.

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 (Figure 1, attachment). Prime retention was determined on the 177th spray by allowing the product to rest for a period of 24 hours or 7 days, followed by collecting the next spray without priming. Based on the data submitted, the test and reference products have the same prime retention characteristics.
5. The unit spray content data are based on both the _____ assay and gravimetric measurements. There is a good correlation between the quantity of the drug delivered per spray obtained by weight and that obtained by assay using an _____ method.
6. The tail off profile characterizes the decrease in emitted dose following delivery of the labeled number of actuations) based on the _____ assay (up to actuations 360) and by tabulating the spray weights up to actuation 460 (corresponding to full spray No. 165) to product exhaustion. Data given in Figure 2 (attachment) indicate that the test product delivers the labeled numbers of doses and its tail off is no more erratic than that of the reference product.

Droplet size distribution

a. Laser Diffraction

Droplet size determination was performed based on the Test Methods GM 155 (vol. 1.1) on 10 units from each of the 3 unit lots of test and reference products. Each unit was tested only at the beginning sector of unit life. Each unit was actuated at three distances relative to the _____ (3 cm, 6 cm, and 9 cm). At each distance, measurements were taken at different delay times. The three delay times characterize three regions in the plume life based on % transmission:

<i>Plume Region</i>	<i>Transmission Characteristic</i>
Plume formation (Initial)	Drops
Fully formed plume (Intermediate)	Stable
Plume dissipation (End)	Rises

The three separate regions constitute the sampling areas on which the droplet size distribution data are based. The delay times representing these regions vary with the actuation distance. In the July 6 amendment (vol. 2.1), the firm has submitted representative time history plots indicative of the three plume regions. Based on these graphs, the firm's selection of the three plume regions is acceptable.

The firm submitted D10, D50, D90 and SPAN data. Equivalence evaluation is based on D50 and SPAN data. A summary of these data based on the reviewer's calculations is as follows:

D50										
Prod.	Distance (cm)	Plume Form.	Mean (N = 30)		Variability (%CV)			TEST/REF		p
			Arith.	Geo.	Intra-lot (N=10)	Inter-lot (N=3)	Total (N=30)	Arith.	Geo	
TEST	3	Initial	30.02	29.95	6.8-7.5	0.81	7.07	0.98	0.98	0.259
		Intermed.	25.22	25.21	2.2-3.9	0.93	3.37	0.95	0.95	0.002
		Dissip.	30.13	30.10	3.2-5.6	1.48	4.61	0.99	0.99	0.475
	6	Initial	37.25	37.18	3.4-8.1	0.93	5.91	1.00	1.00	0.819
		Intermed.	33.49	33.46	3.7-4.3	1.84	4.20	0.99	0.99	0.300
		Dissip.	34.96	34.93	3.2-4.7	1.48	4.23	0.98	0.98	0.068
	9	Initial	42.07	41.83	5.5-12.6	3.81	9.27	1.00	0.99	0.847
		Intermed.	39.78	39.74	2.8-5.3	1.82	4.69	1.00	1.00	0.816
		Dissip.	41.12	41.11	2.2-2.6	0.78	2.55	0.98	0.98	0.011
REF	3	Initial	30.56	30.52	4.4-4.8	3.55	5.05			
		Intermed.	26.45	26.43	2.3-4.1	2.53	3.79			
		Dissip.	30.37	30.35	3.1-3.9	2.51	3.91			
	6	Initial	37.36	37.31	4.5-5.4	2.30	5.10			
		Intermed.	33.87	33.84	3.2-4.6	1.29	3.80			
		Dissip.	35.68	35.65	3.3-4.4	3.38	4.53			
	9	Initial	42.22	42.11	5.8-5.9	5.98	7.36			
		Intermed.	39.91	39.86	3.6-5.8	2.25	5.14			
		Dissip.	41.88	41.87	1.7-2.1	1.56	2.22			

SPAN										
Prod.	Distance (cm)	Plume Form.	Mean (N = 30)		Variability (%CV)			TEST/REF		p
			Arith.	Geo.	Intra-lot (N=10)	Inter-lot (N=3)	Total (N=30)	Arith.	Geo	
TEST	3	Initial	1.41	1.40	9.8-15.5	1.86	12.31	1.02	1.02	0.914
		Intermed.	1.26	1.26	7.4-11.5	3.63	9.63	0.96	0.96	0.080
		Dissip.	2.18	2.17	5.1-11.9	2.70	8.65	1.02	1.01	0.399
	6	Initial	1.04	1.04	8.1-10.6	2.52	8.96	0.95	0.95	0.016
		Intermed.	0.95	0.94	7.5-10.0	4.24	9.11	0.94	0.94	0.013
		Dissip.	0.94	0.94	7.7-12.8	2.20	9.77	1.03	1.03	0.135
	9	Initial	1.12	1.11	6.8-13.6	4.90	10.22	0.90	0.90	0.003
		Intermed.	1.01	1.01	5.2-7.9	1.87	6.62	0.94	0.94	0.002

		Dissip.	0.82	0.82	5.5-7.6	0.70	6.40	1.02	1.02	0.174
	3	Initial	1.38	1.37	4.0-12.3	2.53	10.00			
		Intermed.	1.32	1.31	5.8-11.2	3.79	8.90			
		Dissip.	2.15	2.14	5.3-6.6	2.31	6.11			
REF	6	Initial	1.10	1.09	7.2-8.8	1.64	8.55			
		Intermed.	1.01	1.00	6.3-8.6	2.05	8.91			
		Dissip.	0.91	0.91	6.4-9.9	3.51	8.45			
	9	Initial	1.24	1.24	4.4-9.7	1.56	9.24			
		Intermed.	1.08	1.08	4.7-9.1	2.25	6.77			
		Dissip.	0.80	0.80	2.5-8.6	1.60	5.51			

Comments on Droplet Size Distribution by laser diffraction

1. The test/reference ratios of the geometric means of D50 at initial, middle and end of plume formation for the three distances are in the range of 0.95-1.00. For most comparisons the P values were insignificant.
2. The ratios of the test geometric means to the reference geometric means for SPAN at initial, middle and end of plume formation for the three distances are in the range of 0.94-1.02. For most of the comparisons the P values were insignificant.
3. For D50 and SPAN, the within-lot variability, between lot variability and total variability at the initial, middle, and end of plume formation for the test product are comparable to that of reference product.
4. Based on the mean values:
 - The D50 values were greater at the end of plume formation than at the onset and middle of plume formation.
 - Total variability was generally low at the middle of plume formation for both D50 and SPAN.
 - For the test and the reference products, total variability of D50 was generally less than that of the SPAN.
5. Based on these data, distribution of droplets in the test product spray is similar to that of the reference product spray.

The sponsor was requested to provide the plume duration data used in the laser diffraction analyses. These data were requested for information purpose only, and they are not evaluated for product approval/disapproval. A summary of those data based on the reviewer's calculations is as follows:

Product	Distance	Plume Portion	Duration (msec)			Test/Ref
			Mean	%CV	Range	
Test	3	Intermediate	57.33	18.54	—	1.07
		Entire	100.67	7.98	—	1.12
	6	Intermediate	54.67	16.46	—	1.33
		Entire	128.00	17.94	—	1.02
	9	Intermediate	48.22	27.21	—	1.37
		Entire	173.33	20.81	—	0.97
Ref	3	Intermediate	53.78	8.16	—	
		Entire	90.22	6.84	—	
	6	Intermediate	41.11	18.22	—	
		Entire	125.11	16.55	—	
	9	Intermediate	35.11	26.95	—	
		Entire	178.22	18.17	—	

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

Spray Pattern

The firm submitted spray pattern data at three distances (2.5, 3 and 4 cm) from a plate at beginning and end life sectors for the test product and the reference products. It provided individual results of spray pattern determination in term of D_{max} , D_{min} and ovality ratio (D_{max}/D_{min}).

The firm provided color photocopies of corresponding plates with markings indicating D_{max} and D_{min} (Vol.1.1). The staining agents that react with drug was used to highlight the pattern of the plate. Test Method No. TM-1254 (Spray Pattern Determination for Ipratropium Bromide Nasal Spray 0.03% (21 ug/spray)) can be found in Vol. 1.1, page 156, along with its corresponding validation report.

Comments on the Spray Pattern Data. Reviewer's analysis of the spray pattern data are not presented because these data are unacceptable due to the following reasons:

- Spray patterns in many color photographs submitted by the firm are difficult to visualize. In some cases no patterns were distinguishable from the background (e.g., vol. 1.1, pp. 307, 322, and 336).
- Spray patterns are expected to be more intense at shorter distances, which is not always the case.

- In most cases (where visualized), spray patterns are reddish-orange against yellow background. However, in some cases the patterns are yellow on white background. It is not clear what represents spray patterns.

Acceptable spray pattern quantitation should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (D_{max} and D_{min}) by definition should intersect the center of the spray pattern.

The firm should submit revised spray pattern data after proper visualization quantitation. The sponsor may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative color photographs/photocopies clearly indicative of the quantitation (including marking for spray pattern perimeter, D_{max} and D_{min}) along with identity of distance, product, and lot number.

Plume Geometry: Not required for the lower strength products

DEFICIENCY

Novex Pharma's testing of in vitro performance of its ipratropium bromide (0.03%) nasal spray is incomplete due to following deficiency:

The spray pattern testing is unacceptable because:

- Spray patterns in many color photographs submitted by the firm are difficult to visualize. In some cases no patterns were indistinguishable from the background (e.g., vol. 1.1, pp. 307, 322, and 336).
- In most cases (where visualized), spray patterns are reddish-orange against yellow background. However, in some cases the patterns are yellow on white background. It is not clear what represents spray patterns.
- Spray patterns are expected to be more intense at shorter distances, which is not always the case.

Acceptable spray pattern quantitation should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (D_{max} and D_{min}) by definition should intersect the center of the spray pattern.

The firm should submit revised spray pattern data after proper visualization and quantitation. The sponsor may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative color photographs/photocopies clearly indicative of the quantitation (including marking for spray pattern perimeter, D_{max} and D_{min}) along with identity of distance, product, and lot number.

The firm used [redacted] technology to compare plume geometry of the test and reference product. The same laser-based technology may be used for determination of spray pattern. It eliminates the need for impaction surface and chromogenic reagents. However, the firm should note that quantitation of spray patterns by [redacted] methodology warrants modification.

[redacted] measures spray pattern dimensions based on fitting of "ellipse" to the observed pattern, regardless of true shape of the pattern. The Agency requests spray patterns quantitation in terms of longest diameter (D_{max}), shortest diameter (D_{min}) and Ovality ratio. If spray pattern analyses use [redacted] technology, a geometric center of mass (unweighted for density) or a moment of inertia center (weighted for density) may be computed for each pattern shape. The computer software should then determine the D_{max} and D_{min} axes (the longest and shortest line passing through the center) meeting the computer defined boundaries of the spray pattern.

The appropriate quantitation of spray patterns by [redacted] has not been determined. It warrants further exploratory studies to determine the appropriateness of weighted versus unweighted centers. However, until such studies are performed, spray pattern images produced by [redacted] may be manually quantified. For spray pattern analyses based on the [redacted] methodology, the firm is recommended to use the time-averaged images. These images are produced using the "Sum tool", with the default automatic mode. The true pattern shape is visualized using the "[redacted]" option. D_{max} and D_{min} axes may be manually drawn using the line tool. The sponsors should submit representative ($\geq 20\%$) color prints or electronic files of images based on "rainbow" or "gradient" palette. The images should exhibit the manually drawn lines as well as the computer defined boundaries of spray patterns.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION

The in vitro performance data submitted by Novex Pharma comparing its ipartropium bromide nasal spray (0.03%) with the reference product, Atrovent® nasal spray (0.03%) have been found to be incomplete due to the above deficiency.

The firm should be informed of the above deficiency. It should also note that approval of the lower strength of a nasal spray product based on abbreviated in vitro testing is contingent upon the acceptance of complete in vitro testing of the higher strength product.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence

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FT INITIALED S. NERURKAR

[Handwritten initials: JS]

Date 7/25/2001

Concur:

Date 8/2/01

[Handwritten initials: JS]
Dale P. Connor, Ph.D.
Director, Division of Bioequivalence

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**APPEARS THIS WAY
ON ORIGINAL**

AUG -8 2001

BIOEQUIVALENCY DEFICIENCY

ANDA: 76-156

APPLICANT: Novex

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.03%

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

The spray pattern testing is unacceptable because:

- Spray patterns in many color photographs are difficult to visualize. In some cases no patterns were indistinguishable from the background (e.g., vol. 1.1, pp. 307, 322, and 336).
- In most cases (where visualized), spray patterns are reddish-orange against yellow background. However, in some cases the patterns are yellow on white background. It is not clear what represents spray patterns.
- Spray patterns are expected to be more intense at shorter distances, which is not always the case.

Acceptable spray pattern quantitation should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (D_{max} and D_{min}) by definition should intersect the center of the spray pattern.

Please submit revised spray pattern data after proper visualization and quantitation. You may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative color photographs/photocopies clearly indicative of the quantitation (including marking for spray pattern perimeter, D_{max} and D_{min}) along with identity of distance, product, and lot number.

You have used laser-based technology to compare plume geometry of the test and reference product. The same laser-based technology may be used for determination of spray pattern. It eliminates the need for impaction surface and chromogenic reagents. However,

please note that quantitation of spray patterns by methodology warrants modification.

 measures spray pattern dimensions based on fitting of "ellipse" to the observed pattern, regardless of true shape of the pattern. The Agency requests spray patterns quantitation in terms of longest diameter (D_{max}), shortest diameter (D_{min}) and Ovality ratio. If spray pattern analyses use

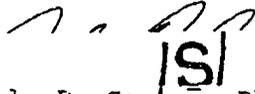
 technology, a geometric center of mass (unweighted for density) or a moment of inertia center (weighted for density) may be computed for each pattern shape. The computer software should then determine the D_{max} and D_{min} axes (the longest and shortest line passing through the center) meeting the computer defined boundaries of the spray pattern.

The appropriate quantitation of spray patterns by has not been determined. It warrants further exploratory studies to determine the appropriateness of weighted versus unweighted centers. However, until such studies are performed, spray pattern images produced by may be manually quantified. For spray pattern analyses based on the methodology, the time-averaged images should be used. These images are produced using the "Sum tool", with the default automatic mode. The true pattern shape is visualized using the " " option. D_{max} and D_{min} axes may be manually drawn using the line tool. Please submit representative ($\geq 20\%$) color prints or electronic files of images based on "rainbow" or "gradient" palette. The images should exhibit the manually drawn lines as well as the computer defined boundaries of spray patterns.

APPEARS THIS WAY
ON ORIGINAL

Please note that approval of the lower strength of a nasal spray product based on abbreviated in vitro testing is contingent upon the acceptance of complete in vitro testing of the higher strength product.

Sincerely yours,



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

APPEARS THIS WAY
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CC: ANDA #76-156
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE
HFD-651/ Bio Drug File
HFD-655/ Reviewer
HFD-655/ Bio team Leader

Endorsements: (Final with Dates)
HFD-655/ Reviewer *GDOS 7/24/01*
HFD-655/ Bio team
HFD-650/ D. Commer *RA 8/2/01*

7/25/01

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BIOEQUIVALENCY - DEFICIENCIES

Submission Date: 3/30/01

1. In Vitro STUDY (ST)

Strengths: ~~10 mg/mL~~ 0.037.

✓ Outcome: IC

BIOEQUIVALENCY - DEFICIENCIES

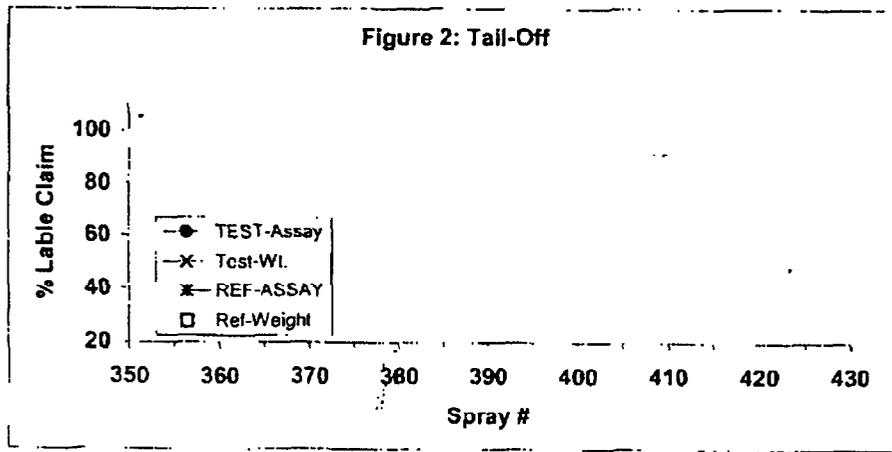
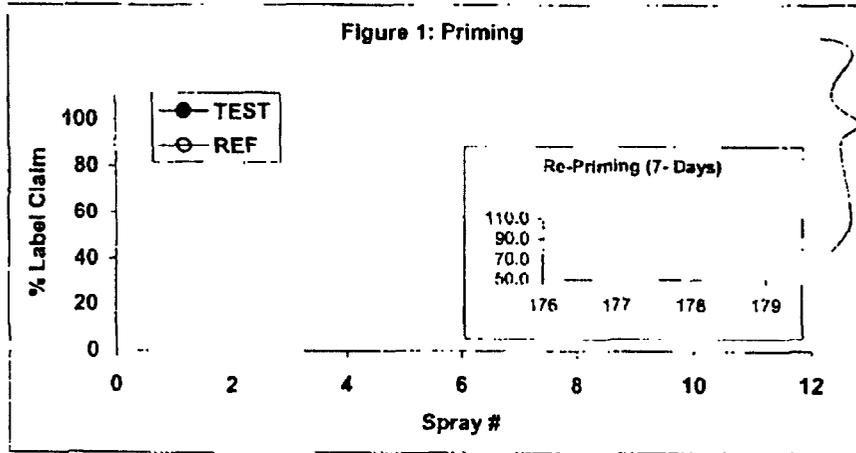
Submission Date: 7/6/01

2. STUDY AMENDMENT (STA) 6/29/00

Strengths: ~~10 mg/mL~~ 0.037.

✓ Outcome: AC

APPEARS THIS WAY
ON ORIGINAL



FEB 12 2003

Ipratropium Bromide Solution
0.03% Nasal Spray, 42 µg/spray
ANDA #76-156
Reviewer: Mamata S. Gokhale
v:\firmsam\apotex\ltrs&rev\76156A1002.doc

Apotex Corporation
50 Lakeview Parkway
Suite 127
Vernon Hills IL 60061
Submission Date: October 25, 2002

Y/G/O.

Review of an Amendment

Background

- 1) The firm submitted original ANDA for its drug product, Ipratropium Bromide Nasal Spray, 0.03% on 3/30/01 and amendments on 7/6/01 and 3/6/02. The reference-listed drug (RLD) is Atrovent® Nasal Spray, 0.03% (42 µg/spray, NDA #20-394), manufactured by Boehringer Ingelheim Pharmaceuticals Ltd.
- 2) The spray pattern testing in the original submission was unacceptable because:
 - Spray patterns in many color photographs were difficult to visualize. In some cases the patterns were indistinguishable from the background.
 - In most case (where visualized), spray patterns were yellow on white background. It was not clear what represented spray patterns.
 - Spray patterns were expected to be more intense at shorter distances, which was not always the case.

The firm was asked to submit revised spray pattern data with proper visualization and quantitation using _____ Technology. The firm was also informed that "approval of the lower strength based on abbreviated in vitro testing is contingent upon the acceptance of complete in vitro testing on the higher strength of the product", i.e. Ipratropium Bromide Nasal Spray, 0.06% submitted to ANDA 76-155.

Firm's response to deficiencies

The firm submitted spray pattern data from the _____ output in a tabulated format for 120 values both hard copies (attachments #1, 5 and 6) and electronic copies (attachment 7, data diskette). In the same amendment the firm submitted similar data on the higher strength (attachments #1, 2, 3 and 4). The spray pattern analysis was repeated at 3 and 5 cm distances on both the strengths, i.e. 0.03% and 0.06%.

Deficiency Comment on the firm's response

After reviewing the data on the higher strength, the DBE encouraged the firm to repeat spray pattern analysis using the _____ technique at different forces, i.e. actuator settings and increasing the dose time to 22 msec (teleconferences on 1/15/03 and 1/29/03). Since approval of the lower strength, based on abbreviated in vitro testing, is contingent upon the acceptance of complete in vitro testing on the higher strength of the product, the firm has been asked to repeat the

1

abbreviated spray pattern testing on the lower strength, using the — method. Therefore the spray pattern data submitted in this amendment does not warrant regulatory evaluation.

Recommendation

The in vitro performance testing conducted by Apotex on its Ipratropium Bromide Nasal Spray, 0.03%, Lots #5633, 5634 and 5635 comparing it with the reference product, Atrovent® Nasal Spray, 0.03%, Lots #157479A, 057080A and 156431A has been found incomplete due to the deficiency mentioned above.

The firm should be informed of the recommendation.

Mamata S. Gokhale, Ph.D.
Division of Bioequivalence

ISI

2/11/03

RD INITIALED GJP SINGH, Ph.D.
FT INITIALED GJP SINGH, Ph.D.

ISI

Date

2/11/03

Concur:

ISI

Date

2/12/03

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

cc: ANDA# 76-156 (original), Gokhale, HFD-658, Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:76-156

APPLICANT: Apotex Corporation

DRUG PRODUCT: Ipratropium Bromide Nasal Spray 0.03%

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

The approval of the lower strength, 0.03% based on abbreviated in vitro testing is contingent upon the acceptance of complete in vitro testing on the higher strength, 0.06, submitted to ANDA 76-155. The spray pattern data on the higher strength has been found to be incomplete. Therefore, the data submitted on the 0.03% strength does not warrant a review at this time.

Sincerely yours,


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

CC: ANDA # 76-156
 ANDA DUPLICATE
 DIVISION FILE
 HFD-651/ Bio Drug File
 HFD-658/ Reviewer: M. Gokhale
 HFD-658/ TL: Gur J.P. Singh

VAFIRMSAMAPOTEXLTRS&REV76156W1002.DOC
Printed in final on 2/11/2003

Endorsements: (Final with Dates)
HFD-658/ M. Gokhale *mark 2/11/03*
HFD-658/ Gur J.P. Singh *WJPS 2-11-03*
HFD-650/ D. Conner
HFD-617/ S. Mazzella *SM 2/12/03*

BIOEQUIVALENCY - Incomplete

3/4/02 (1)
Submission Date: 10/23/2002 (NL)

Biowaiver (WAI)

Strength: 0.03%
Outcome: IC

Outcome Decisions:

IC - Incomplete

WinBio Comments: Biowaiver request is incomplete

APPEARS THIS WAY
ON ORIGINAL

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # : 76-156 SPONSOR : Novex Pharma

DRUG AND DOSAGE FORM : Ipratropium Bromide Nasal Spray

STRENGTH(S) : 0.03%

TYPES OF STUDIES : In Vitro Studies

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : Novex Pharma, _____

STUDY SUMMARY : In Vitro Studies are acceptable.

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic <u> No </u>	Inspection requested: (date)	
New facility <u> </u>	Inspection completed: (date)	
For cause <u> </u>		
Other <u> </u>		

PRIMARY REVIEWER : Lin-Whei Chuang BRANCH : J

INITIAL : LWC DATE : 4/9/03

TEAM LEADER : Yih-Chain Huang, Ph.D. BRANCH : J

INITIAL : YCH DATE : 4/2/2003

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

INITIAL : DC DATE : 4/9/03

APR -9 2003

Ipratropium Bromide Solution
0.03% Nasal Spray, 42 µg/spray
ANDA #76-156/BE Amendment
Reviewer: Lin-Whei Chuang
V:\FIRMSNZ\NOVEXLTRS&REV\76156A0203.doc

Novex Pharma
Richmond Hill, Ontario
Canada
Submission Date:
February 18, 2003
March 14, 2003

Review of an Amendment

Background

This is the lower strength of the firm's ipratropium bromide solutions. The application for the higher strength (0.06%) is through ANDA #76-155.

Chronology for ANDA #76-156:

3/30/2001 & 7/6/2001: Comparative Formulations and results of the abbreviated *in vitro* testing results were submitted. The spray pattern testing was found to be unacceptable by the DBE.

10/23/2002: An amendment was submitted to report spray pattern data which was found to be incomplete due to the following deficiency:

"After reviewing the data on the higher strength, the DBE encouraged the firm to repeat spray pattern analysis using the — technique at different forces, i.e. actuator settings and increasing the dose time to 22 msec (teleconferences on 1/15/03 and 1/29/03). Since approval of the lower strength, based on abbreviated in vitro testing, is contingent upon the acceptance of complete in vitro testing on the higher strength of the product, the firm has been asked to repeat the abbreviated spray pattern testing on the lower strength, using the — method. Therefore the spray pattern data submitted in this amendment does not warrant regulatory evaluation."

Review

The firm has conducted spray pattern test using the — technique at two distances — and —, from — plate at the beginning life sector for the test product and the reference products. It provided individual results of spray pattern determination in term of longest diameter (D_{max}), shortest diameter (D_{min}) and ovality ratio (D_{max}/D_{min}).

The firm also provided color photocopies of corresponding — plates with markings indicating D_{max} and D_{min} (pages 18-30, Vol. 5.1) for 20% of samples. The staining agents — and —, that react with drug was used to highlight the pattern of the — plate. Test Method No. TM-1254 (Issue No.2) can be found in Vol. 5.1, pages 9-11.

Drug Products:

Test: Novex Pharma's Ipratropium Bromide Nasal Spray, 0.03%, Lot #0X400, using 3 batches of pumps (Novex Pharma QC Nos. 5630, 5631 and 5632).

Reference: Boehringer Ingelheim's Atrovent^R Nasal Spray, 0.03%; Lots 158413A, 256881A and 256181A, expire 11/2003, 05/2004 and 03/2004, respectively.

A summary of the spray pattern data based on the reviewer's calculations is presented in Table 1.

Table 1: Spray Pattern at the Beginning of Product Life							
Dist (cm)	Parameter	Mean (Geometric Mean) for N=30	Variability (%CV)			Test Mean/Ref. Mean (*)	P Value (1-tail ttest)
			Within-lot (N=10)	Between-lot (N=3)	Total (N=30)		
TEST PRODUCT - NOVEX							
3	Dmax (cm)	4.02 (4.01)	4.2 - 9.1	0.173	8.25	0.92 (0.92)	0.00157
3	Dmin (cm)	2.93 (2.92)	6.3 - 11.0	0.058	8.46	0.88 (0.88)	0.00005
3	Ovality	1.39 (1.37)	8.6 - 17.1	0.098	14.44	1.04 (1.04)	0.12097
5	Dmax (cm)	6.34 (6.33)	6.2 - 9.8	0.153	7.80	0.95 (0.96)	0.05596
5	Dmin (cm)	4.43 (4.41)	5.9 - 10.9	0.208	9.61	0.90 (0.92)	0.01854
5	Ovality	1.44 (1.43)	8.4 - 15.7	0.100	13.44	1.04 (1.05)	0.24311
REFERENCE PRODUCT - BOEHRINGER INGELHEIM							
3	Dmax (cm)	4.39 (4.36)	7.7 - 17.4	0.058	12.35		
3	Dmin (cm)	3.33 (3.31)	7.7 - 14.6	0.153	11.38		
3	Ovality	1.33 (1.32)	7.6 - 13.3	0.085	11.17		
5	Dmax (cm)	6.65 (6.60)	6.0 - 19.1	0.231	13.35		
5	Dmin (cm)	4.91 (4.82)	10.1 - 21.2	0.551	20.76		
5	Ovality	1.39 (1.37)	7.0 - 32.1	0.124	21.32		

* = Ratio of Geometric means

Comments:

1. As shown in Table 1, the ratios of the test geometric means to the reference geometric means for D_{max}, D_{min} and Ovality were within 0.92-1.05 except for D_{min} at 3 cm (0.88) which is deemed acceptable because the D_{max} at the same distance was 0.92 and the test product is the lower strength of the acceptable product of ANDA #76-155 (per G. Singh of DBE).
2. Total variability in the three parameters was similar between the test and reference product.
3. The spray pattern data are acceptable.
4. The test and reference formulations were found to be equivalent based on Q1 and Q2 sameness (see the review for the submission of 3/30/2001).
5. The spray devices of the test and reference products have been found to be comparable (see the review for the submission of 3/30/2001).
6. Other required in vitro tests were found to be acceptable (see the review for the submission of 3/30/2001).

Recommendation:

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

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

The firm should be informed of the above recommendation.

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

ISI u 4/7/2003

RD INITIALED YCHUANG
FT INITIALED YCHUANG

ISI 4/7/2003

Concur: _____

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

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-156

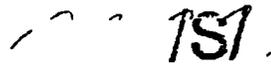
APPLICANT: Novex Pharma

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.03%

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

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

Sincerely yours,



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

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #76-156
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer L. Chuang
HFD-652/ Bio team Leader YC Huang

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Endorsements: (Final with Dates)
HFD-652/ Reviewer L. Chuang *ZWC 4/7/03*
HFD-652/ Bio team Leader YC Huang *YH 4/7/03*
HFD-650/ D. Conner *DC 4/9/03*
HFD-617/ A. Sigler

BIOEQUIVALENCY - ACCEPTABLE submission date: 2-18-03

- | | | |
|----|--------------------------------------|------------------|
| 1. | STUDY AMENDMENT (STA) <i>SL</i> | Strengths: 0.03% |
| | | Outcome: AC |
| 2. | STUDY AMENDMENT (STA) | Strengths: 0.03% |
| | (3-16-03 for expiration date of RLD) | Outcome: AC |

Outcome Decisions: AC - Acceptable

~~APPEARS THIS WAY
ON ORIGINAL~~