CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211039Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 131170

MEETING MINUTES

Valeant Pharmaceuticals Luxembourg S.à.r.l. (VPL)
Attention: Jeremy Brace, VP of Regulatory Affairs, Point Guard Partners
400 N Ashley Drive
Suite 2150
Tampa, FL 33602

Dear Mr. Brace:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Fluorescein Sodium (b) (4)% and Benoxinate Hydrochloride (b) (4)% Ophthalmic Solution.

We also refer to the meeting between representatives of your firm and the FDA on August 18, 2016. The purpose of the meeting was to discuss CMC aspects of the development program for Fluorescein Sodium (b) (4)% and Benoxinate Hydrochloride (b) (4)% Ophthalmic Solution.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have questions, call me, at 240-402-3815.

Sincerely,

{See appended electronic signature page}

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: CMC Pre-NDA

Meeting Date and Time: August 18, 2016, 1:30 PM – 2:30 PM, EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 131170
Product Name: Fluorescein Sodium and Benoxinate Hydrochloride
Indication: For ophthalmologic procedures requiring a disclosing agent in combination with an anesthetic (b) (4) .
Sponsor/Applicant Name: Bausch and Lomb Inc.

Meeting Chair: Balajee Shanmugam
Meeting Recorder: Navdeep Bhandari

FDA ATTENDEES

Balajee Shanmugam, Ph.D.	Acting Branch Chief
Chunchun Zhang, Ph.D.	Acting CMC Lead
Yushi Feng, Ph.D.	Drug Product Reviewer
Maria Cruz-Fisher, Ph.D.	Product Quality Microbiology Reviewer
Navdeep Bhandari, Pharm.D	Regulatory Health Project Manager
Wendy Zhang, Ph.D	Process & Facilities Reviewer
Wiley Chambers, M.D.	Deputy Director, DTOP
William Boyd, M.D.	Clinical Team Leader, DTOP
Derek Smith, Ph.D.	Facilities Acting Branch Chief
Hyun Son, Pharm.D	Senior Program Management Officer

SPONSOR ATTENDEES

David Silberstein	Executive Director, Regulatory
Matt Jonasse	Executive Director, R&D
Sharad Agarwal	Sr. Manager, CMC
Shankar Swaminathan	Director, Regulatory CMC
Patrick H. Witham	President and CEO
Lauren Mc Bluett	Director of Quality Assurance
Mike Bush	Sr. Regulatory Project Manager
William Stringer	Head of Quality and CMC
Mike Hanrahan	Quality and CMC Manager

Jeremy Brace VP of Regulatory Affairs

1.0 BACKGROUND

A Type B meeting briefing package was submitted July 18, 2016, for an August 18, 2016, CMC Meeting for Bausch and Lomb Inc.

2.0 DISCUSSION

The Agency sent preliminary responses on August 10, 2016, to the Sponsor. The Sponsor asked to discuss all three questions. A slide deck was provided by the Sponsor on August 18, 2016 (attached below).

2.0 Questions

Question 1

The Sponsor proposes to utilize historical stability data from the commercially available product for the 12-month real time ICH stability requirement. However, the historical product was manufactured with fluorescein sodium active pharmaceutical ingredient (API) that is not currently the subject of a Type II DMF. The Sponsor has manufactured and placed on stability three (3) exhibit batches utilizing API from a new supplier of fluorescein sodium that does have a Type II DMF. The new supplier is the proposed source of API for commercial product following NDA approval. The stability data from the new exhibit batches will be approximately nine (9) months in duration at the time of NDA submission. In an effort to avoid interruption in supply and thereby, a potential drug shortage of this medically necessary drug, will the strategy of utilizing the new exhibit batches as a bridge to the historical stability data be acceptable to the Division?

The historical stability was generated for Bausch & Lomb products on batches utilizing (b) (4) *API. At the time the NDA is submitted there will be 12 months of stability data for the exhibit batches manufactured with the new API* (b) (4)*.*

Agency Response:

Note that the initial NDA submission should contain 6-month accelerated and at least 12-month long-term stability data for three registration batches of the drug product packaged in the proposed commercial container closure system. The manufacturing process used for these batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. For further recommendations regarding the batch selection, testing conditions, etc., refer to ICH Q1A (R2) Stability Testing of New Drug Substances and Products.

Please clarify how much stability data will be submitted at the time of NDA submission on the drug products manufactured with the proposed source of API.

Discussion: The sponsor stated that Fluorescein API will reference a Type-II DMF # from (b) (4) The agency recommended the sponsor to provide an LoA in the NDA for the referenced DMF from the DMF holder.
Refer to Question #2 for discussion on the drug product stability studies.

Question 2

The Sponsor is transferring manufacture of the drug product to a contract manufacturing site prior to the proposed NDA submission. Drug product information will be included in the NDA for the existing site only, along with a comparability protocol outlining development activity and post-approval filing requirements for the new manufacturing site. In an effort to avoid interruption in supply and thereby, a potential drug shortage situation of this medically necessary drug, is the content described in the comparability protocol and post-approval filing requirements satisfactory to the Division?

The existing manufacturing site is Bausch & Lomb, Tampa, FL, the new manufacturing site will be Siegfried AMP, Irvine, CA.

Agency Response:

The FDA acknowledges your plan to initiate drug product manufacture transfer activities at a second facility (Siegfried AMP, Irvine, CA) during the NDA review period. During the NDA review cycle, the proposed commercial manufacturing facility (Bausch & Lomb, Tampa, FL) will APPEARS THIS WAY ON ORIGINAL be assessed on its readiness for commercial manufacturing as it will be the sole facility proposed in the submission.

The Comparability Protocol to transfer drug product manufacturing to a second facility is inadequate and needs additional information. The completed protocol should include a table comparing equipment (e.g. manufacturer, model, capacity), process parameters with justification, in process controls and tests performed to compare material manufactured at the two sites. Additionally, the approaches and acceptance criteria that will be used to evaluate the transfer should be described. The Comparability Protocol should also clarify whether equipment at the AMP site is of the same design and operating principles as the original B&L site.

In regard to the sterility assurance validation studies, the comparability protocol should include a detailed description of each validation study (i.e., heat distribution studies, heat penetration studies with biological or endotoxins challenge studies, number of runs, loads descriptions, details on the media fills simulations, etc.), including the acceptance criteria and a description of the analytical procedures.

Upon receipt, the filing category (e.g. PAS, CBE-30) for the described manufacturing facility addition supplement and Comparability Protocol Report will be assigned in accordance with

FDA Guidance for Industry.

For additional information, see "FDA Guidance for Industry: Changes to an Approved NDA or ANDA":

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf

Discussion: The sponsor clarified that the manufacturing line at Bausch & Lomb (B/L) Tampa, FL has been decommissioned and not available for inspection. Also, the sponsor confirmed Alliance Medical Products (AMP), Irvine, CA to be the new commercial manufacturer. The agency stated that AMP site may be inspected prior to approval and as such will need to be ready for inspection at time of NDA submission. The sponsor confirmed that the AMP site is ready for inspection. Regarding stability data, the Agency mentioned that any stability data from the B & L site will only be considered as supportive data and that the NDA at the time of submission should provide at least 6 months of long-term and 3-months accelerated stability data for three primary registration batches manufactured at the commercial AMP site in the intended commercial configuration. Two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified.

Question 3

The drug product that is currently commercially available contains (b) (4) (b) (4)

commercialize the same drug product that is currently manufactured without interrupting supply of this medically necessary drug, the Sponsor proposes including the same quantities of the APIs and preservative that are currently in the commercially available drug product and reflecting these concentrations in the label. Are the proposed drug product specifications that incorporate the (b) (4) into the labeled drug concentration satisfactory to the Division?

FDA Response:

Please provide justification for the API (b) (4) used in the formulation.

For the drug product specifications, use either one specific identity method or two non-specific tests for the active ingredients (see ICH Q6A). For example, two chromatographic procedures, where separation is based on different principles, or a combination of tests into a single procedure, such as HPLC/UV diode array, are generally acceptable.

The acceptance criteria on the impurities should be set according to ICH Q3B(R2) guidelines. Based on the evaluation of the data presented, additional tests and/or tightening of the

specification limits may be required.

We recommend you to

- Add tests and acceptance criteria for osmolality and specific gravity in the drug product specifications

- Monitor deliverable volume and weight loss during drug product storage and stability, and propose specification tests and acceptance criteria if appropriate

The drug product specifications state that the antimicrobial effectiveness testing (AET) will be performed only when (b) (4) Please note that the drug product should not be released when (b) (4) In addition, the AET testing, if included in the drug product release specifications, needs to be tested for every lot.

Additional Comments:

NDA should provide study results on

- Freeze-thaw cycling studies (3 cycles).

- A one-time study for leachable/extractable using the to-be-marketed container closure system using screening analytical methods (such as HPLC, GC etc.) on at least one primary (registration) batch through expiry. Refer to USP <1663>, <1664> for recommendations.

- Details of all analytical methods, specifically those which are non-compendial and the respective methods validation should be submitted to the NDA.

- If any CMC information including drug substance and container closure systems will be referenced to DMFs, please provide Letters of Authorization of the referenced DMFs from the respective DMF holders.

Not discussed.

Additional Comments: The agency recommendedkeeping the (b) (4) (b) (4) and agreed that the proposed labeling reflect Fluorescein Sodium (b) (4)% and Benoxinate Hydrochloride 0.4%.

The sponsor shared their observation (b) (4) . The sponsor stated the container closure system has been used since 1994, and agreed to the recommendation by the agency to verify to if any change has been made to the CCS.

The applicant asked if the NDA will be a priority review, and the agency stated that it will be determined at the time of the NDA submission.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NAVDEEP BHANDARI
09/19/2016