**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| CBER/OCBQ/Division of Manufacturing and Product Quality<br>10903 New Hampshire Avenue, Silver Spring, MD 20993<br>Lead Insp.: Ou Olivia Ma<br>Telephone: 301-796-8213<br>Industry Information: www.fda.gov/oc/industry | February 19 - March 1, 2024 |
| | FEI NUMBER<br>3008334517 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Brian M. Kevany, Senior Vice President, Chief Technical Officer & Chief Scientific Officer

| FIRM NAME | STREET ADDRESS |
|---|---|
| Abeona Therapeutics Inc | 6555 Carnegie Ave, 4th Floor |
| CITY, STATE AND ZIP CODE | TYPE OF ESTABLISHMENT INSPECTED |
| Cleveland, OH 44103 | Cell and Gene Therapy |

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. The aseptic manufacturing process lacks sufficient controls to ensure sterility of the prademagene zamikeracel final product, specifically:
a. The [redacted] used in the preparation of media and other components that are used in the aseptic process have not been validated (including not having an established [redacted] bioburden limit) nor are the [redacted] tested for integrity after use. Therefore, the sterility of these media and components have not been verified.
b. The [redacted] for the LZRSE-Col7A1 retroviral vector (RVV) has not been validated (including not having an established [redacted] bioburden limit).
c. The final DP sterility sample for lot release collected from the final [redacted] does not capture the risk of the final product manipulations, including [redacted].
d. The [redacted] step involving the [redacted] of the final assembled cell sheet (placed in a [redacted] culture dish which is [redacted]) between two [redacted] located in [redacted] rooms [redacted] by an ISO [redacted] and ISO [redacted] gowning rooms (representing the worst-case [redacted] in the process) is not included in the aseptic process simulation to assess the impact of this [redacted] on maintaining aseptic conditions of the drug product.

2. Media and reagents (e.g., [redacted] are not adequately controlled for quality prior to being used in the aseptic manufacturing process.
a. Media and reagents [redacted] are not tested for sterility, endotoxin, and identity. Therefore, the safety of these media and reagents has not been determined prior to being in direct contact with the drug substance (DS) and drug product (DP).
b. Studies have not been conducted to support the expiry of the media and reagents [redacted] to ensure adequate performance.

3. The inefficient management of deviations by Quality Assurance resulted in delayed investigations for which risk assessments were inadequate and adversely impacted final decisions and actions. Specifically:
a. Numerous deviations were not addressed in a timely manner ([redacted] deviations [redacted] to be opened, [redacted]

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|---|---|---|
| | Ou Olivia Ma, Consumer Safety Officer; Christine Harman, Lead Consumer Safety Officer; Alyssa Kitchel, Supervisory Biologist; Bao-Ngoc Nguyen, Staff Fellow; Joshua Kufera, Staff Fellow | 03/01/2024 |

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deviations [redacted] to be closed), creating a backlog of deviations which negatively impacted quality control of the RVV and DP.

b. Delays in deviation management resulted in repeated testing failures. Out-of-specification (OOS) results should have been retested per SOP-000061 for several assays described in DEV-00538 ([redacted] to open, [redacted] to close), affecting multiple stability timepoints thus compromising assessment of the proposed RVV shelf-life. Unidentified gaps in [redacted]-000035 were not promptly addressed as observed in DEV-00530 ([redacted] to open, [redacted] to close), leading to errors in [redacted] PPQ runs and two subsequent stability timepoints.

c. Corrective actions and preventative actions (CAPA) were initiated for deviation DEV-00188, a major deviation with multiple identified root causes. A CAPA should have been initiated and/or justification provided as per SOP-000046, "Quality Events" to prevent recurrence.

d. Classification of deviations (minor, major, or critical) are not always based on appropriate risk of the incidences, and therefore, might not be investigated sufficiently. Many of the environmental monitoring excursions occurring during aseptic operations involving action levels for personnel monitoring and monitoring inside the [redacted] were classified as minor but this classification does not adequately reflect the risk of the event.

e. Several product lots, despite OOS results, were released based on inadequate risk assessments. In DEV-00241 ([redacted]-101 lot [redacted]), a DP sheet was observed to have [redacted] due to reagent contamination, yet it was released for administration. In DEV-00258, three DP lots ([redacted]-101 Lots [redacted]) had inconclusive results for the presence of replication-competent retrovirus (RCR) but were considered low risk and were released for clinical use.

f. During an investigation, the suspected root cause was not verified by confirmatory testing, as observed in DEV-00243. Specifically, [redacted] suspected [redacted] RCR results were not confirmed by a [redacted]-based RCR assay.

4. Retesting procedures (per SOP-000061 - Investigating Invalid and Out of Specification (OOS), version 3.0) for lot release testing do not provide clear procedures to determine retesting criteria for DS and DP. Specifically, retesting plans do not specify the number of retests allowed and analytical samples may be retested without adequate justification or identification of root cause. For example,

a. As observed in DEV-00258, [redacted] DP lots were retested multiple times for the presence of RCR due to repeated system suitability failures. No root cause was identified for these system suitability failures. All [redacted] DP product lots were released for clinical use, even though for [redacted] DP lot, a [redacted] sample was [redacted] for RCR in one of the retests.

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b. As observed in DEV-00243, - DP lot was retested after the RCR test result was OOS with no system suitability failures. The DP sample was retested without identification of a root cause. The retest result was also OOS. Thus, the lot was rejected and no product from the lot was administered.

5. Disinfectant efficacy studies performed to support the disinfectants used in the facility and during the manufacturing processes are deficient. Specifically,

a. (b)(4) which is used as the primary disinfectant (including for use to disinfect materials in the (b)(4)) has not been qualified as this disinfectant was not included in the disinfectant efficacy studies which were performed in -.

b. Facility isolates were not evaluated in the - (and only) disinfectant efficacy studies performed in -.

c. The efficacy of disinfectants used in the facility do not undergo a periodic review based on environmental monitoring trending to determine if a re-evaluation study is needed.

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."