CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-830

BIOEQUIVALENCE REVIEW(S)

A Waiver

ANDA 74-830

MAY 20 1996

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

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Desmopressin Acetate Nasal Solution, 0.01%.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA File: 74-830

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

REQUEST FOR CONSULTATION

TO (Division/Office)		FROM:	
TI-Attn:Leah Ripper, Forward to HFD-510		HFD-600 Office of Generic Drugs	
IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
8/6/97		Memo	8/6/97
NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Desmopressin Acetate	High	Antidiuretic Hormone	9/6/97

NAME OF FIRM

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ SOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Please provide a determination whether the previous refrigerated formulation, approved for NDA 17-922, DDAVP (Desmopressin Acetate) Nasal Solution, 0.01%, was withdrawn for safety or effectiveness reasons.

Please Refer to the attached memo.

Please return the completed consult to:

Office of Generic Drugs
HFD-600
MPN II
Attention: Cecelia Parise
Room N-276

If you need further information please contact:
Cecelia Parise
827-5845

Thank You

OFFICE OF DRUGS REC'D AUG 27 1997

SIGNATURE OF REQUESTER		METHOD OF DELIVERY *(Check one)*
Cecelia Parise /S/	8/6/97	☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

#2024

DATE: August 13, 1997

FROM: Elton Herman, M. D. /S/
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: DDAVP Nasal Solution, older refrigerated formulation vs newer room-temp formulation

THROUGH: Solomon Sobel, M. D. /S/ 8/15/97
Director, Division of Metabolic and Endocrine Drug Products

There were no safety or efficacy issues involved in reformulation and replacement of older refrigerated solution of DDAVP Nasal Spray by new formula that may be stored at room temp. Of course, if patients did not store the older preparation under proper conditions, then individual patients may conceivably have experienced problems re loss of effectiveness, but this was not a systematic problem involving groups of pts or the drug per se. In addition, one of the chemists located in HFD-510 has today informed me informally that there may be some economic issue involved in using the new formula preservative vs the chlorbutanol in old formula. However, there were no intrinsic issues of safety or effectiveness as we define them in usual usage in FDA.

Biopharm review also showed that the 2 preparations were equivalent.

8/14/97
10:00
Of course the generic of the "old formulation" will require refrigeration
/S/

for /S/ HFD-102
8/15/97

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 6, 1997

FROM: Douglas L. Sporn
Director
Office of Generic Drugs (OGD)

/S/

SUBJECT: OGD is seeking a determination whether the refrigerated product approved under, NDA , DDAVP (Desmopressin Acetate) Nasal Solution, 0.01%, was withdrawn from marketing due to safety or effectiveness reasons.

TO: Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products

THROUGH: James M. Bilstad, M.D.
Director
Office of Drug Evaluation II

In accord with 21 CFR 314.161(a)(1)&(c) the Agency may make a determination whether a listed drug that has voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons prior to approving an abbreviated new drug application that refers to the listed drug. The Agency shall publish its determination in the Federal Register.

The Office of Generic Drugs (OGD) has a pending application for Desmopressin Acetate Nasal Solution, 0.01%, that relies upon the listed drug DDAVP (refrigerated) that was withdrawn from marketing. This ANDA was submitted to OGD prior to the approved reformulation of the reference listed drug. The formulation of the ANDA is qualitatively and quantitatively the same as the old refrigerated formulation of DDAVP. Before the ANDA can be approved, the Agency must seek a determination whether the drug product was withdrawn for safety or effectiveness reasons. The determination will then be forwarded to the Regulatory Policy Staff for publication in the Federal Register.

OGD has obtained informal information via E-Mail (see attachments), that the product was reformulated for patient convenience. The previous formulation required refrigeration and the new formulation can be stored at room temperature, which is more convenient for patients. In addition, information was provided to the OGD that the new room temperature formulation is bioequivalent to the old refrigerated formulation.

At the behest of the Office of Chief Counsel, OGD is requesting a formal determination from the Division of Metabolism and Endocrine Drug Products whether the previously approved formulation of DDAVP Nasal Solution, 0.01%, which required refrigeration has been withdrawn from sale for safety or effectiveness reasons.

We are looking forward to your response. Because the pending approval of this application is dependent upon your determination, we ask that you expedite this request. If you have any questions or require further information regarding this issue you may contact Cecelia Parise, Special Assistant to the Director, Office of Generic Drugs at 301-827-5845.

Pharmaceutical Division 8500 Hidden River Parkway Tampa FL 33637 813 975 7700 Fax 813 975 7770

November 4, 1997

BAUSCH & LOMB
Healthcare and Optics Worldwide

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%
Bioequivalence Telephone Amendment

Dear Sir or Madam:

The purpose of this correspondence is to address the Agency's facsimile communication, dated October 20, 1997, for the above referenced application. The information contained in the October 20, 1997 communication was discussed during a October 17, 1997 teleconference between the Agency and Bausch & Lomb Pharmaceuticals, Inc. Enclosed in Attachment A of this submission is a copy of the October 20, 1997 communication, and a copy of Bausch & Lomb's minutes of the October 17, 1997 teleconference.

During the teleconference, the focus of the discussion from the Bioequivalence Division was the In Vitro testing results submitted in support of a waiver of In Vivo Bioequivalence Study requirements contained in Section 6 of the Original ANDA filing of December 31, 1995. For ease of review, a copy of Section 6 from the original ANDA is included in Attachment B.

Presentation of Requested Data in Fulfillment of the *In Vitro* Testing Requirements for a Nasal Delivery System

As requested by the Agency, the individual data for the *in vitro* testing submitted

Page(s) 14

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

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.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's October 17, 1997 communication. As such, we hope that a rapid review and subsequent product approval will be forthcoming. If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775 or by fax at 813-975-7757.

Sincerely,

Joseph B. Hawkins
Manager
Regulatory Affairs

enclosure

Desmopressin Acetate
Nasal Solution (Metered Manual Pump), 0.01%
Reviewer: Gur J.P. Singh
ANDA #74-830
74830WI.N97

Bausch & Lomb
8500 Hidden River Ave
Tampa, FL 33637
Submission Date:
November 4, 1997

An Amendment to the May 13, 1996, Division of Bioequivalence Review Based on a Study Amendment

On February 8, 1996, Bausch and Lomb submitted an application for a 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 additional data for some of the *in vitro* performance tests. The sponsor submitted these data on November 4, 1997. This review is based on the November 4, 1997, amendment with reference to previously submitted data, where necessary.

Page(s) 9

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

The sponsor should be informed of comments 3, 4, 6 and 8.

/S/

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

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR /S/ Date: 1/15/1998

CONCUR: /S/ Date: 1/16/98

Dale Conner, Pharm. D.
Director
Division of Bioequivalence

GJP Singh 12/5/97 74830WI.N97

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:74-830 APPLICANT:Bousch and Lomb

DRUG PRODUCT: Desmopressin acetate nasal spray, 0.01%.

The Division of Bioequivalence has completed its review of your November 4, 1997, amendment. The following deficiencies have been identified:

Page(s) 3

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

/S/

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

CC:

1/15/98

X:\NEW\FIRMSAM\BAUSCH\LTRS&REV\74830WI.N97
Printed in final on 1/15/98

Endorsements: (Final with Dates)
HFD-658/ SINGH
HFD-655/ NERURKAR /S/ 1/15/98 /S/ 1/15/98
HFD-650/ D. Conner 1/16/98

Deficiency:

5. **STUDY AMENDMENT** (STA)

Strengths: 0.01%
Outcome: **UN**

OF 21

4,1

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:74-830 APPLICANT:Bousch and Lomb

DRUG PRODUCT: Desmopressin acetate nasal spray, 0.01%.

The Division of Bioequivalence has completed its review of your November 4, 1997, amendment. The following deficiencies have been identified:

Page(s) 3

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Sincerely yours,

/S/

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

4.1

DATE: January 13, 1998 Time: 5:00 p.m. HFD-650, MPN-II

Subject: ANDA 74-830/ Bausch & Lomb Pharmaceuticals/
DESMOPRESSIN ACETATE NASAL SPRAY (MANUAL METERED DOSE PUMP);
IN VITRO TESTING RECOMMENDATIONS

Meeting Type: Telecon

Meeting Chair: Gordon Johnston

External Contact: Donald H. Chmielewski

Meeting Recorder: Lizzie Sanchez, Pharm.D.

FDA Participants:
Gordon Johnston, Director, Office of Generic Drugs
Dale Conner, Pharm.D., Director, Division of Bioequivalence
Gur J.P. Singh, Reviewer, Division of Bioequivalence
Shriniwas Nerurkar, Team Leader, Reviewer, DOB
Wallace Adams, Ph.D., OPS
Lizzie Sanchez, Project Manager, DOB

External Constituents:
Don Chmielewski, Regulatory Affairs, Bausch & Lomb
Joe Hawkins, Regulatory Affairs
Mike Brubaker, Sr. Manager, Product Development
Ruth Katimy, Supervisory Chemist
Chris Teo, Chemist
David Whitaker, Chemist
Harold Shlevin, Vice President, Research & Development
Chris Simmons, Vice President, Regulatory Affairs

Meeting Objective: To discuss in-vitro testing submitted on November 4, 1997 for Desmopressin Acetate Nasal Spray.

Discussion:

... of the changes

Page(s) 4

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

Drafted ALS 1/14/98 X:\new\firmsam\bausch\telecons\74830.003

Revisions:
Wally Adams 1/14/98
Dale Conner 1/15/98