CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125294Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125294/0

COMPLETE RESPONSE
September 29, 2010

Teva Pharmaceuticals U.S.A.
Attention: Deborah A. Jaskot, M.S., R.A.C.
Vice-President, Regulatory Affairs
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Ms. Jaskot:

Please refer to your Biologics License Application (BLA) dated November 30, 2009, received November 30, 2009, submitted under section 351 of the Public Health Service Act for "Neutroval."

We acknowledge receipt of your amendments dated December 8, December 21, and December 23, 2009 and January 11, 2010, January 22, February 1, February 12, March 26, April 5, April 23, April 30, May 7, May 12, June 3, June 11, June 15, June 24, June 30, July 8, July 12, July 14, July 20, July 30, and August 19, 2010.

We also acknowledge receipt of your amendment dated August 27, 2010, received September 2, 2010, regarding verification of the integrity of the clinical data base for Study XM02-02-INT, which was not reviewed for this action. Information regarding withdrawal of the protocol for the qualification of new cell banks included in the August 27, 2010 amendment was reviewed. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

DEFICIENCIES

1. Based on the FDA inspection of BioGeneriX AG (b) (4) there is concern that the integrity of the database for Study XM02-02-INT, the single trial submitted to support the efficacy of your product, may have been compromised. Specifically, after the initial database lock on January 2, 2006, and subsequent data unblinding, the database was unlocked and the data were altered on at least two separate dates, i.e. January 17th and January 23rd, 2006. Describe the quality control and/or quality assurance activities at each stage of data handling, from initial

entry into the database through the final database lock, that were undertaken to ensure the integrity of safety and efficacy data. In addition, provide documentation, including justification and the audit trail, for all changes made to the database after unblinding. Finally, provide a detailed analysis of the impact of all changes made to the database after initial lock and unblinding on the evaluation of safety and efficacy data.

2. (b) (4)

3. You have not provided adequate information concerning your device closure system. Based on our assessment, you appear to be relying solely on the fill weight as the definitive property to decide if the correct amount of therapy is being delivered through the syringe. There are physical aspects of syringes and needles such as dead space/volume, bond strength between the syringe/needle, and spacing of volumetric graduation markings that can impact the performance of the device. We are also aware that there have been several complaints from the medical community regarding the (b) (4) and the ability for the user to manipulate these pre-filled syringes. Additionally, based on our review of DMF (b) (4) (Drug Master File for (b) (4) (b) (4)), it appears that your syringes may not conform to current FDA consensus standards regarding syringes and needles.

Provide performance testing to demonstrate that your pre-filled glass syringe is safe and effective to deliver your drug product (DP) and that this syringe meets the specifications of the following guidance document and FDA Consensus Standards (most recent editions):

- (b) (4)
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In addition, there are aspects of other syringe standards that may still apply to your device. Specifically, the device constituent of this combination product consists of a [redacted] (b) (4). In this capacity, all specifications of the current consensus standards such as [redacted] (b) (4) However, you must still consider the application of specific elements of these standards as they impact your device. [redacted] (b) (4) Modify your testing procedures and pass/fail criteria to reflect the relevant portions of the standards that affect the performance of your device (such as bond strength).

4. The literature assessment of the potential reproductive toxicity of granulocyte colony stimulating factor(s) provided in support of BLA 125294 does not fulfill the regulatory requirements for nonclinical developmental and reproductive toxicity studies with Neutroval. Your BLA submitted under section 351(a) of the PHS Act may not rely on published literature describing studies of other biological products, including studies regarding a licensed biological product, to fulfill this requirement for approval.

   To complete the application for BLA 125294 under the 351(a) pathway, provide the results of a nonclinical embryo-fetal toxicity study conducted with Neutroval in rabbits as a single, pharmacologically responsive species [refer to ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085389.pdf)]. We recommend that you submit a draft protocol for this study as an amendment to the BLA for review and comment by the nonclinical reviewers prior to initiation of this study.

5. We have determined that your proposed proper name [redacted] (b) (4) is not acceptable for this BLA submitted under section 351(a) of the PHS Act. [redacted] (b) (4) :

   - [redacted] (b) (4)
   - [redacted]

(b) (4)

INFORMATION REQUESTS

6. You have proposed several changes to the DS manufacturing process to improve microbial control. Submit the following data in support of the proposed changes:

   a. In-process and final XM-02 bioburden and endotoxin data for the (b) (4) following the proposed changes.

   b. Microbial control data for storage (b) (4).

   c. Identify any additional changes that could affect microbial process control (for example, changes in hold times). The safety of such changes should be supported by appropriate testing and controls.

7. You have not fully characterized the potential effects of Neutroval on cardiac conductions (QT interval). You must conduct and provide the results of a single-dose, three-way crossover thorough QT clinical trial in a sufficient number of healthy volunteers receiving the highest subcutaneous dose of Neutroval studied (10 mcg/kg). The clinical trial should perform continuous cardiac monitoring (telemetry or Holter monitors) and/or concurrent detailed serial electrocardiogram (ECG) monitoring, and electrophysiologic studies. In addition, serum Neutroval pharmacokinetic and pharmacodynamic measurements should be performed at multiple time points prior to and following Neutroval administration. Time points should include, but are not limited to: during pre-treatment, at the estimated Tmax of Neutroval blood concentration, several other time points up to 24 hours post-dose, and at a post-therapy washout time point. Serial ECGs should be collected in triplicate and read by a qualified physician. The clinical trial protocol and data analysis plan should be submitted to us for review prior to starting trial enrollment.

   In your response, provide the protocol for the requested clinical trial. In addition, provide information on the following milestones:
   - Study completion date
   - Final report submission date

8. Please submit a description of your plan for development of a validated screening assay for the assessment of an anti-product antibody response to Neutroval. The validation of the assay should include the sensitivity and specificity for detection of anti-Neutroval antibodies that are also cross-reactive with native human granulocyte colony stimulating

factor (G-CSF). In your response, provide the protocol for the requested clinical trial. In addition, provide information on the following milestones:

- Date of submission of the validation protocol
- Final report submission date

If you require clarification on the deficiencies of the current assay, we recommend that you submit a request for a type C meeting with FDA.

9. Please submit a description of your plan for development of a validated assay for confirmation of anti-product antibodies identified by the screening assay. The validation of the assay should include the sensitivity and specificity for detection of anti-Neutroval antibodies that are also cross-reactive with native human granulocyte colony stimulating factor (G-CSF).

   In your response, provide the protocol for the requested clinical trial. In addition, provide information on the following milestones:

   - Date of submission of the validation protocol
   - Final report submission date

   If you require clarification on the deficiencies of the current assay, we recommend that you submit a request for a type C meeting with FDA.

10. Please submit a description of your plan for development of a validated assay for identification of anti-product antibodies that neutralize the bioactivity of Neutroval. The validation of the assay should include the sensitivity and specificity for detection of anti-Neutroval antibodies that are also cross-reactive with and neutralize the bioactivity of native human granulocyte colony stimulating factor (G-CSF). In your response, provide the protocol for the requested clinical trial. In addition, provide information on the following milestones:

    - Date of submission of the validation protocol
    - Final report submission date

    If you require clarification on the deficiencies of the current assay, we recommend that you submit a request for a type C meeting with FDA.

11. Provide a plan for assessing for the presence, persistence, and effects of anti-Neutroval and anti-native human GCSF binding and neutralizing antibodies using validated assays in at least 500 patients enrolled or to be enrolled in one or more clinical trials. You should provide a listing of the clinical trials in which this assessment will be conducted. In your plan, you should provide information on the following milestones:

    - Date of submission of the protocol for clinical immunogenicity assessment
    - Date of completion of the study
    - Final report submission date

12. Provide a written commitment to submit the results of the re-evaluation of the bioburden limit after 30 commercial batches are manufactured and to propose a new (b) (4) bioburden action limit that more accurately reflects process capability.

13. You use SE-HPLC to measure aggregates in the DS and DP. This assay detects monomers, dimers and high molecular weight (HMW) species. You have validated the assay for the detection of monomers and dimers using AUC as your orthogonal method. We note that you did this study using release (unstressed) samples. Because of the low amount of aggregates at release, there is little sensitivity for determining whether the assay provides accurate results regarding aggregate content. Because AUC may monitor species of aggregates that are not detected by SEC and different aggregates can accumulate over time, it is important to understand whether SEC provides accurate information on aggregate content over the shelf-life of the product.

    Provide data indicating that SEC provides an accurate measure of aggregate content through the product's shelf life and conditions of use or consider use of an alternative assessment of aggregate content. As one possible approach, we suggest that you stress the product under multiple conditions (such as temperature, agitation and light) and determine if SEC provides an accurate assessment of aggregate contents as compared to AUC.

14. You are proposing to set specifications for subvisible particles after 12 batches of the DP have been produced. Instead, we recommend you provide a risk assessment of the potential impact these particulates may have on the quality, safety and efficacy of your product and propose a strategy that provides an appropriate level of control. As part of the risk assessment, we recommend that you conduct a robust characterization of the subvisible particle content at release, on stability and in use. This characterization should include the use of multiple orthogonal techniques to quantitate the amount and types of particulates and the use of multiple stress conditions to fully understand the propensity to form large protein aggregates. In your response, provide a timeline for your risk assessment and control strategy for subvisible particles.

15. You currently use peptide mapping as an identity test. However, when appropriately analyzed, the peptide map data also provide a measure of the purity of the DS and DP. Please revise the peptide mapping assay to include quantitative acceptance criteria for peak areas, relative peak heights, and new peaks. We also recommend, when validating the assay for purity, that the acceptance criteria should be based on more than one lot of DS and DP. In your response, provide your proposal for establishing specifications for purity based on peptide mapping.

16. You have provided data for extractables and leachates (b) (4) used for the container closure system of the DP. You did not provide such data on the (b) (4) in the presence of the DP (b) (4) Because the presence of leachates in the DP may impact product quality in multiple ways, you should assess the risk to product quality posed by such leachates. Please include testing for leachates at the end-of-shelf-life for the DP in the final container closure system in presence of the DP (b) (4) and

provide a plan for submission of these data and include your evaluation of the risk to product quality.

17. The plasmid copy number varies between the Master Cell Bank ((b) (4)), Working Cell Bank (b) (4) and batches of end-of-production cells ((b) (4) . Provide optimization data for the current assay used to determine plasmid copy number or develop a new assay.

18. You have revised the release and retest specification for in Polysorbate 80 to be not more than (b) (4) and you have submitted information on how an investigation will be conducted for any lots formulated with out of specification Polysorbate 80. However, you have not provided long-term product quality data for XM02 formulated with Polysorbate 80 at the upper limit (b) (4) . Also, your investigation procedure is inadequate to assess XM02 product quality in that you do not require affected lots to be placed on stability. Please provide data showing that Polysobate 80 with (b) (4) values at or close to the upper limit of the specification does not impact the quality of your G-CSF product over time. In addition, please revise your investigation procedure to include a provision for assessing long-term stability of the product when formulated with expired Polysorbate 80. Please note, if lots have been released with out of specification Polysorbate 80, you will need to submit a Biological Product Deviation Report to the Agency.

LABELING

19. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all new non-clinical and clinical studies of the drug, and post-marketing safety data from the E.U. Data from all indications, dosage forms or dosage levels should be included.

20. Describe in detail any significant changes or findings in the safety profile.

21. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

22. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on "Formal Meetings Between FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Danyal Chaudhry, Regulatory Project Manager at (301) 796-3813 or Erik Laughner, Senior Regulatory Health Project Manager, at (301) 796-1393.

Sincerely,

/Richard Pazdur/
Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research