Desmopressin Acetate
Nasal Solution (Metered Manual Pump), 0.01%
Reviewer: Gur J.P. Singh
ANDA #74-830
74830WI.698

Bausch & Lomb
8500 Hidden River Ave
Tampa, FL 33637
Submission Date:
October 6, 1998.

Review of an ANDA Amendment

On February 8, 1996, Bausch and Lomb submitted an application for the waiver of *in vivo* bioequivalence study requirements for its desmopressin acetate 0.01% nasal solution. The sponsor submitted data to support comparative formulation *and in vitro* performance of its product and the reference product DDAVP® 0.01% solution manufactured by Rhone-Poulenc Rorer. A review of those data was completed on May 13, 1996.

On October 20, 1997, the Office of Generic Drugs requested data for some of the *in vitro* performance tests. The sponsor submitted the requested data on November 4, 1997. Based on the review of those data, the Agency requested the sponsor (letter date: January 21, 1998) to repeat the *in vitro* performance tests, including Unit Dose and Uniformity of Unit Dose, Droplet Size Distribution, Spray Pattern, Plume Geometry, and Primming and Tail Off characteristics.

On June 17, 1998, the sponsor submitted the above data. The amendment was reviewed by the Division of Bioequivalence (Review date: 9/21/98). On September 22, 1998, the sponsor was informed that the application was still incomplete due to certain deficiencies. On October 6, 1998, the sponsor submitted its response to deficiencies listed in the September 22, 1998 letter. A list of deficiencies and review of firms responses are as follows:

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Contain Trade Secret, Commercial/Confidential Information and are not releasable.

RQ 2-7 , 10/6/98

RECOMMENDATION

Data submitted by Bausch and Lomb comparing its desmopressin acetate (0.01%) nasal spray with the reference listed drug, DDAVP® nasal spray manufactured by Rhone-Poulenc Rorer indicate that the formulation of the test products is same as that of the reference product. In addition, the *in vitro* performance of manual metered dose pumps of these products is comparable. Therefore, in terms of dose delivered per actuation, and size, shape and droplets distribution of the spray, the test product is equivalent to the reference product. Therefore the Division of Bioequivalence deems the test product to be equivalent in dose delivery and performance of the device to the reference product, DDAVP® nasal spray manufactured by Rhone-Poulenc Rorer .

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

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR /S/ 12/3/1998

CONCUR: /S/ Date: 12/3/98

Dale Conner, Pharm. D.
Director
Division of Bioequivalence

GJP Singh 12/03/98 74830WI.O98

Page(s) 3

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

mechanical delivery system data.

MAY 13 1996

Desmopressin Acetate Nasal Solution	Bausch & Lomb
5 mL 0.01% Nasal Spray with Finger Pump	Tempa, FL
ANDA #74-830	Submission Date:
Reviewer: Moo Park	February 8, 1996
Filename: 74830W.296	

Review of a Waiver Request

I. Objective

Review of Bausch & Lomb's waiver requests on Desmopressin Acetate Nasal Solution, 0.01%. Reference product is Rhone-Poulenc Rorer's DDAVP^{R} Nasal Spray, 0.01%, in 5 mL package.

II. Background

Desmopressin acetate is an antidiuretic hormone affecting renal water conservation and a synthetic analogue of 8-arginine vasopressin. It contains as active substance 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin, which is a synthetic analogue of the natural hormone arginine vasopressin. One mL (0.1mg) of DDAVP has an antidiuretic activity of about 400 IU; 10 mcg of desmopressin acetate is equivalent to 40 IU.

- The biphasic half-lives for desmopressin acetate were 7.8 and 75.5 minutes for the fast and slow phases. As a result, desmopressin acetate provides a prompt onset of antidiuretic action with a long duration after each administration.

- Indications and dose: For primary nocturnal enuresis, the recommended initial dose for those 6 years of age and older is 20 mcg or 0.2 mL solution intranasally at bedtime. Adjustment up to 40 mcg is suggested if the patient does not respond.

  For central cranial diabetes insipidus, dosage should be adjusted according to the individual.

III. Requirements for waiver

In vitro data showing the test and reference products are same:

- Formulation
- Performance of the finger pump: Volume per actuation, plume geometry, spray pattern, droplet size, number of doses deliverable, etc.

IV. Formulation

Formulations for the test and reference products are identical except the quality of water. The reference product uses sterile water and the test product uses purified water. The test formulation is shown in Table 1.

Table 1. Test Formulation

Ingredient	Amount
Desmopressin Acetate	0.1 mg
Sodium Chloride	[illegible]
Chlorobutanol	[illegible]
Hydrochloric Acid	[illegible]
Purified Water	[illegible]
Total	[illegible]

V. *In Vitro* Evaluation of finger pump

1. Volume (dose) delivered

Three bottles each of the test and reference products were used to determine dose per actuation. The average volume delivered for both the test and reference products in single actuation testing was 0.1 mL as summarized in Table 2. The target delivery and actual delivery per actuation are matching for the test and reference products.

Table 2. Mean Volume Delivered per Single Actuation

Spray stages	Test Product lot #66393	Reference Product Lot #UM3112
Initial(Sprays 11-20)	0.1017 mL	0.0975 mL
Middle(Sprays 25-35)	0.1014 mL	0.1019 mL
End(Sprays 40-50)	0.1016 mL	0.0981 mL
Total sprays	90	90
Mean volume per spray	0.1016 mL	0.0992 mL
%CV	0.1	0.6

2. Dose delivery throughout the use life

The labeling shows that the test and reference products deliver 50 doses of 0.1 mL per actuation. The data in Table 2 show that both test and reference products deliver a minimum of 50 doses.

3. Droplet size distribution

light scattering device was used to measure the droplet size. The measured median diameter, d(0.1), d(0.5), d(0.9), range and the % less than 9.48 μm for the test and reference products are shown in Table 3. The data show that distribution of the droplets are comparable for the test and reference products.
Cascade Impactor was also used and the results show that approximately 1.3% of the dose was found to be below 9 microns for both the test and reference products. The test and reference products are equivalent in the droplet size distribution.

Table 3. Summary OF Droplet Size Results BY

Product	d(10) 10 per-centile nm	d(50) 50 per-centile nm	d(90) 90 per-centile nm	Mode nm	Range nm	% of <9.48 nm
Test #663931	32.3	63.3	230	51.8	0.5-600	0.98
Ref UM3112	35.0	57.2	252	52.3	0.5-600	0.85

4. Spray pattern and plume geometry

Spray pattern was captured on TLC plates at 10 cm distance and diameters and angle of spray cone was calculated as shown in Table 4. Plume geometry was captured on video film at a speed of 30 frames per second. Plume angle and diameter of the spray at 10 cm distance were measured.

Results of the spray pattern testing on TLC plates and plume geometry testing using a video camera match each other as shown in Table 5.

Data in Tables #4 and 5 show that the test and reference products have similar spray pattern and plume geometry even though the reference product has wider spray angle.

Table 4. Spray Pattern Analysis on TLC Plate

Product	Diameter-minimum cm	Diameter-maximum cm	Spray angle minimum degree	Spray angle maximum degree
Test	7.7	10.0	41.8	52.7
Reference	11.3	15.0	58.1	73.7

Table 5. Plume Geometry by Video Camera at 0.133 second

Product	Plume Angle, degree	Diameter at 10 cm
Test	57	10.9
Reference	83	17.9

VI. Comments

1. Volume (or dose) delivered: The average volume delivered for both the test and reference products in single actuation testing was 0.1 mL per spray (equivalent to 10 mcg of desmopressin acetate). The delivery from the device used on the test product is equivalent to that from the reference product.

2. Droplet size distribution: Median diameters were 63 nm and 57 nm for the test and reference products, respectively. The test and reference product show comparable droplet size distribution.

3. Spray pattern and flume geometry are comparable for the test and reference products. Reference product showed a wider spray angle.

4. The formulations for the test and reference products are identical except the type of water used. The test product contains purified water whereas the reference product contains sterile water. Purified water is not sterile.

5. OGD microbiologist should look at the type of water used in the test formulation in terms of microbial load and product specifications.

6. Waiver of *in vivo* bioequivalence study requirements is granted for the test product.

VII. Deficiency

None.

VIII. Recommendation

The Division of Bioequivalence agrees that the information submitted by Bausch & Lomb demonstrate that Desmopressin Acetate Nasal Solution, 0.01%, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test formulation to be bioequivalent to Rhone-Poulenc Rorer's DDAVP^{R} Nasal Spray, 0.01%.

The firm should be informed of the recommendation.

/S/

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ 5/8/96

Concur: /S/ Date: 5/13/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: 30,

File history: Draft (4/11/96); Final (5/8/96)

Keith:

The firm only showed that the volume of spray was the same for each actuation (.1ml) they never measured the concentration of dr delivered as we have previously requested T Because AQ.

You may want to look At before Signing

True solution

-2096

/S/

P ~~Do you think he should require~~ the ton

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:74-830 APPLICANT: Bausch and Lomb

DRUG PRODUCT: Desmopressin Nasal Spray (0.01%)

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,

/S/

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

CC:

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Printed in final on 12/03/98

Endorsements: (Final with Dates)
HFD-65/ Reviewer 12/3/98
HFD-655/ Bio team Leader
HFD-650/ D. Conner 12/3/98 12/3/98

BIOEQUIVALENCY - ACCEPTABLE submission date: 10/6/98

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

WinBio Comments: Study Amendment acceptable.

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

If you have any questions or comments concerning this amendment, please contact me at the above address or at (813) 975-7786.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski
Director
Regulatory Affairs

Enclosure

Pharmaceuticals, Inc. 8500 Hidden River Parkway Tampa FL 33637 813 975 7700 Fax 813 975 7770

December 30, 1998

BAUSCH & LOMB

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

Re: ANDA 74-830
Desmopressin Acetate Nasal Solution, 0.01%
Telephone Amendment

Dear Sir or Madam,

Reference is made to the above reference abbreviated new drug application and to your telephone communication of December 30, 1998, and to our facsimile amendment of December 22, 1998.

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ch

Methods Validation Commitment:

Our September 12, 1997 amendment committed to cooperate with the Agency to resolve any methods issues.

Pharmaceuticals, Inc. 8500 Hidden River Parkway Tampa FL 33637 813 975 7700 Fax 813 975 7770

January 4, 1999

BAUSCH & LOMB

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

Re: ANDA 74-830
Desmopressin Acetate Nasal Solution, 0.01%
Telephone Amendment

Dear Sir or Madam,

Reference is made to the above reference abbreviated new drug application, to our telephone amendment of December 30, 1998, and to telephone conversations with Mike Smela and Dr. Gene Shafer on January 4, 1999.

We hereby make the following commitments to the Agency regarding this application:

A. Other Individual Chromatographic Related Substance:

We hereby commit to revise our release specifications (Final Chemical Summary) and our stability specifications (Pre-marketed and Marketed Stability Protocols) to add an acceptance criteria for Other Individual Chromatographic Related Substance. The limit at release and on stability is set at Not More Thar

B. Impurity Peak Interference:

We hereby commit to track and monitor the peak
nt) at approximate tes. If the area
% of this peak exceeds commit to performing a thorough investigation which shall include but not be limited to PDA analysis to identify the nature of the peak.

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

If you have any questions or comments concerning this amendment, please contact me at the above address or at (813) 975-7786.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski
Director
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001.
Expiration Date: December 31, 1995.
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT
Bausch & Lomb Pharmaceuticals, Inc.

DATE OF SUBMISSION
1-4-99

ADDRESS *(Number, Street, City, State and ZIP Code)*
8500 Hidden River Parkway
Tampa, FL 33637

TELEPHONE NO. *(Include Area Code)*
(813) 975-7775

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER *(If previously issued)*
74-830

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Desmopressin Acetate Nasal Solution, 0.01%

PROPRIETARY NAME *(If any)*

CODE NAME *(If any)*

CHEMICAL NAME

DOSAGE FORM
Solution

ROUTE OF ADMINISTRATION
Nasal

STRENGTHS(S)
0.01%

PROPOSED INDICATIONS FOR USE PRIMARY NOCTURNAL ENURESIS: Desmopressin Acetate Nasal Solution is indicated for the management of primary nocturnal enuresis. CENTRAL CRANIAL DIABETES INSIPIDUS: Desmopressin Acetate Nasal Solution is indicated as antidiuretic replacement therapy in the management of central cranial diabetes insipidus and for managment of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21 CFR 314.420)* REFERRED TO IN THIS APPLICATION:

DMF
DMF
DMF
DMF

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☒ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) *(21 CFR 314.55)*

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG
DDAVP Nasal Spray (desmopressin acetate)

HOLDER OF APPROVED APPLICATION
Rhone-Poulec Rorer Pharmaceuticals, Inc.

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Summary (21 CFR 314.50) (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
▒	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Donald H. Chmielewski	Donald H. Chmielewski	1/4/99

ESS *(Street, City, State, ZIP Code)*	TELEPHONE NO. *(Include Area Code)*
8500 Hidden River Parkway Tampa, Fl 33637	(813)975-7775

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

ANDA 74-830

Bausch & Lomb Pharmaceuticals, Inc.
Attention: Peter Stoelzle
8500 Hidden River Parkway
Tampa, FL 33637

AUG 21 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated December 31, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Desmopressin Acetate Nasal Solution, 0.01%.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies