NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The reference listed drug for this product is DDAVP®(Rhone-Poulenc Rorer; N17922; Approved April 13, 1998).

2. The following patents are in existence for this product:

Patent #	Expires	Patent Certification by Applicant
5500413 (Process for manufacture)	6-29-2013	?
5674850 (High purity desmopressin in large single batches and method of treating diabetes insipidus)	12-23-2103	Paragraph IV (Innovator has decided not to file suit)
5498598 (Composition for Nasal Administration of desmopressin)	6-29-2013	?
5482931 (Stabilized pharmaceutical peptide compositions)	6-29-2013	Currently does not apply but applicant states it may reformulate to an unrefrigerated formulation similar to innovator's.
5763407 (high purity desmopressin produced in large single batches and a method of treating diabetes insipidus)	12-23-2013	?

Vol. 5.1, page 9., telecon dated 7-17-97, and Vol. 1.1, page 2 of New Correspondence.

4. Container/Closure

This product will be packaged in a 6 cc amber glass vial with nasal pump and dip tube. Actuator Head, nasal pump and overcap.

5. Bausch & Lomb will perform all manufacturing. all outside firms are utilized for testing. See pages 216 and 325.

6. Package Line

The innovator packages this product in a 5 mL spray bottle and a 2.5 mL vial with rhinal tube applicators.

The generic intends to market this product in a 5 mL spray bottle.

7. Storage/Dispensing Recommendations

USP: Not USP.

NDA: Firm has changed the formulation of its product. DDAVP Nasal Solution can now be stored at room temperature.

ANDA: Store in refrigerator at 2° - 8°C (36°-46°F). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 22°C (72° F).

NOTE: Since the formulation change for DDAVP occurred after B&L's application had been submitted, it was decided that OGD's approval would be based on the previous formulation and labeling for DDAVP which included the preservative chlorbutanol and instructions to refrigerate the product. However, all new applications will have to be Q&Q with the new formulation.

B&L have committed to reformulating their product to be the same as the innovator and will keep the Agency informed.

8. The newly approved carton labeling has revised the "Note to pharmacist" box to read:

Detach patient's instructions from package insert and dispense with spray pump. Since labeling is in FPL and this change is minor, B&L will be asked to revise their carton labeling at a future time.

Date of Review: December 7, 1998
Date of Submission: November 25, 1998

Reviewer: /S/ **Date:** 12/7/98

Team Leader: /S/ **Date:** 12/8/98

Concur

/S/ 12/8/98

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

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Date of Review: October 23, 1998
Date of Submission: October 6, 1998

Reviewer: /S/ **Date:** 11/30/98

Team Leader: **Date:**

/S/ 11/30/98

ANDA APPROVAL SUMMARY

ANDA:	CHEMIST:	DATE:
74-830	Eugene L. Schaefer, Ph.D.	January 5, 1999

DRUG PRODUCT:

Desmopressin Acetate **FIRST GENERIC FOR THIS DRUG PRODUCT**

FIRM:

Bausch & Lomb Pharmaceuticals, Inc.

DOSAGE FORM:	STRENGTH:
Nasal Solution	0.01%

cGMP:

The facilities were found to be acceptable on 2/20/98.

BIO:

The applicant requested a waiver. The Bio division issued a "**no further questions**" letter on 12/3/98.

VALIDATION - ***(Description of dosage form same as firm's):***

An MV request was sent to the Division of Drug Analysis, STL, because of need for special equipment, on 9/4/97. I received a report from Dr. Henry Drew on 1/11/99. The methods are **satisfactory**.

STABILITY:

The containers in the stability studies are identical to those in the container section.

LABELING:

Teresa Watkins recommended approval on 12/7/98.

STERILIZATION VALIDATION ***(If applicable)***:

Satisfactory per review of Ken Muhvich, Ph.D. on 7/25/96.

SIZE OF BIO BATCH ***(Firm's source of NDS ok?)***:

There was no bio batch because a waiver was requested.
as found adequate on 11/25/98.

SIZE OF STABILITY BATCHES ***(If different from bio batch, were they Manufactured via the same process?):***

The size of the exhibit batches was iters. The maximum size of production batches will be Liters.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

The proposed production batch iters . The manufacturing process is identical to the exhibit batch.

Signature of chemist:	Signature of supervisor:
/S/ 1/13/99	/S/
Eugene L. Schaefer, Ph.D.	Michael Smela

V:\FIRMSAM\BAUSCH\LTRS&REV\74830AP.SUM

CDER Establishment Evaluation Report for December 18, 1998

Application: **ANDA 74830/000**
Stamp: **03-JAN-1996** Regulatory Due:
Applicant: **BAUSCH AND LOMB**
8500 HIDDEN RIVER PKY
TAMPA, FL 33637

Priority:
Action Goal:
Brand Name:
Established Name: **DESMOPRESSIN ACETATE**
Generic Name:
Dosage Form: **SOL (SOLUTION)**
Strength: **0.01%**

Org Code: **600**
District Goal: **03-MAR-1997**

FDA Contacts: **J. BUCCINE (HFD-617) 301-827-5848 , Project Manager**

Overall Recommendation:

ACCEPTABLE on 20-FEB-1998 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 21-OCT-1996 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: **1049418**
DMF No:
ADA No.

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **15-DEC-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE OTHER TESTER**

Establishment: **1052807**
BAUSCH AND LOMB PHARMACEUT
8500 HIDDEN RIVER PKY
TAMPA, FL 33637
DMF No:
AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-DEC-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: **2210008**
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **15-DEC-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE OTHER TESTER**

Establishment: **1419992**

DMF No:
ADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **15-DEC-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE OTHER TESTER**

Establishment: **2529719**

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **20-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE RELEASE TESTER**

Establishment: **9610703**

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **15-DEC-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Branch 2 HFD-625

FROM: Michael J. Smela, Jr. Team Leader DATE:6/23/98

NAME/TITLE OF INDIVIDUAL(S): Joe Hawkins
FIRM:B & L
PRODUCT NAME:Desmopressin Nasal
TEL #: 8139757775
Reference:ANDA 74830

Notes of Conversation: I referred to the 6/17/98 amendment which responds to bioequivalence deficiencies. I advised the applicant that amendments should not be classified as facsimile/minor/major unless they specifically respond to a deficiency requesting such. I said this amendment is in response to bio deficiency and is not a complete respponse to the minor NA issued 1/27/98 from chemistry. I noted that deficiencies in have not been responded to.

I advised that the 6/17/98 amendment would be considered coorespondence which will not start the review clock. I advised that a minor amendment in response to the 1/27/98 communication will be needed to start the clock after the DMF has been responded. Mr. Hawkins thanked me for the information and understood that his ANDA is not now in the que for review.

SIGNATURE OF OGD REPRESENTATIVES:

/S/ 6/23/98

Location of Electronic Copy:
X:\new\firmsam\bausch\telecons\062398

RECORD OF TELEPHONE CONVERSATION/MEETING

Mr. Smela and Dr. Schaefer called Mr. Chmielewski re fax amendment of 12/22/98. They relayed the oral equivalent of the following:

"We have concerns about the proposed regulatory method:

a. Page 53 of the amendment indicates an in-house standard could be used, but the preparation of an in-house standard stock solution has been deleted from p 50, and the calculation based on an in-house standard has been deleted from p 52.

b. In the chromatogram on page 059, please label the three peaks eluting before Unknown 1, and the peak eluting at 3.7 minutes.

c. Since desmopressin and]desmopressin have been detected by the method (page 28), and since deamidation and racemization are known potential degradation pathways for peptides and proteins, these impurities should be included in the related substances chromatogram."

Mr. Chmielewski said he would have the method revised.

Mr. Smela asked if B&L had provided commitment to cooperate w FDA re MV issues. Mr. Chmielewski reminded us they had.

X:\NEW\FIRMSAM\BAUSCH\TELECONS\74830.005

12/30/98
MSmela

DATE
12/30/98

ANDA NUMBER
74-830

TELECON

INITIATED BY / **MADE BY**
_ APPLICANT/SPONSOR — X TELE.
X FDA — _ IN PERSON

PRODUCT NAME
Desmopressin Acetate Nasal Solution

FIRM NAME
B&L

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Donald H. Chmielewski, Director, Regulatory Affairs

TELEPHONE NUMBER
813-975-7786

SIGNATURE ES 12/30/98
ELSchaefer, Chemist, Br II
MSmela, TL, Br II

RECORD OF TELEPHONE CONVERSATION/MEETING

~11:20 am:

Dr. Schaefer called Mr. Chmielewski. Dr. Cai was a witness. Dr. Schaefer relayed the oral equivalent of the following:

"We have additional concerns about Response A.1.c of your facsimile amendment of 12/22/98, and about Response C of your telephone amendment of 12/30/98.

a. We repeat our request for release and stability limits for "Other Individual Chromatographic Related Substance" as determined by method

b. Comparison of Attachment 2 of the telephone amendment with Attachments D and F of the method suggests potential interference with the]desmopressin peak by the mobile phase peak eluting at approximately

~3:00 p.m.:

Mr. Chmielewski and others called Dr. Schaefer and Mr. Smela. The representatives of B&L agreed to set release & stability limits for "Other … Substance" at NMT They committed to monitor the peak at as an unknown impurity, and if its level rises above to conduct an investigation to ID the peak, and relative contribution of related substance vs. mobile phase.

DATE
1/4/99

ANDA NUMBER
74-830

TELECON

INITIATED BY _ **APPLICANT/SPONSOR** X **FDA**

MADE BY X **TELE.** _ **IN PERSON**

PRODUCT NAME
Desmopressin Acetate Nasal Solution 0.01%

FIRM NAME
B&L

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Am: DChmielewski; P.m.: DChmielewski, MBrubaker, KMoorthy, DWhitaker, & BKatimy

TELEPHONE NUMBER
813-975-7786

SIGNATURE
ELSchaefer & BCai, Chemists; MSmela, TL; Br II

/S/
1/4/99

ELS 1/4/99
BC 1/4/99

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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: September 2, 1997

FROM: Douglas L. Sporn
Director
Office of Generic Drugs

SUBJECT: Safety and Effectiveness Determination regarding the withdrawn formulation of DDAVP (Desmopressin Acetate) Nasal Solution 0.01%.

TO: Howard Muller
Regulatory Policy Staff
MPNI/Room 116

An ANDA filed with the Office of Generic Drugs is approaching the approval stage. The Office of Generic Drugs is requesting that the Federal Register publish the Agency's determination.

Please initiate the publication of this Federal Register Notice regarding the attached determination from the Division of Metabolism and Endocrine that the prior, refrigerated formulation of NDA DDAVP (Desmopressin Acetate) Nasal Solution was not withdrawn due to safety or effectiveness issues in accord with 21 CFR 314.161(a)(1) and (e).

Thank you,

cc:

x:\new\firmsam\bausch\memo\74-830.mem

MEMORANDUM

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

DATE: 28 October 1997 /S/

FROM: Enid Galliers
Chief, Project Management Staff,
Division of Metabolic and Endocrine Drug Products (HFD-510)

SUBJECT: Request for reasons applicant stopped marketing a formulation of Desmopressin Acetate Nasal Spray that required refrigeration (NDA 17-922/SCF-023)

TO: Ms. Cecelia Parese, HFD-615, OGD

THROUGH: Elton Herman, M.D. /S/ 11/3/97
Medical Officer, DMEDP

Stephen K. Moore, Ph.D. /S/ 11/4/97
Chemistry Team 1 Leader, DNDC II

Solomon Sobel, M.D. /S/ 97
Director, Division of Metabolic and Endocrine
Drug Products (HFD-510)

/S/
HFD-102
11/13/97

On August 7, 1996, DMEDP approved [redacted] supplemental application which provided for a formulation of desmopressin acetate nasal spray that can be stored at room temperature. The firm stated that it would not market the product that required refrigeration after receiving approval for the room temperature formulation. RPR indicated in an April 11, 1995, amendment to the supplemental application that the change provides the patient with a non-refrigerated product for ease of convenience in storage. There were no safety or effectiveness issues responsible for this change.

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

REQUEST FOR CONSULTATION

COPY

TO (Division/Office)			FROM:	
ODEII-Attn:Leah Ripper, Forward to HFD-510			HFD-600 Office of Generic Drugs	
DATE	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

- ☐ DISSOLUTION
- ☐ 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

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)

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 /S/
Director
Office of Generic Drugs (OGD)

SUBJECT: OGD is seeking a determination whether the refrigerated product approved under, NDA [redacted] AVP (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.

TELECON

RECORD OF TELEPHONE CONVERSATION/MEETING

After attending an internal OGD meeting, I called the sponsor and provided the following information.

Reference was made to B&L correspondence dated 11/1/96 noting that the RLD changed formulations. The change allows the RLD to be stored without refrigeration. The proposed generic drug requires refrigeration.

OGD is willing to proceed with the review approval process provided that the innovator's reason for changing the formulation does not involve safety or efficacy concerns. In order to resolve this issue, B&L should file a citizen petition under CFR 314.122. The petition will require review by the new drug review division and should be submitted asap. OGD will work closely with NDE for timely resolution. In addition, OGD encourages B&L to reformulate to match the RLD's new formulation.

B&L is already developing the new formulation and plans to file a supplement. They would greatly appreciate a timely petition review that would not delay approval of their ANDA.

cc:

DATE 7/17/97

ANDA NUMBERS: 74-830

TELECON

INITIATED BY FDA

PRODUCT NAME
Desmopressin Acetate Nasal Solution

FIRM NAME
Bausch & Lomb

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Joseph Hawkins

TELEPHONE NUMBER
(813)975-7775

SIGNATURE
Joseph Buccine