



Our STN: BL 125807/0

COMPLETE RESPONSE

April 16, 2024

Abeona Therapeutics, Inc.
Attention: Carl Denny
Vice President, Regulatory Affairs
6555 Carnegie Ave, 4th Floor
Cleveland, OH 44103

Dear Carl Denny:

Please refer to your Biologics License Application (BLA) received September 25, 2023, for prademagene zamikeracel manufactured at your Cleveland, OH location and submitted under section 351(a) of the Public Health Service Act.

We have completed our review of all the submissions you have made relating to this BLA, with the exception of the information in amendments 51 and 52, received April 15, 2024, as noted below. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

1. You did not demonstrate adequate suitability of the microbiological test methods listed below for your final drug product, prademagene zamikeracel (PZ).

- a. Sterility Test Method: You proposed to conduct (b) (4) rapid sterility testing (b) (4) on final drug product (DP) samples using the (b) (4). However, data to demonstrate the suitability of these (b) (4) sterility methods were not provided. Without adequate validation of the sterility methods, the sterility of your PZ DP is not assured. To demonstrate that each method can reproducibly detect appropriate levels of microbial contamination, you should provide a report that includes the (b) (4) as well as acceptance criteria (AC) with justification, for at least (b) (4) DP lots. The impact of any deviations that occurred during testing should be described in the report. In addition, method validation should be performed in accordance with (b) (4). To demonstrate your rapid sterility test methods provide assurance of effectiveness equal to or greater than the assurances provided by the (b) (4) sterility test

method under the actual condition of use, you should provide data from comparability studies.

- b. Mycoplasma Test Method: The data you provided does not demonstrate the suitability of your mycoplasma test method because assay specificity and equivalency to (b) (4) methods were not adequately demonstrated. To complete demonstration of assay specificity, you should conduct a specificity study for the (b) (4) method using your (b) (4) (b) (4). To demonstrate comparability/equivalency of the (b) (4) and the proposed (b) (4) (b) (4) system, data from a comparability study must be provided to assure that the sensitivity of the (b) (4) method is equal to or greater than the (b) (4) method (b) (4) under the actual condition of use.
- c. Bacterial Endotoxin Test: The test sample dilution (b) (4) you proposed for determining endotoxin concentration is not acceptable because it is at the limit of the test, i.e., the (b) (4). Testing at the (b) (4) may detect endotoxin in the sample at the specification limit; however, testing at the (b) (4) should only be performed if dilutions (b) (4) (b) (4) do not provide valid test results. To identify the appropriate sample dilution to use in the endotoxin test, you need to provide data from a test for interfering factors that show positive product control recoveries for a series of test dilutions (b) (4). As per (b) (4) the dilution equation must include the media volume. You should use this information to identify the dilution that provides optimal recovery and use as the sample dilution in release assays.
- d. Supporting (b) (4) Studies: You did not provide adequate evidence of endotoxin or microorganism recovery in media that has been in (b) (4) with DP after assembly of the P1 packaging (i.e., clamshell inside (b) (4) bag). Data should be provided for (b) (4) studies for all assays that will utilize this media as a test sample, including endotoxin, (b) (4), and all sterility tests. The (b) (4) tests should be designed to demonstrate that the proposed (b) (4) time allows for adequate detection and recovery of appropriate levels of contaminants in the DP and use an (b) (4) volume that is appropriate for the intended test method. The (b) (4) studies for bacterial endotoxin must comply with (b) (4) for bacterial endotoxin (b) (4) volume and (b) (4) process. A full test report including a description of the test methods, acceptance criteria (AC) with justification, and sensitivity of the evaluated assays with the media samples, is needed to demonstrate your endotoxin, (b) (4) and rapid sterility testing methods are appropriate

for their intended use.

(b) (4)

4. You proposed to conduct additional identity testing on your final DP as part of lot release testing to assess and confirm the cell populations in your DP. You propose to utilize a (b) (4) (b) (4) to “detect the presence of keratinocytes” in your product. However, you did not provide an adequate method description, protocol, or validation report for your proposed identity assay. In order to ensure the identity and purity of your final DP, a validated identity assay is necessary. Please submit a method validation report demonstrating that your proposed method can adequately detect and identify the cell populations present in your DP. The report should include the AC, with justification, description of the test method, including test sample and sample size, discussion of results, and deviations, if any.

5. As part of the final product lot release testing, you conduct (b) (4) visual inspection on the DP. You indicate that these (b) (4) methods are qualified and operators are adequately trained to conduct these visual tests. However, you did not provide adequate validation reports for these methods to demonstrate that these assays can be consistently and accurately performed. Specifically, we identified the following issues in the method validation reports provided in Amendment 45, received on March 28, 2024:
- (b) (4) identified a contaminant (hemoclip) in the DP during visual inspection that the other (b) (4) operators missed during the (b) (4) validation run. The discrepancy described resulted in out-of-specification results of the visual inspection.
 - (b) (4) that identified the contaminant (hemoclip) did not perform (b) (4), as the (b) (4) tests were performed concurrently. This resulted in (b) (4) the visual inspection validations to be conducted on only (b) (4) DP validation runs.
 - A discrepancy was described where all operators missed a tear in the cell sheet during visual inspection.

To address these issues, you indicated that you intend to make additional protocol changes for the visual inspection validation protocol, after which you plan to manufacture (b) (4) to complete the (b) (4) validation run that did not pass specifications. However, with a revised visual inspection protocol, (b) (4) is inadequate to sufficiently validate (b) (4) visual testing methods. Therefore, please utilize at (b) (4) DP lots to validate the final validation protocols for the (b) (4) visual inspection test. Please provide validation reports including the AC, with justification, description of the test methods, including test sample and sample size, discussion of results, and deviations, if any. Please also provide a justification for the changes implemented in the protocols.

6. You manufacture several media and reagents at your manufacturing facility which are used in the aseptic manufacturing of PZ DP. (b) (4) of the reagents, (b) (4)
- However, as this proposed change was made after completion of your process performance qualification (PPQ), you did not provide adequate data to support the change in reagent. Therefore, in order to replace the (b) (4) reagent with a (b) (4) alternative, please submit data to demonstrate that the reagent change does not impact the final DP.

7. You describe your control of materials in Section 3.2.S.2.3, indicating that as part of your raw material qualification program, all incoming reagents are, (b) (4). Additionally, you perform material qualification and requalification testing of the incoming materials to ensure that they meet the QC requirements. Regarding these activities, we have the following comments:

- a. You state that (b) (4) testing is conducted on all incoming materials. However, you did not provide a list of these (b) (4) tests and did not provide information to demonstrate the testing is performed using appropriately qualified or validated assays. In order to assess the (b) (4) (b) (4) of your reagents, you should utilize (b) (4) tests which are appropriately qualified or validated to (b) (4) of all incoming materials. Please provide a list of all (b) (4) assays performed as part of your raw material qualification program, including a description of the assay/method, as well as the validation method protocols and reports. If using (b) (4) methods, then providing qualification protocols and reports would be sufficient.
 - b. In Table 2 of Section 3.2.S.2.3, you state that certain testing is conducted on incoming materials as part of the material qualification requirements, including minimum incoming QC tests and (b) (4) re-qualification testing performed (b) (4) lot to verify the reagent's certificate of analysis (CoA). However, you did not specify the methods or assays used to perform these qualifications/re-qualifications. Per 21 CFR 211.82(d)(2), you should establish "the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals." Therefore, you should provide additional details regarding your raw material qualification program, including the methods or assays used to perform these qualifications/re-qualifications, and how you are validating the reagents' CoA at appropriate intervals.
8. Your corrections to FDA's inspectional observations issued to you at the conclusion of the inspection conducted between February 19 and March 1, 2024, of your Cleveland, OH facility are still ongoing.
9. (b) (4)
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1 page has been determined to be not releasable: (b)(4)

(b) (4)

12. To support the container closure integrity of the PZ drug product, you performed a (b) (4) test per (b) (4)

[Redacted]

The integrity of the container closure should be demonstrated to ensure sterility is maintained and to prevent contamination of the drug product (21 CFR 211.94b Drug Product Containers and Closures). The studies provided do not satisfy the requirement of ensuring the final drug product packaging is integral.

We requested additional CCIT studies through an information request (IR) on March 11, 2024. In your response to the IR submitted on March 27, 2024, you

indicated that this study will be performed. However, the studies could not be provided in sufficient time to review prior to the action due date.

Please provide a CCIT study for the PZ DP primary containers per (b) (4) (b) (4) and include details of the test method performed with an established sensitivity of the method (b) (4) (b) (4)

ADDITIONAL COMMENTS

In addition to the deficiencies that were the basis for not granting approval, we have identified the following comments:

LABELING

13. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

14. In your BLA submission, you provided stability data in support of a proposed shelf-life of 84 hours for the PZ DP. However, the data you provided is insufficient to support your proposed shelf-life. Specifically, you did not provide adequate data to demonstrate robust viability and sheet integrity in a sufficient number of samples. For example, you indicated that cell viability results were not available for (b) (4) out of (b) (4) tested DP lots at the 60 hour timepoint due to equipment failure. In addition, the AC you proposed for (b) (4) is that (b) (4). However, at some timepoints you tested (b) (4) per (b) (4). Thus, the (b) (4) acceptance criterion is not adequate because you did not demonstrate you have enough product (b) (4) to treat a patient from a (b) (4) at all timepoints. Therefore, to demonstrate the stability of your product, we recommend the AC for the (b) (4) be revised to show that at (b) (4) per (b) (4) at any given timepoint remain intact. Please also refer to comment 5 above related to the validation of (b) (4).
15. In response to information requests (IRs) during the review cycle, you proposed modified AC for (b) (4) lot release testing. Please note that AC for (b) (4) lot release testing will be finalized upon review of your complete response. We reserve comment on your proposed AC until the application is otherwise acceptable.
16. In response to IRs during the review cycle, you changed criticality designations for several process parameters in (b) (4) manufacturing. Please note that criticality designations for in-process parameters and AC for in-process

testing of your (b) (4) will be finalized upon review of your complete response.

17. In section 3.2.S.7 of your BLA submission, you propose a shelf-life of (b) (4) for your LZRSE-Col7A1 RVV. Your proposed LZRSE-Col7A1 RVV shelf-life is still under review, pending FDA receipt of additional stability data. In your resubmission, please include any stability data collected prior to the resubmission date, including but not limited to the following:
 - a. Data collected from (b) (4) stability studies you proposed in amendment 33 received on March 1, 2024, which was expected to be submitted to the FDA by June 30, 2024.
 - b. Any additional long-term stability data collected according to your stability protocols STA-DS-000001 and STA-DS-000003.
18. In amendment 21 received on January 22, 2024, you noted that a report of (b) (4) testing of your (b) (4) (b) (4) for (b) (4) would be submitted to the FDA by April 30, 2024. Please include this report in your resubmission.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (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 with us to discuss the steps necessary for approval.

Please submit your meeting request as described in the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf>, and CBER's SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>.

We acknowledge receipt of your amendments 51 and 52, dated April 15, 2024. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of amendments 51 and 52, dated April 15, 2024, in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Hawa Camara, at 240-402-8097 or by email at Hawa.Camara@fda.hhs.gov.

Sincerely,

Lola Fashoyin-Aje, MD, MPH
Director
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics Evaluation and Research