CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761084Orig1s000

OTHER ACTION LETTERS

BLA 761084

COMPLETE RESPONSE

Kashiv BioSciences, LLC
Attention: John Pakulski
Senior VP, Global Regulatory Affairs
20 New England Avenue
Piscataway, NJ 08854

Dear Mr. Pakulski:

Please refer to your biologics license application (BLA) dated and received August 11, 2020, submitted under section 351(k) of the Public Health Service Act for TPI-120.

We have completed our review of this application 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.

MICROBIOLOGY

1. Information regarding media fill studies is inadequate. Please update Section 3.2.P.3.5 of the BLA with the following:

    a. Summarized results (media fill date, container closure, filled volume, duration, number of units filled/incubated/rejected, positive) from the three initial media fill validation runs and the latest requalification run that was performed to validate the syringe line filling process relevant to the drug product.

    b. Description of the hold periods (date, temperature, duration) simulated in each media fill run.

    c. Description of confirmatory growth promotion test. Include a list of microorganisms used in the test.

2. The bacterial retention study for the sterilizing-grade filter was performed using the drug substance, which is not adequate. Please update BLA section 3.2.P.3.5 with the following:

    a. Protocol and data from the validation studies using three different lots of the sterilizing filter intended for commercial production using the final drug product solution.

b. Study/report # and the date of the study.

c. Comparison of validation test parameters with those used during routine operation (i.e., temperature, filtration time, filtration pressure, flow volume, and flow rate, etc.)

d. Description of the challenge microorganism, membrane lot numbers, pore size rating, pre- and post-filtration bubble point, challenge (CFU/cm2).

e. Demonstration of viability of the challenge organism in the presence of drug product.

PRODUCT QUALITY

3. Insufficient information and data were provided in the submission, including in the response to the Agency's information request (sent on May 24, 2021, received on June 3, 2021, seq. 0025), to support that the filling line operations for the manufacture of the drug product on the (b) (4) are appropriately controlled and can result in a product with consistent protein concentration.

   a. Limited process validation data were provided for the downstream drug product filling operations (Section 3.2.P.3.5, Report CMO-0174). (b) (4) Provide individual data points from additional process validation runs by analyzing multiple individual syringes at the beginning, middle, and end of fill to support the homogeneity of the filling operation to ensure the label claim is met for all syringes filled.

   b. The fill step includes (b) (4)

(b) (4) Provide data and information to support that the control strategy allows for the consistent and accurate fill volume for the drug product. In your response, provide data to support that drug product lots that were filled at the lowest allowed volume will ensure the appropriate extractable volume for all syringes.

4. Your control strategy (b) (4) is deficient with regard to sequence variants. (b) (4) Develop an appropriate control strategy (b) (4) to ensure that all sequence variants in TPI-120 are adequately controlled at levels that do not exceed clinical experience using appropriate methods that are validated for their intended purpose. As part of your response, provide a robust characterization of peaks detected by RP-HPLC and CEX-HPLC for the presence of sequence variants to assist in determining your control strategy. Provide information and data to show a clear understanding of the source of each sequence variant (b) (4) and the potential impact on potency.

5. Inadequate stability protocols were provided to support the requalification of Primary Reference Standards (PRS) and Working Reference Standards (WRS) that are used for testing against intermediate product, drug substance, and drug product samples. The deficiencies observed in the protocols are described below:

(b) (4)

(b) (4)

Because of the above issues, we do not agree that the aforementioned stability protocols are adequate to requalify PRS and WRS that are intended to be used to test against intermediate product, drug substance, and drug product samples. To address the above issues, provide adequate trending analysis strategies for the EC50 values of the reference standards, and when applicable, provide quantitative, appropriately justified, acceptance criteria to control for (b) (4)

6. Insufficient data were provided to support the qualification of the WRS lot (b) (4)

Data provided in the qualification report (PTL-2306-R) shows out of specification results or results that are not comparable, such as the following:

(b) (4)

Because of the above issues, we do not agree that the current in-house WRS (b) (4) has been qualified appropriately. To address the above issues, provide an updated qualification report for an adequately qualified in-house WRS.

7. Inadequate information was provided to support recent changes made to the cell-based potency assays (b) (4) In response to an information request (received on 01/08/2021, Seq. 0010), you provided additional information stating that the potency assays have been revised according to change control procedures (CC-20-036 and CC- 20-045). However, inadequate information to support the proposed changes to the potency assays was provided. To ensure that the proposed changes have no

impact on the potency assay method validation and test article data, provide adequate information to support the proposed changes.

8. Inadequate method validation data were provided to support the intended use of the CEX-HPLC method (STM-0282) (b) (4) The method validation exercise did not include adequate samples to allow for the validation of the method (b) (4) Provide additional method validation data to clearly demonstrate that the CEX-HPLC method is precise, accurate, linear, and robust (b) (4)

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

9. You provided a design verification (DV) plan (DCP-0037), DV protocol (PRL-1712), and T=0, 6, 24, and 36 month reports, as well as a (b) (4) safety device verification summary (DCP-0025) which were assessed for adequacy of testing to support verification of the device and the proposed shelf life. However, you did not provide adequate data for needle safety performance to support verification of the design and the proposed shelf life for the following reasons:

   a. In the Prefilled Syringe Design Verification Protocol, PTL-1712, Section 6.6 details the deliverable volume and automatic safety device activation. 30 samples were tested for deliverable volume and activation force sequentially and another 30 samples were solely tested for activation force. However, automatic safety device activation was conducted for an attribute method and as such quantitative data was not measured to verify that the activation forces met specifications. As such, the acceptance criteria for activation force testing as detailed in section 6.6 is inadequate.

Section 6.9 details how you will test safety device activation force using a variable method. However, in Section 6.9.2.2-6.9.2.3 of the protocol, it is stated to "[redacted (b) (4)] which is not a representative method of forces that would be required to activate the needle guard. As such, the method for testing activation force as detailed in section 6.9 is inadequate.

b. You reference DCP-0023, attachment 1 to demonstrate that needle safety activation force meets a 95% confidence level/99% reliability criteria. While your firm's vendor, [redacted (b) (4)] appears to have tested activation force to demonstrate a confidence and reliability of 95/99%, the testing does not appear to have been conducted with the to-be-marketed configuration of TPI-120 containing the TPI-120 drug solution. Since the activation force may be impacted by the pre-filled syringe glide force, this testing must be conducted on the final finished combination product. Additionally, AQL testing represents T=0 and does not assess performance of aged product. As such, you have not provided sufficient data to support a confidence and reliability of 95/99% for needle safety activation force to support verification of the design and the proposed shelf life.

c. You reference [redacted (b) (4)] testing to demonstrate control of needle safety override force over shelf life. However, while [redacted (b) (4)] conducted testing on the needle safety feature, which includes compression force testing, the testing appears to only be conducted for T=0. Additionally, while [redacted (b) (4)] performs AQL testing before releasing each lot which Kashiv performs verification of Certificate of Conformance, lot release testing also represents only T=0 timepoint. Thus, you have not provided adequate data to support needle safety override performance over the proposed shelf life.

Per FDA's Guidance for Industry and FDA Staff "Medical Devices with Sharp Injury Prevention Features" bench testing should be conducted to assess the force to activate and deactivate the safety feature (i.e., activation force and override force). As such, the following data is required to support design verification and the proposed shelf life of TPI-120:

a. Provide design verification and shelf-life testing to demonstrate needle safety activation force performance meeting specification. Please ensure forces are evaluated after sequential shelf-life, shipping, and drop/freefall, with final finished combination product, utilizing a variable method that is representative of forces that a user would experience to activate the needle guard (i.e., measured after depressing the drug product out of the syringe), meeting a confidence and reliability of 95/99%.

b. Provide test data for needle safety override force over shelf life.

PRESCRIBING INFORMATION

10. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] 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. In addition, we encourage you to review the FDA guidance for industry *Labeling for Biosimilar Products*.

    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 FDA.gov.[3]

CARTON AND CONTAINER LABELING

11. We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

12. Please refer to correspondence dated, December 28, 2020, 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.

FACILITY INSPECTIONS

13. Following an evaluation of an inspection performed at Kashiv BioSciences (FEI 3011289655) manufacturing facility at Chicago, IL, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the remaining objectionable conditions, and verification by FDA, is required before this application may be approved. We recommend you contact your manufacturing facility if more information is needed.

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[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

We will continue to monitor the public health situation as well as travel restrictions. Please see the FDA's "Resiliency Roadmap for FDA Inspectional Oversight" for more information on FDA's plan to resume inspections (https://www.fda.gov/media/148197/download). Please also see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid- 19/covid-19-relatedguidance-documents-industry-fda-staff-and-other-stakeholders

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:

Manufacture and Control

(b) (4)

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Stability

19. Stability data was not provided for volume of injection testing to support the proposed shelf-life of 24 months for the drug product. Submit stability data under long-term storage conditions for volume of injection to support the proposed 24-month shelf life for the drug product.

20. In-use stability studies were performed to support the proposed in-use conditions for the drug product (Report PTL-2260-R). A single freeze-thaw cycle was evaluated for one drug product lot, and post-thaw product quality data was provided for the selected lot. Clarify the product quality data generated from the pre-thaw that was used to inform whether product quality was impacted by the thaw process. Furthermore, the label does not specify the number of freeze-thaw cycles allowed for non-diluted drug product, which could potentially allow for multiple re-uses. Provide additional in-use stability data to support multiple freeze-thaw cycles or limit the number of freeze-thaw cycles in the label to the number that is supported by data.

Shipping Validation

21. Real-time shipping validation studies are proposed to be performed for the drug substance (Report PTL-2376, Section 3.2.S.2.5) and drug product (Report PTL-2374, Section 3.2.P.3.5) according to the provided protocols. The acceptance criteria for product quality testing are proposed to be per release testing specification effective at the time of protocol execution. This is insufficient and additional criteria should be implemented to assess whether the change in product quality during shipment is acceptable. In addition, the protocols should also clearly list all attributes that will be tested and provide sufficient justification if any of the attributes that are routinely assessed on stability are not performed. Update the protocols for the real-time shipping studies for drug substance and drug product to include all product quality attributes that will be assessed pre- and post- shipment and include sufficiently narrow acceptance criteria for appropriate attributes that indicate the allowed change in product quality from

before and after shipment. The pre-shipment result should be obtained prior to shipment, not at release.

22. Section 3.2.S.2.2 states that drug substance is stored at [(b) (4)]°C and shipped under a controlled temperature condition of [(b) (4)]°C in a qualified shipper container, which is described as capable of maintaining a temperature [(b) (4)] (Report PTL- 2376). Based on the information provided, the drug substance may potentially be exposed to temperatures as high as [(b) (4)]°C during shipping. We recommend that the drug substance real-time shipping study be performed with drug substance stored at [(b) (4)]°C and shipped at [(b) (4)]°C in order to support that product quality of drug substance is not impacted by the higher temperature that may occur during shipping conditions. If the study does not consider the highest temperature the drug substance may be exposed to during commercial shipping, then shipping of the drug substance may be restricted to -[(b) (4)]°C. As part of this study, you should report the temperature data for the qualified drug substance shipper for the duration of the shipping study. With respect to the evaluation of product quality, implement appropriate and justified acceptance criteria (e.g., sufficiently narrow range or limits for allowable change for quantitative attributes) to demonstrate commercial shipping does not impact product quality. The evaluation of pre- and post-shipment samples should be performed by methods that are suitable for their intended purpose.

Filter Validation

23. The results generated from the filter validation studies performed to support the [(b) (4)] filters were briefly summarized with insufficient details. Address the following comments:

[(b) (4)]

(b) (4)

Immunogenicity

24. You have committed to provide updated immunogenicity data based on the analysis of additional clinical samples that tested positive using the re-calculated immunogenicity assay cut-points (Seq. 0018, May 15, 2021 and Seq. 0033 July 2, 2021). Provide data from this assessment upon re-submission of your application.

Microbiology

(b) (4)

30. Update BLA Section P.5.6 with the justification of the endotoxin specification.

31. The stability protocol includes container closure integrity testing (CCIT) only at the 12-month time-point. Revise the stability protocol to include CCIT for stability samples every 12 months until expiry. Please update the BLA accordingly.

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 guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

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

BsUFA II APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs under BsUFA II ('the Program'). The BsUFA II Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a BsUFA II applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call May Zuwannin, Regulatory Project Manager, at 301-796-7775.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Deputy Division Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

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/s/

ALBERT B DEISSEROTH
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