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Bausch & Lomb Pharmaceuticals, Inc.
Regulatory Affairs
8500 Hidden River Parkway
Tampa, Florida 33637

MINUTES OF FDA TELECON

PRODUCT: Desmopressin Acetate Nasal Solution	DATE: 1-13-98
AGENCY: FDA, OGD	PHONE: 301-827-5845
FDA Telecon Participants: Dale Conner, Gur Singh, Gordon Johnston, Wally Adams, VJ Nerurkar, and Lizzie Sanchez	
B&L Participants: Don Chmielewski, Chris Simmons, Harold Shlevin, Mike Brubaker, Ruth Katimy, David Whitaker, Chris Teo, Joe Hawkins	
SUBJECT: Desmopressin ANDA Review Status - Bioequivalence Review	

Re: Telecon on 1-13-98

Gordon Johnston began the teleconference by discussing the nature of the change that B&L was investigating for the pump/device. It was explained by B&L that the only change was in the spray insert in the actuator. No change in formulation or in the pump was being investigated. Gordon and others stated that any change in the pump/device is viewed by the Agency as a formulation change since the characteristics of the product dispensed is affected.

Given those changes being investigated, FDA stated that the data currently submitted is too variable and not approvable. Therefore, rather than focusing on what additional testing needs to be done on the pending pump/device, FDA would like to focus on the testing that will be the subject of future submissions to assure that equivalence can be demonstrated.

It was mentioned that not all issues regarding the in vitro testing have been resolved, that this is in process and will take some time. FDA expressed their desire to work with B&L to resolve the issues. FDA further stated that their intention is to approve such applications with in vitro testing only.

1. In General

The reviewer then provided general comments about the data in the 11-4-97 submission. He said that the unit dose content uniformity testing was not performed on 10 bottles of innovator versus test. USP requires 10 bottles. He said that the droplet size data was not comparable at all distances, specifically variability ir Statistical analysis performed was ratio of the means. He said that all testing should involve mechanical actuation only.

It was suggested that future testing should be with blinded samples, so that the person actuating the pump or analyzing the data does not know the identity of the sample. After discussion, it was stated that if B&L takes issue with this suggestion, they should present their justification in the submission. It was further mentioned that some testing as already been completed using unblinded testing, and that B&L should justify the acceptability of this unblinded testing.

B&L needs to submit SOPs or descriptions of methods used at the time of testing for all procedures performed to compare test to reference product. This would include: (1)

In all instances of testing, raw data for all tests should be submitted in Excel 5.0 spreadsheet format (PC) - hard copy and electronic.

Specific Tests Discussed:

A. Unit Dose/Content Uniformity/QDS

This testing should be performed at beginning (B), middle (E), and end (E) of the dosing life of the product. 10 units should be tested. 1 dose equals 1 spray (10mcg). Amount actuated should be measured by analysis, not by weight. Data should demonstrate priming and tail off at end.

B. Droplet Size Determination

testing should be performed at B, M, and E of dosing life. Distances should be 3, 5, and 7 cm; report d10, d50, d90 and span; report volume and # of particles; report cumulative histograms, % undersize, obscuration and instrument manufacturer's recommended obscuration range. Statistics will be applied to BME separately.

C. Cascade Impactor

This test is performed to protect against excessive fines, and is a confirmation of the testing of droplet size, as per '89 MDI Guidance. Testing should be done at beginning (sprays 11-20) and end (sprays 41-50) of dosing life. Analyzing stations 0, 1 and filter should be adequate. We did too much testing in the cascade data submitted. 10 actuations per test is OK.

D. Spray Pattern (TLC Plate Testing)

Spray pattern testing should be conducted at 3, 5, and 10 cm, and tested at B, M and E. For visualization, a drug specific reagent should be used. This should be captured by color photographs to capture the longest and shortest distances used in calculating the spray angles. We should also provide the elliptical ratio (longest/shortest). The color photos should be submitted.

E. Plume Geometry

The freeze frame photography should capture the beginning of the spray life. At least 3 time delays should be used. The plume should be geometrically characterized using length, width and angle per time.

F. Priming and Tail Off

This data should also be analyzed using nalysis of the actuations. Raw data should be submitted in Excel spreadsheet (PC-compatible, electronic + hard copy).

G. Standard for BE Testing Evaluation

It was made clear that the uniformity of dosing specification in the ANDA, i.e., of labeled amount, and all % of labeled amount does not apply to the criteria being used to determine bioequivalence.

Submission Requirements:

Gordon Johnston discussed the filing and timing requirements for the ANDA. The revision in the actuator must be submitted as an amendment to the ANDA. It will be evaluated as a major or minor amendment depending upon the time to complete the review. The burden is upon B&L to present the amendment in such a way to qualify as a minor. The chemistry review will drive the bio review. A bioequivalence amendment will be submitted with all the testing presented as discussed.

The FDA will summarize the telecon and their current bioequivalence requirements by the end of the month. FDA stated that no in vivo bioavailability work will be needed for this nasal product. It was also stated that the limits and specifications developed for Desmopressin Nasal Solution may or may not apply to other nasal products, depending on the specific product itself.

Don Chmielewski

DH Chmielewski 1/21/98

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

January 26, 1998

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

NC

This submission does not fully address the DE identified in the 1-27-98 FAX It has been reclassified as a NC & will be reviewed when the ANDA becomes pen

JB 3-4-98

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

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application for a minor change in the spray device used to administer the drug product. This change will allow the spray characteristics to more closely resemble the innovator product.

Explanation of Proposed Change:

The only change proposed in this amendment is a change in the spray insert of the actuator piece of the device. This spray insert is largely responsible for the plume geometry and droplet size of the drug product. The plume geometry and droplet size using this insert is currently being evaluated through extensive *in vitro* testing, and the results will be submitted in a Bioequivalence Amendment shortly. Refer to Attachment A for an illustration of the actuator and pump assembly, with specific reference to the part being changed. This spray insert (ne part number 3000.019.101) is composed of the same resin as the previously submitted spray insert, i.e., . No other changes are proposed. No changes are proposed in the pump composition or assembly.

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1-30-98

Documents to Support Proposed Change:

Attachment A: Illustration of Actuator and Pump Assemblies

Attachment B: NEW Specification No. XD40018-00
"Actuator Head, Nasal Pump with Overcap"

Attachment C: OLD Specification No. XD40016-05 (previously submitted)
"Actuator Head, Nasal Pump with Overcap"

Attachment D: Correspondence from Pump Supplier,
regarding the part number of the spray inserts for the old actuator, new actuator for B&L, and the spray insert for the innovator (DDAVP) also supplied by

Documentation is supplied to demonstrate that the only change proposed in this amendment is the change of the spray insert in the actuator. As stated previously, this spray insert is composed of the same resin s the previously submitted spray insert (see Attachments B, C, and D). In addition, the pump supplier has provided information that the part number of the new spray insert is identical to the spray insert part number for the innovator reference product, DDAVP Nasal Spray (RPR).

Stability Considerations:

The new spray insert in the actuator is not in contact with the drug product during the storage phase. Because the new part comes in contact with the drug product only at the time of administration, and is composed of the same resin as the previously submitted spray insert, there is no effect on the stability of the drug product, and no need to perform additional stability studies. In the stability commitment, Bausch & Lomb committed to put the first three commercial lots and one annual lot on stability.

Product Specifications Considerations:

There are no changes in any drug product specifications.

Conclusion:

Due to the straightforward nature and the few documents needed, we contend that this change in the spray insert can be processed as a Minor Amendment to the pending ANDA.

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 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.

Sincerely,

Joseph B. Hawkins

Joseph Hawkins
Manager,
Regulatory Affairs

Enclosure

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

February 4, 1998

NEW CORRESP

NC

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%
Patent Certification Amendment

Dear Sir or Madam:

The purpose of this correspondence is to amend the above referenced application to provide certification for a recently listed patent .

In accordance with 21 CFR 314.94 (a)(12)(i)(A)(4), we are providing a Paragraph IV Certification for U. S. Patent No. 5,674,850 filed by ls. The signed certification is enclosed immediately following the 356h.

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 regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775.

Sincerely,

Joseph B. Hawk

Joseph Hawkins
Manager,
Regulatory Affairs

Enclosure

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GENERIC DRUGS

File 74-830

Bausch & Lomb Pharmaceuticals, Inc.
Regulatory Affairs
8500 Hidden River Parkway
Tampa, Florida 33637
phone: 813-975-7700
fax: 813-975-7757

FAX TRANSMISSION LETTER

DATE: April 20, 1998

DELIVER TO: Peter Rickman, OGD 301-594-1174

FROM: Donald H. Chmielewski, Director, Regulatory Affairs

NO. OF PAGES (including cover sheet): 9 pages

SUBJECT: Desmopressin Acetate Nasal Solution ANDA 74-830

Peter,

We have discussed the issue of notifying the patent holder in the past. I sent you a copy of our February 5th letter in March for your comments.

We now have a March 26th letter (copy enclosed) that says that we will not be sued. In this letter they acknowledge the February 5th letter, which I trust will support the starting of the clock by this letter (since we lacked the official US Mail postage receipt).

Can you give me your take on this letter? Do we satisfy OGD's concerns that the notification of the patent holder had taken place, and that no suit will be filed. The enclosed documents are all we have.

We are currently working on our bioequivalence submission, and I don't want this to be an unresolved issue.

Looking forward to hearing from you. 800-227-1427 ext 7786

Thanks.

Donald H. Chmielewski

Donald H. Chmielewski
Director, Regulatory Affairs

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MICHAEL EBERT
OF COUNSEL

*NOT ADMITTED IN NEW YORK

March 26, 1998

Looks acceptable per 314.95(c) "letter acknowledging receipt by the person provided the notice"
4/2/98

VIA FEDERAL EXPRESS

Denis A. Polyn, Esq.
Staff Vice President and Assistant
General Counsel Patent Law
Bausch & Lomb
One Bausch & Lomb Place
Rochester, New York 14604-2701

John H. Thomas, Esq.
Millen, White, Zelano & Branigan, P.C.
1561 East Main Street
Richmond, Virginia 23219

Re: Desmopressin Acetate ANDA 74-830

Dear Denis & John:

This is to advise you that Ferring AB and Rhone Poulenc Rorer have decided not to take any action at this time with respect to the above identified ANDA referenced in Mr. Polyn's communication of February 5.

As agreed, we are enclosing in our letter to Mr. Thomas one copy of the materials that he sent to us. Three additional copy sets were made for the three attorneys in

our firm (myself, Janet Linn and Edward Reisner) reviewing the confidential information. Those copies, which have attorney notations, have been shredded.

We ask that Mr. Thomas retain a copy of the documents we are returning, in order to have a record of the materials we reviewed should a question arise in the future. For your convenience, I have attached as Schedule A a list of the documents that we are returning.

Very truly yours,

Dennis J. Mondolino

DJM:cp
Enclosure
cc: Arnold Chase, Esq.
Ross J. Oehler, Esq.
Jeffrey I.D. Lewis, Esq.

SCHEDULE A

LIST OF DOCUMENTS RETURNED TO JOHN THOMAS

1. Letter dated February 27, 1998 to Dennis J. Mondolino from John H. Thomas enclosing portions of Drug Master File.

2. Letter dated March 2, 1998 to Dennis J. Mondolino from John H. Thomas with enclosure outlining manufacturing process.

3. Letter dated March 4, 1998 to Janet B. Linn from John H. Thomas.

4. Letter dated March 5, 1998 to Janet B. Linn from John H. Thomas.

5. Letter dated March 12, 1998 to Dennis J. Mondolino from Karen B. Luther enclosing the complete Drug Master File.

6. Letter dated March 16, 1998 to Janet B. Linn from John H. Thomas enclosing portion of batch record.

7. Letter dated March 17, 1998 to Janet B. Linn from John H. Thomas enclosing batch record.

8. Letter dated March 19, 1998 to Jeffrey I.D. Lewis from John H. Thomas enclosing batch analysis report.

One Bausch & Lomb Place
Rochester NY 14604-2701
716 338 8417
Fax 716 338 6007

Denis A. Polyn
Staff Vice President and
Assistant General Counsel
Patent Law

BAUSCH & LOMB
Healthcare and Optics Worldwide

WORLDWIDE SPONSOR 1996 OLYMPIC GAMES

February 5, 1998

CERTIFIED MAIL, RETURN RECEIPT REQUESTED

Ferring B.V.
Marsstraat 9
P.O. Box 3129
2130 KL, Hoofddorp
The Netherlands

Ross J. Oehler, Esq.
Assistant General Counsel
Patents & Trademarks
Rhone-Poulenc Rorer, Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19246-0107

Re: Notice of Certification of Non-Infringement
of U.S. Patent No. 5,674,850
Pursuant to 21 U.S.C. §355(j)(2)(B)

Dear Sir and Mr. Oehler:

Notice is hereby given pursuant to Section 505(j)(2)(B) of the Drug Price Competition and Patent Term Restoration Act of 1984, 21 U.S.C. § 355 (j)(2)(B), that FDA has received an Abbreviated New Drug Application (ANDA No. 74-830), submitted by Bausch & Lomb Pharmaceuticals, Inc., for a Desmopressin acetate Nasal Solution USP. The ANDA

contains the required bioavailability or bioequivalence data or information.

Bausch & Lomb certified to FDA pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that Ferring B.V.'s U.S. Patent No. 5,674,850, ("the '850 patent") due to expire on October 7, 2014 will not be infringed by the manufacture, use or sale by Bausch and Lomb Pharmaceuticals, Inc., of the drug for which the application was submitted, and requested FDA approval to engage in the commercial manufacture, use, or sale of Bausch & Lomb's Desmopressin acetate Nasal Solution USP before the expiration of that patent.

The factual and legal basis for Applicant's Certification follow.

Claims 1 and 7-11 of U.S. Patent No. 5,674,850 ("the '850 patent") are directed to manufacturing processes. Accordingly, claims 1 and 7-11 do not claim a drug and therefore no certification is required under 21 U.S.C. § 355 (b)(2)(A).

Claims 2-6, 14 and 15 depend from claim 1 and therefore incorporate all of the limitations of that claim.

Claim 1 of the '850 patent is not infringed because the process used to make Bausch & Lomb Pharmaceuticals, Inc.'s Desmopressin Acetate Nasal Solution USP: (1) does not produce a single batch of "desmopressin having a weight of at least about 500 g", (2) does not include the final synthetic step defined in claim 1 to produce a batch "containing at least 98.5% by weight of desmopressin", (3) does not employ "at least about 1 kg of mercapto-propionyl-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-NH_2 [] or a derivative thereof", and (4) does not employ a "second solution of iodine in a protic solvent". Accordingly, neither claim 1, nor any of claims 2-11, 14 and 15 will be infringed. Wahpeton Canvas Co. v. Frontier, Inc., 870 F.2d 1546, 1553 (Fed. Cir. 1988).

Claims 12 and 13 each require a "single oral dose" of desmopressin. Bausch & Lomb Pharmaceuticals, Inc.'s Desmopressin Acetate Nasal Solution USP is not an oral dosage form, but rather is for nasal administration. Accordingly, claims 12 and 13 of the '850 patent will not be infringed.

Furthermore, Bausch & Lomb Pharmaceuticals, Inc. certifies that claims 2-6 and 12-15 of the '850 patent are invalid for at least the following reasons.

Claims 2-6 are invalid under 35 U.S.C. § 103(a) in view of the prior art of record in the prosecution of the application for the '850 patent. Desmopressin and the processes for making it were known in the prior art. The scale of manufacture and degree of purity are the only features alleged to distinguish the subject matter of claims 2-6 from the prior art. As such, it would have been obvious to a person of ordinary skill in the art to increase batch size and level of purity in order to obtain the alleged economic benefits recited in the patent specification. See In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990).

Claims 12-15 are invalid because they are anticipated under 35 U.S.C. § 102(b). The subject matter of each of claims 12-15 is a composition of matter which was known in the prior art. The only aspect of those claims which is purported to be novel is the allegedly new process for making these known compositions. However, product-by-process claims are not patentable if the claimed product is known in the prior art even if it was made by a different process. In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985). Accordingly, claims 12-15 are invalid.

Claims 12-15 are also invalid under 35 U.S.C. § 112, paragraph one, because the specification of the '850 patent does not include a written description of any "single oral dose" as recited by claims 12 and 13, or any "single dose for intranasal administration" as recited in claims 14 and 15, nor of how to make or use such compositions. To the extent such information was known to the inventors and not disclosed in the specification, there was a failure to comply with the best mode requirement of 35 U.S.C. § 112.

If a patent infringement action is brought on the '850 patent, Bausch & Lomb reserves the right to assert additional grounds of non-infringement and other defenses as they become known during discovery and to amend the assertions of non-infringement, invalidity and unenforceability made herein to conform to the evidence.

For each of the above reasons, each claim of the '850 patent will not be infringed by the manufacture, use or sale by Bausch & Lomb of Desmopressin acetate Nasal Solution USP.

Sincerely,

Denis A. Polyn