CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761066Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761066

COMPLETE RESPONSE

Samsung Bioepis Co., Ltd.
c/o Biologics Consulting Group, Inc.
400 N. Washington Street, Suite 100
Alexandria, VA 22314

Attention: Kelly T. Boyle
CFO, Biologics Consulting Group

Dear Ms. Boyle:

Please refer to your Biologics License Application (BLA) dated May 25, 2017, received May 25, 2017, and your amendments, submitted under section 351(k) of the Public Health Service Act for SB4.

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

PRODUCT QUALITY

1. The data and information provided in your response on January 12, and February 14, 2018, to the Agency's information requests (IRs) dated December 19, 2017 (IR #13) and February 7, 2018 (IR #1) demonstrate that the primary reference standard (PRS) was not appropriately qualified with respect to biological activity (i.e., TNF-α binding activity and TNF-α neutralization activity) and protein concentration, and therefore, is not appropriate for its intended use. Because the PRS was not appropriately qualified, the working reference standard (WRS), which was qualified against the PRS, is also not appropriate for its intended use. Therefore, there is a lack of assurance that the commercial materials are not going to drift from SB4 clinical materials and the materials used to establish the analytical similarity.

    a. Generate an appropriately qualified reference material based on the advice provided in the Agency's IRs dated December 19, 2017 and February 7, 2018. Upon the generation of the new qualified reference material, provide data to adequately link this material to the materials used in the clinical studies and analytical similarity assessment. We recommend using a two-tiered system for utilizing reference standard material for routine testing of commercial product.

b. Re-assess and revise SB4 drug substance and drug product lot release and stability specifications, as appropriate.

c. Re-test the currently manufactured SB4 lots for release and stability using the appropriately qualified reference material, as appropriate, if these lots are intended to be released for commercial use in the US.

d. Provide an updated requalification protocol for the reference material (e.g. primary and working reference standards) to include the advice that was given in the Agency's information requests dated December 19, 2017, and February 7, 2018.

2. The data and information provided in the submission and in your response dated February 13, 2018, to the Agency's information request dated February 2, 2018 (IR #1) was insufficient to support the limit of in vitro cell age (LIVCA) of (b) (4) and the proposed control limit of the (b) (4) Characterization and assessment of LIVCA using (b) (4) study is not considered sufficiently representative of cell culture behavior during the commercial cell culture process. In addition, the information provided in the IR response on February 13, 2018 (IR #7) concerning the generation of the SB4 Master Cell Bank (MCB) suggests that the cell bank is not clonal (b) (4) Taken together, the overall control strategy for the upstream cell culture process is inadequate and requires additional levels of control. To ensure product quality and cell culture process consistency, implement the following controls and update all the appropriate sections of the BLA with this information:

a. Establish LIVCA using an appropriate cell culture model that is sufficiently representative of the commercial cell culture process. For example, (b) (4)

b. Establish key controlled parameter (KCPs) for (b) (4) These ranges should be supported by data from development studies using an appropriate cell culture model, PPQ and/or commercial manufacturing runs.

c. Implement a critical control limit for the (b) (4) to ensure that the LIVCA (based on comment 2a) is not exceeded by the (b) (4) during routine

manufacturing. Provide information and/or data to justify the control for the limit of (b) (4)

3. The information provided in the submission and in the responses received by the Agency on February 2, 6, and 14, 2018, and during the teleconference held with the Agency on February 8, 2018, is not adequate to support that the currently proposed drug product filling control strategy provides sufficient assurance that each pre-filled syringe (PFS) is filled with sufficient SB4 product to meet the current US label claim of 50 mg/mL and 25 mg/0.5mL for Enbrel.

   a. Although the protein concentration for drug product process validation batches filled at (b) (4) are within the acceptance criterion range of (b) ( ) at release, the protein concentration is consistently less than 50 mg/mL while the drug substance lots used to fill these drug product lots did not have this issue. For example, drug substance lot 15-602E-002 had a protein concentration of (b) (4) at release and the resulting drug product lot, 00003, had a protein concentration of (b) (4) Because the drug product is (b) (4), it is unclear why there is such variability between the drug substance protein concentration and the subsequent drug product protein concentration. Explain this discrepancy.

   b. While the labeling allows (b) (4) when considering the control strategy, the current criteria would allow the release of PFS filled outside appropriate limits. The 50 mg/mL syringes may be underfilled, because a volume of (b) (4) deliverable volume) is allowed, and the 25 mg/0.5 mL syringes may be filled to an inappropriately high level of (b) (4) deliverable volume). As requested previously on February 7, 2018, revise the lower limits for extractable volume (Section 3.2.P.5.1) and (b) (4) (Section 3.2.P.3.3) for the 50 mg/mL syringe (i.e., increase the extractable volume criterion from (b) (4), and revise the upper limits for extractable volume and (b) (4) for the 25 mg/0.5 mL syringe (i.e., decrease the extractable volume criterion from (b) (4) to ensure the delivery of appropriate volume of product.

   c. In the IR response received by the Agency on February 6, 2018, (Question 1) and during the teleconference with the Agency on February 8, 2018, insufficient information was provided regarding the filling control strategy including how (b) (4) is monitored and controlled and how (b) (4) excursions are investigated and handled. For both (b) (4) provide a detailed description in Section 3.2.P.3.3 of how the (b) (4) is controlled in real time during manufacturing. Include the monitoring frequency, number of samples taken, and rejection/action and alert limits. (b) (4)

[redacted] Clearly define the actions taken when samples are outside the rejection/action limit; these should include activities such as segregation of the portion of the lot associated with the out of range sample(s), [redacted]

4. The information and data provided to support the commercial drug product shipping do not provide sufficient assurance that the quality of the DP is maintained during commercial shipping and distribution. The air transport simulation study parameters tested are not representative of routine distribution conditions and cannot on their own be used in lieu of performing real-time DP shipping validation studies. In addition, it is unclear how the supply chain cycling study (Section 3.2.P.8.1) can be used to support the validation of shipping of the drug product from either [redacted] or [redacted] DP manufacturing sites. Provide shipping validation data for the drug product from real-time shipping studies or from studies that are sufficiently representative of the commercial shipping conditions. The data should include an assessment of product quality pre- and post-shipping. Include a detailed description of how the study was performed and if performed using simulated studies, provide a justification for how the simulated studies are sufficiently representative of the commercial shipping conditions.

5. As requested in an IR, dated February 6, 2018 and via teleconference with the Agency on February 8, 2018, update the drug product manufacturing process in Section 3.2.P.3.3 to ensure that samples for identity testing for drug product release will be taken after the labeling operations have been completed to comply with 21 CFR 610.14.

6. The sterilization validation data provided to support the [redacted] sterilization of items used to manufacture SB4 at [redacted] was deficient, as there is no minimum [redacted] validated. Inadequate validation of sterile product-contact equipment may result in a non-sterile product. Provide sterilization validation for the minimum [redacted] in the BLA resubmission.

7. The BLA does not include [redacted] as a critical process parameter for sterile filtration. Performing sterile filtration outside of the parameters validated by the microbial retention study may result in a non-sterile product. Include the sterile filtration [redacted] as a critical process parameter and provide the respective acceptance criteria in section 3.2.P.3.4.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations

and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. 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

PROPRIETARY NAME

Please refer to correspondence dated, March 21, 2018, which addresses the proposed proprietary name, (b) (4) This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.
   - Present tabulations of the new safety data combined with the original BLA data.
   - Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

6. Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

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

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. We do not agree that the information provided on February 13, 2018, is adequate in response to the Agency's IR on February 7, 2018 (IR #2) for the classification of (b) (4) s non-key control parameters. Upgrade these process parameters to key-controlled parameters (KCPs). In addition, the (b) (4) is not supported by appropriate data. Tighten the upper end of the range to (b) (based on data provided in the viral clearance studies. Update Section 3.2.S.2.2 or Section 3.2.S.2.4 as appropriate.

2. The response received on February 6, 2018, to the Agency's information request on January 29, 2018 (IR #1 and #2) regarding the revision of acceptance criteria for release and stability was not adequate. The following acceptance criteria should be revised (see also comment 1b under "Product Quality") based on information provided in the resubmission and in the IR response on February 6, 2018, and Sections 3.2.S.5.1 and 3.2.P.5.1 updated accordingly:

    a. The upper end of the acceptance criteria for the TNF-α binding assay should be lowered for DS and DP at release and stability.

    b. The upper end of the acceptance criteria for the TNF-α neutralization assay should be lowered for DS and DP at release and stability.

    c. The acceptance criteria for HIC peak 2 and peak 3 should be tightened further for DS and DP at release and stability.

    d. DP stability acceptance criterion for HMWS by SEC method should be tightened further.

e. DP stability acceptance criteria for purity by reduced CE-SDS method and HSI should be tightened further.

3. The description of the Total Sialic Acid method did not include the procedure for qualifying new N-acetylneuraminic acid (NANA) and N-glycolylneuraminic acid (NGNA) standard stock solutions. Provide information in the method description on how new stock solutions of NANA and NGNA will be qualified before use to ensure method consistency.

4. As discussed in your response dated February 13, 2018, to the Agency's IR on February 7, 2018, (IR #5a and #5b), include the use of an in-house reference standard for the HIC method system suitability in the resubmission. In addition, include a clear definition of what constitutes as test sample data comparable to reference standard (with respect to number of peaks, rank order of peak area, relative retention time, etc.) for all chromatography methods in the resubmission.

5. The method co-validation reports for the TNF-α binding and TNF-α neutralization assays did not include the data from the intermediate precision assessment performed at (b) (4) Provide this information in the resubmission.

6. The leachables evaluation of the intended pre-filled syringe only included data for up to 12 months at long-term storage conditions. Provide updated data for the evaluation of leachable material and commit to providing updated data up to the proposed expiry date of (b) (4) months under long-term storage conditions in annual reports.

7. Provide data to support the limit for light exposure time (b) (4) during labeling, assembly of plunger rod and backstop, and finished product packaging operations at (b) (4) for drug product manufacturing.

8. (b) (4) validation study (TR-MS-006703) was performed to demonstrate that the (b) (4) used during SB4 upstream manufacturing does not affect cell growth rate or viability; however, this study was performed to support Process A. Because of differences in the media composition between Process A and Process B, the data from this study cannot be leveraged to support the (b) (4) of Process B. Provide data from Process B validation studies that show the maximum allowable (b) (4) does not impact cell growth and viability.

9. (b) (4) compatibility studies were provided for up to 12 months of storage in the final drug product presentation under long-term storage conditions. Provide all available product quality data to support the compatibility of the SB4 drug product with expected levels of (b) (4) in the intended pre-filled syringe at long-term conditions up to the proposed expiry period of (b) (4) months in the resubmission.

10. Specify that the post-approval stability protocol and commitment for the drug product (Section 3.2.P.8.2) will include one batch of the 50 mg and 25 mg from (b) (4) as well as one 50 mg batch from (b) (4) will be placed on annual stability.

11. Clarify if (b) (4) performs stability testing of the drug product and update Section 3.2.P.3.1, if applicable.

12. The preliminary action limit of total number of rejected units for filling at (b) (4) is not acceptable. Lower the preliminary action limit of the total number of rejected units for filling at (b) (4) and update section 3.2.P.3.4 accordingly.

13. Include break loose force and glide force into the lot release specifications.

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 in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. 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 draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants," November 2015 at https://www.fda.gov/downloads/drugs/guidances/ucm345649.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, call Brandi Wheeler, Regulatory Project Manager, at (301) 796-4495.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

LYDIA I GILBERT MCCLAIN
03/23/2018
Acting Division Director