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 10903 New Hampshire Avenue Silver Spring, MD 20993 Lead Inspector: Massoud Motamed TEL: 301-796-0742 Industry Information: www.fda.gov/oc/industry	04/21/2025-04/25/2025 FEI NUMBER 3025268614

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
Thomas H. Lauzon, SVP, Gene Therapy Manufacturing

TO: FIRM NAME	STREET ADDRESS
Ultragenyx Pharmaceutical Inc.	170 Middlesex Turnpike
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Bedford, MA 01730 USA	Drug product Manufacturer

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 WE OBSERVED:

OBSERVATION 1

The integrity of data via controlled documentation is deficient. For example,

a. (b) (4) of the (b) (4) (Room (b) (4) contained the following controlled, good manufacturing practice (GMP), and batch record documents intended for destruction. For example,
   i. A partially completed, unofficial (b) (4) batch record, document Drug Product (b) (4) Aseptic Process (b) (4) This batch record represents an unauthorized (b) (4)
   ii. Multiple completed or partially completed (b) (4) documents.
   iii. Completed training documentation.
   iv. A visual inspection (b) (4)

b. The following practices that are inconsistent with Good Documentation Practices were observed:
   i. Your firm uses (b) (4) to instruct manufacturing personnel to review/ revise records. On April 23, 2025, (b) (4) encompassing (b) (4) comments were observed in the trash can to (b) (4) (Room (b) (4)
   ii. Your firm uses an uncontrolled logbook titled "DP Process Batch Record Tracking (non-GMP)" in Room (b) (4) to provide batch record accountability. This uncontrolled logbook is not updated accurately, as you could not locate three batch records that were marked "Needs Review" on April 21, 2025. The batch records were later discovered in (b) (4) Room and provided to inspectors on April 22, 2025.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	/s/	Massoud Motamed, CSO, Lead Inspector Kula N. Jha, Biological Reviewer Jacob L. Bitterman, Biological Reviewer Timothy Kamaldinov, Biological Reviewer	04/25/2025

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OBSERVATION 2

Documentation and/or maintenance of buildings and facilities used in the manufacture of viral vector drug products are not maintained in a good state of repair. For example,

a. On April 21, 2025, it was observed that a portion of the (b) (4) flooring of the (b) (4) to drug product manufacturing area was (b) (4) and thus exhibited (b) (4) from the remainder of the (b) (4) flooring due to (b) (4) the building. However, your firm failed to open a deviation to document the (b) (4) prior to rectification or evaluate the potential implications of (b) (4) environment of the classified areas. Moreover, general work requests are not trended or evaluated to identify recurring issues.

b. On April 22, 2025, the (b) (4) (b) (4) (b) (4) General Work Request (b) (4) describes an initial leak and subsequent leak (December 17, 2024). However, your firm failed to open a deviation to document the extent of leakage or (b) (4) (b) (4) Moreover, General Work Requests are not trended or evaluated to identify recurring issues.

c. Biological Safety Cabinet BSC (b) (4) inside the (b) (4) room (room (b) (4) exhibited an incompletely assembled HEPA grill and debris. Production explained that the debris originated from the (b) (4) of the biological safety cabinet. Engineering elaborated that the (b) (4) (b) (4) of the biological safety cabinet is not cleanable. Engineering explained that the cleaners have been informed not to clean (b) (4) of the biological safety cabinet despite procedure VV-15616 titled "Cleaning and Sanitization of (b) (4) detailing that cleaning should encompass (b) (4) (b) (4)

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d. On April 22, 2025, an accumulation of water was observed to have seeped through the (b) (4) (b) (4) Upon an evaluation of the (b) (4) a gross accumulation of water was observed that appeared to have seeped through the (b) (4) (b) (4) in the area exhibited discoloration consistent with the prolonged presence of stagnant water, and therefore a potential source for microbial growth. These events have not been identified or documented according to your facility's procedures.

e. The (b) (4) flooring (b) (4) exhibited (b) (4) discoloration and what appeared to be desiccation.

OBSERVATION 3

Deviation management is inadequate to demonstrate quality oversight of the manufacturing process and does not adequately identify, document, or investigate the impact to the product quality. For example,

a. Investigations to identify the root cause of contamination events are inadequate. (b) (4) (b) (4) has repeatedly experienced excursions, including recurrent identification of mold. (b) (4) Specifically, excursions QE-005180, QE-005539, QE-004296, QE-003877, QE-003592, and QE-003487 (b) (4) (b) (4) (b) (4) You have failed to implement an effective resolution to preclude (b) (4) (b) (4) as a root cause and concluded that all excursions had no impact on (b) (4)

b. Your Deviation and CAPA Management SOP (procedure VV-002189) does not describe the procedure to escalate repeated minor deviations into a major deviation category. For example, deviation QE-005811 was the third instance of a deviation related to a desiccated (b) (4) (b) (4) for environmental monitoring (also QE-005675 and QE-005811). All three deviations were classified as minor despite the identified deviation trend. In addition, you identified a similar protocol deviation for desiccated (b) (4) in (b) (4) issue report (VV-209494) which was not reported as a deviation in your deviation management system.

c. You fail to identify an adequate root cause for repeated deviations. For example, deviations QE-004714, QE-005536, and QE-006173 are related to mislabeling of quality control samples for (b) (4) testing. The second deviation, QE-005536, was identified as a repeated, minor deviation, and its root cause was determined to be "inattention to detail," despite an inadequate system to prevent mislabeling. In the separate deviation QE-005677, the employee missed the (b) (4) review of 16 logbooks, which requires review within (b) (4) of (b) (4) The root cause was again determined to be "inattention to detail" as opposed to a lack of a system and/or clearly defined dates in the SOP. This deviation is part of a total of five similar deviations. For deviations QE-005536 and QE-005677, no corrective and preventive actions were implemented.

d. Deviation events are inadequately classified. For example,
   i. In deviation QE-004196, you (b) (4) (b) (4) with an unapproved/non-qualified instrument due to failure to (b) (4) (b) (4) . Despite the use of a non-qualified instrument during the aseptic manufacturing process, you classified the deviation as minor.
   ii. In deviation QE-005302, you observed a leak in the (b) (4) during the (b) (4) (b) (4) process step. Despite the leak representing (b) (4) (b) (4) , you classified the deviation as minor.

OBSERVATION 4

Quality oversight is deficient to assure (b) (4) drug product has the identity, strength, quality, and purity it purports or is represented to possess. For example,

a. Aseptic process simulations are performed in Rooms (b) (4) manufactured, as part of training without quality's approval and oversight. No assessments were performed regarding the room's environment status following these unapproved aseptic process simulation trainings.

b. Quality oversight and integrity of electronic data captured in the environmental monitoring systems have not been established. For example, the following (b) (4) testing events were manually aborted and lacked supporting documentation:
   i. Test (b) (4) conducted on August 29, 2024.
   ii. Test conducted on August 30, 2024.
   iii. Test conducted on August 30, 2024.

   The aborted testing events were not documented in batch production records for the quality control unit's review. Further, from a review of 139 test reports from the (b) (4) 16 aborted testing events were noted, and no deviation was opened in response to aborted testing.

OBSERVATION 5

Areas designed to prevent contamination in a biological safety cabinet are deficient with regards to the characterization and mapping of the areas and operations for aseptic processing of drug products. Specifically, you failed to perform adequate smoke studies to determine acceptable airflow patterns within the biological safety cabinet (equipment BSC- (b) (4) used to aseptically formulate drug product. Airflow patterns were not easily distinguishable and could not be evaluated due to the inconsistent density of smoke and consistent reorientation of the smoke generator. Further, there appears to be (b) (4) of the smoke stream (b) (4) which is not supportive of unidirectional airflow. Moreover, due to the conduct of the smoke studies, it was observed that first pass air contacted a non-viable (b) (4) prior to critical operations. Nonetheless, document (b) (4) (b) (4) supporting the suitability of the smoke study was approved October 31, 2023.

OBSERVATION 6

Procedures designed to prevent microbiological contamination and cross-contamination of (b) (4) purporting to be (b) (4) are not established. Specifically,

a. Your firm stores a quality control cart utilized for environmental monitoring (EM) in Grade (b) (4) Room (b) (4) This cart is then brought into Grade (b) (4) Room (b) (4) to conduct EM during the

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aseptic processing (b) (4) No cleaning or disinfection of the cart is performed before and after use.

b. Grade (b) (4) Room (b) (4) used in the aseptic processing of (b) (4) is not maintained in a clean and sanitary condition. For example, operators place trash and waste matter such as used wipes and plastic bags into makeshift waste bags consisting of outer plastic wrap bags from the single-use articles (e.g., (b) (4) . Additionally, during EM, quality control personnel retain soiled gloves on the (b) (4) of the quality control cart.

***DATES OF INSPECTION**

04/21/2025 (Mon), 04/22/2025 (Tue), 04/23/2025 (Wed), 04/24/2025 (Thu), 04/25/2025 (Fri)

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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 judgment, 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."