

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125858/0

pariglasgene breCAParvovec, (DTX401); GENGLYCOS

Miriam Ngundi, Consumer Safety Officer, OCBQ/DMPQ/MRB1

1. BLA: STN 125858/0

2. APPLICANT NAME AND LICENSE NUMBER

Ultragenyx Pharmaceutical Inc.: License No: 2390

3. PRODUCT NAME/PRODUCT TYPE

Non-proprietary/proper/USAN: pariglasgene breca parvovec (DTX401)

Proprietary name: GENGLYCOS

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological category: AAV8 vector-based gene therapy product
- b. Dose form: Solution for infusion formulated in 20 mM Tromethamine (Tris base), 200 mM sodium chloride (NaCl), (b) (4) magnesium chloride (MgCl₂), 0.01% (w/v) poloxamer 188 with a target product concentration of 3.0×10^{13} genome copies (GC)/mL and pH of (b) (4)
- c. Strength/potency: 3.0×10^{13} GC/mL
- d. Route of administration: Intravenous infusion
- e. Indication(s): Treatment of glycogen storage disease type Ia (GSDIa) in adult and pediatric patients (*Reviewer's note: The Indication(s) may be modified following the finalization of this memo. See the Office of Therapeutic Products' memo for the final indication.*)

5. MAJOR MILESTONES

Filing action date: February 20, 2026

Facility inspection (manufacturing facility): April 06 – 14, 2026

Facility inspection (testing facility): April 15 – 17, 2026

Mid-cycle meeting with Ultragenyx: April 21, 2026

Late-cycle meeting with Ultragenyx: June 08, 2026

PDUFA action date: August 23, 2026

6. DMPQ CMC/FACILITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Miriam Ngundi, OCBQ/DMPQ/MRB1	3.2.S – Drug substance, 3.2.P – Drug product, 3.2.A.1 – Facilities and equipment, and 3.2.R – Regional information (microbial controls and equipment)

7. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
12/23/2025	STN 125858/0	Original submission / Reviewed
02/05/2026	Amendment STN 125858/0.2 Response to information request (IR) dated 01/30/2026	Information to prepare for pre-license inspection (PLI) / Reviewed
02/11/2026	Amendment STN 125858/0.3 Response to IR dated 02/10/2026	Information to prepare for PLI / Reviewed

Date Received	Submission	Comments/ Status
02/27/2026	Amendment STN 125858/0.7 Response to IR dated 02/25/2026	Information to prepare for PLI / Reviewed
03/05/2026	Amendment STN 125858/0.9 Response to IR dated 02/18/2026	Manufacturing process / Reviewed
03/25/2026	Amendment STN 125858/0.11 Response to IR dated 03/09/2026	Information to prepare for PLI / Reviewed
03/25/2026	Amendment STN 125858/0.12 Response to IR dated 03/12/2026	Manufacturing process, container closure system, stability, facilities / Reviewed
03/31/2026	Amendment STN 125858/0.14 Response to IR dated 03/27/2026	Environmental monitoring performance qualification (EMPQ) and EM / Reviewed
04/07/2026	Amendment STN 125858/0.16 Response to IR dated 04/03/2026	Facilities / Reviewed
05/05/2026	Amendment STN 125858/0.17 Response to Form FDA 483	PLI - Response to Form FDA 483 observations issued on 04/14/2026 / Reviewed
05/06/2026	Amendment STN 125858/0.18 Response to IR dated 04/22/2026	EM and utilities / Reviewed
05/26/2026	Amendment STN 125858/0.21 Response to IR dated 05/12/2026	Equipment / Reviewed
05/29/2026	Amendment STN 125858/0.24 Response to IR dated 04/22/2026	EM trends / Reviewed
06/12/2026	Amendment STN 125858/0.26 Response to IR dated 06/02/2026	Filter validation, CCIT, DS (b) (4), shipping / Reviewed
06/18/2026	Amendment STN 125858/0.28 Response to RAI dated 06/01/2026	PLI - Response to Form FDA 483 Observation 2 issued on 04/14/2026 / Reviewed
06/23/2026	Amendment STN 125858/0.29 Updated stability data	Stability data / Reviewed
06/26/2026	Amendment STN 125858/0.30 Response to RAI dated 06/23/2026	PLI - Response to Form FDA 483 Observation 2 issued on 04/14/2026 / Reviewed
06/29/2026	Amendment STN 125858/0.34 Response to IR dated 06/26/2026	DS (b) (4) / Reviewed
07/10/2026	Amendment STN 125858/0.37 Status update of the response to Form FDA 483	PLI - Response to Form FDA 483 observations issued on 04/14/2026 / Reviewed
07/10/2026	Amendment STN 125858/0.38	Shipping validation report / Reviewed
07/14/2026	Amendment STN 125858/0.39 Response to IR dated 07/09/2026	Acceptable quality limit (AQL) / Reviewed
07/21/2026	Amendment STN 125858/0.41 Response to IR dated 07/15/2026	CCIT and shipping validation / Reviewed
08/03/2026	Amendment STN 125858/0.48 Response to IR dated 07/31/2026	Reporting category for the executed CP / Reviewed
08/05/2026	Amendment STN 125858/0.50 Status update of the response to Form FDA 483	PLI - Response to Form FDA 483 observations issued on 04/14/2026 / Not reviewed

Date Received	Submission	Comments/ Status
08/05/2026	Amendment STN 125858/0.51 Update Module 3 to include all agreements in previous IRs that were not implemented yet	Update to Module 3 sections / Reviewed

8. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Ultragenyx Pharmaceutical Inc. (referred to as Ultragenyx or the applicant) submitted a Biologics License Application (BLA) STN 125858/0 to support the licensure of pariglasgene brecaparvovec (DTX401), GENGLYCOS, an adeno-associated virus (AAV) vector-based gene therapy.

GENGLYCOS is a non-replicating, recombinant AAV serotype 8 viral vector encoding a codon-optimized human glucose-6-phosphatase- α gene. The viral particle is comprised of (b) (4) which encapsidate viral DNA containing the human glucose-6-phosphatase, catalytic subunit (G6PC) expression cassette (b) (4). The expression cassette contains a codon-optimized version for the human G6PC coding sequence. GENGLYCOS (b) (4) drug product (DP) (b) (4) formulation (i.e., 20 mM Tris, 200 mM NaCl, (b) (4) MgCl₂, 0.01% (w/v) poloxamer 188 at a target pH of (b) (4)). The DS is formulated at a target concentration of (b) (4). The DP is a clear to translucent, colorless solution for infusion, formulated at a target concentration of 3.0×10^{13} GC/mL. The DP is aseptically filled into Type (b) (4) clear borosilicate glass vials with an (b) (4) gray chlorobutyl rubber stopper and an aluminum seal with a plastic flip-off cap. Each DP vial is aseptically filled to a target volume of approximately (b) (4) mL to allow for an extractable volume of 2.0 mL.

GENGLYCOS is intended for the treatment of glycogen storage disease type Ia and is designed to deliver a functional human G6PC to hepatocytes, resulting in the hepatic production of Glucose-6-phosphatase- α and the restoration of glycogen breakdown to produce glucose.

On February 20, 2026, FDA issued a filing notification to the applicant stating that the BLA had been filed and had received a Priority Review designation.

GENGLYCOS DS and DP are manufactured at Ultragenyx Pharmaceutical Inc. located in Bedford, MA. The facility is also referred to as Gene Therapy Manufacturing Facility (GTMF). This review memorandum provides summaries and assessments of the following: 1) GENGLYCOS manufacturing process, including product quality attributes with emphasis on microbial controls; and 2) facility and equipment, including qualification of utilities and manufacturing equipment, cross-contamination controls, qualification and maintenance of classified environments, and cleaning/sterilization as well as maintenance of equipment.

The Office of Compliance and Biologics Quality, Division of Manufacturing and Product Quality (OCBQ/DMPQ); the Office of Inspections and Investigations, Office of Biologics Inspectorate (OII/OBI); and the Office of Therapeutic Products (OTP) conducted a pre-license inspection (PLI) of the Ultragenyx Pharmaceutical Inc. facility (Bedford, MA, FEI # 3025268614). A five-item Form FDA 483 Inspectional Observations was issued at the conclusion of the PLI, and the PLI was classified as Voluntary Action Indicated (VAI). DMPQ, OBI, and OTP also conducted a PLI of the DP release testing facility, Ultragenyx Pharmaceutical Inc. (Woburn, MA, FEI: 3023224237). The PLI was classified as No Action Indicated (NAI).

Following evaluations of the inspection compliance histories and experience with proposed manufacturing and testing responsibilities, PLIs were waived for the following DP release testing and DP labeling facilities, respectively:

(b) (4)

Note, the inspection waiver for these facilities is documented in a separate inspection waiver memo dated April 22, 2026.

Based on the information submitted to BLA 125858/0, PLIs, and inspectional compliance history evaluations, the facilities, equipment, and microbial controls appear acceptable for the licensure of GENGLYCOS, and approval is recommended.

B. RECOMMENDATION

I. APPROVAL

Based on the information provided in the original application and amendment, DMPQ recommends the approval of pariglasgene breCAParvovec (DTX401), GENGLYCOS.

GENGLYCOS DS and DP are manufactured at Ultragenyx Pharmaceutical Inc., 170 Middlesex Turnpike, Bedford, MA 01730.

GENGLYCOS DP is labeled at (b) (4)

The approval includes the following inspectional recommendation for the Ultragenyx Pharmaceutical Inc. facility located at 170 Middlesex Turnpike, Bedford, MA 01730 (FEI 3025268614).

Although EM limits were met for the data submitted in support of the EMPQ, (b) (4) was recovered in Grade (b) (4) and Grade (b) (4) areas. Due to the risk of (b) (4) transfer to Grade (b) (4) and potentially Grade (b) (4) manufacturing areas, (b) (5), (b) (7)(E)

CBER understands the inspectional recommendation may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Miriam Ngundi, CSO, OCBQ/DMPQ/MRB1	Concur	
Kathleen Jones, Acting Deputy Director, OCBQ/DMPQ; Branch Chief, OCBQ/DMPQ/MRB1	Concur	
Nicole Li, Acting Director, OCBQ/DMPQ	Concur	

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3.2.S.1 DRUG SUBSTANCE

(b) (4)



(b) (4)



11 pages have been determined to be not releasable: (b)(4)

(b) (4)



3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

GENGLYCOS DP is a sterile clear to translucent colorless solution for infusion, formulated in 20 mM Tris base, 200 mM NaCl, (b) (4) MgCl₂, 0.01% (w/v) poloxamer 188 at a target product concentration of 3.0×10^{13} GC/mL and a target pH of (b) (4). The

GENGLYCOS DP is preservative-free. The DP is aseptically filled into (b) (4) (8 mL) Type (b) (4) clear glass vials with an (b) (4) gray chlorobutyl rubber stopper and an aluminum seal with a plastic flip-off cap. Each DP vial is filled to a target volume of approximately (b) (4) mL to allow for an extractable volume of 2.0 mL. The DP is stored at $\leq -60^{\circ}\text{C}$ for a proposed shelf life of 24 months.

3.2.P.2.5 Microbiological Attributes

Microbial controls during the manufacture of sterile GENGLYCOS DP include the following:

The following tests and acceptance criteria support microbial control during the manufacture of the DP:

Reviewer's comment: The information provided appears acceptable. The manufacture of GENGLYCOS DP is conducted in areas that are monitored to meet the requirements of Grade (b) (4) and Grade (b) (4) environments, and incoming materials and components are evaluated to meet sterile properties. The product release specifications also meet criteria of low-risk bioburden (b) (4) and endotoxin (b) (4). Testing of the CCS and validation of the CCIT by (b) (4) (b) (4) method are documented under sections 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures, and the results appear to indicate that the CCS is acceptable to provide a sterile barrier for GENGLYCOS DP.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

GENGLYCOS DP is manufactured at Ultragenyx Pharmaceutical Inc.'s GTMF in Bedford, MA.

Reviewer's comment: See section 3.2.A.1 for a complete list of the manufacturing activities performed at the Ultragenyx facility as well as other facilities used to manufacture the DP (i.e., labeling, testing, and storage).

3.2.P.3.3 Description of Manufacturing Process

Ultragenyx stated that each GENGLYCOS DP lot is manufactured from a (b) (4)

All open DP processes are performed in a Grade (b) (4) environment (i.e., (b) (4)). The manufacture of GENGLYCOS DP consists of following unit operations:

- (b) (4)
(b) (4) is performed (b) (4). The process parameters for this step were provided in Table 4 (updated in amendment STN 125858/0.51).

- (b) (4)

- (b) (4)
(b) (4)

- Aseptic filling, stoppering, and sealing/capping
(b) (4)

In amendment STN 125858/0.12, Ultragenyx provided the sampling plan for filled DP vials. Sterility samples are pulled from the (b) (4) of the vial (b) (4). The number of vials collected from each segment is based on the number of vials in a lot, as detailed in Table 9 of amendment STN 125858/0.12. Ultragenyx stated that (b) (4) pulled for endotoxin; however, the applicant did not specify from which (b) (4) process this sample is pulled. The applicant stated that the sampling strategy for routine manufacture of GENGLYCOS has not changed from that used for the PPQ lots.

- Visual inspection

The filled DP vials are 100% manually inspected for visible particulates and defects in the glass, crimp seal, and/or stopper. The rejects are categorized as critical, major, and minor. The acceptable range for rejects is (b) (4) for critical rejects, (b) (4) for major rejects, and (b) (4) for minor rejects. The rejected vials are removed, and unacceptable vials are quarantined then disposed using approved written procedures. Ultragenyx stated that an acceptable quality limit (AQL) sampling and inspection is performed by the quality unit following 100% manual visual inspection to ensure the effectiveness of visual inspection. The process parameters for this step were provided in Table 8.

In amendment STN 125858/0.39, Ultragenyx clarified that the sample size for the AQL inspection is determined in accordance with (b) (4). The applicant provided the AQL (%) for each defect category: critical (b) (4); (b) (4), major (b) (4), and minor (b) (4). In Table 1, Ultragenyx provided the acceptance and rejection limits for major and minor defects based on batch size. Ultragenyx stated that if any acceptance limit is exceeded during AQL inspection, 100% re-inspection of the lot will be performed. A deviation must be initiated prior to re-inspection. Following 100% re-inspection, a (b) (4) AQL sampling is performed using a tightened sample size. If the tightened AQL inspection fails, the batch will be segregated pending a deviation investigation.

- Vial (b) (4) packaging and stored at (b) (4). Acceptable filled vials are packaged into (b) (4). Each (b) (4) is labeled with (b) (4) lot-specific labels with a tamper evident seal and stored at (b) (4). The (b) (4) are packed and shipped to the secondary packaging site (i.e., (b) (4) for vial labeling and secondary packaging. The process parameters for this unit operation were provided in Table 9. The cumulative manufacturing process time at (b) (4) conditions (b) (4). The (b) (4) conditions are defined as the total time (b) (4) are stored at (b) (4) °C.

- Vial labeling and secondary packaging

Ultragenyx stated that unlabeled vials are centrally labeled with a permanent adhesive label, packaged into (b) (4), tamper sealed, and stored ≤ -60 °C. During secondary packaging performed (b) (4), the required quantity of labeled vials are inserted into vial tray and then placed into a printed carton with a folded package leaflet and tamper sealed. A label is adhered to the carton with kit specific information (patient weight band, vial quantity, and national drug code (NDC)). The cartons are coded with lot number, expiry, and serialization information. The applicant stated that filled vials from multiple DP lots may be combined into a finished goods kit in order to support patient dosing. The expiry applied to a multi-DP

lot kit is based on the DP lot with the earliest expiry. The finished goods are stored at $\leq -60^{\circ}\text{C}$.

Preparation of Formulation Buffer

Ultragenyx stated that the formulation buffer (i.e., 20 mM Tris base, 200 mM NaCl, mM MgCl_2 , 0.01% (w/v) Poloxamer 188, pH ^{(b) (4)} is prepared using compendial

(b) (4)

Reprocessing

Ultragenyx stated the (b) (4)

(b) (4)

The applicant provided the flow diagram for the manufacturing process (Figure 1) and the process parameters and controls for each operation unit. The classifications (i.e. CIPC, IPC, CPP, and KPP) of the process parameters and controls were defined.

Reviewer's comment: The information provided to describe DP manufacturing process appears acceptable. Ultragenyx provided a clear stepwise description used to manufacture GENGLYCOS DP. The protocol provided for reprocessing appears acceptable from a microbial control perspective. The acceptance criteria for microbial controls appear acceptable to support the manufacture of sterile DP.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Ultragenyx identified the following critical steps and IPCs with acceptance criteria for the manufacture of GENGLYCOS DP.

- (b) (4)

- (b) (4)

The applicant considers operations or results outside these ranges as deviations.

Ultragenyx stated that there are no intermediates in the manufacture of GENGLYCOS DP.

Reviewer's comment: The information provided appears acceptable. (b) (4) testing is performed using a compendial method, and (b) (4) is monitored for all vials. Any vials that are outside the acceptable range are removed. The acceptance criteria for the IPCs appear to indicate an appropriate control strategy is implemented to assure product quality and sterility and process consistency.

3.2.P.3.5 Process Validation and/or Evaluation

Process Performance Qualification Batches

Ultragenyx provided a summary of the process validation study performed that manufacture three GENGLYCOS DP PPQ lots. Ultragenyx stated that the PPQ lots were manufactured consecutively at the commercial process scale under normal operating conditions. According to the applicant, DP PPQ 2 and PPQ 3 lots utilized (b) (4) (b) (4) (b) (4) batch, as indicated in the following:

(b) (4)

According to information provided in the Post-Approval Change Management Protocol (document VV-43600), Ultragenyx considers (b) (4) vials to be the maximum DP batch size.

4 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment: The information provided regarding sterilizing filter validation appears acceptable. The microbial viability and bacterial challenge studies appear to have been performed in accordance with industry standard. The parameters applied to the bacterial challenge study represent worst-case conditions relative to routine process parameters. While the (b) (4) was not measured at determined intervals during the execution of the validation study, the worst-case (b) (4) was demonstrated at (b) (4) when a (b) (4) was measured. Ultragenyx proposed filtration duration of (b) (4) appears acceptable.

Aseptic Process Simulation (APS) of GENGLYCOS Manufacturing Process

Ultragenyx executed three APS runs in September 2023. Additional (b) (4) validations were performed in (b) (4) as well as (b) (4). The applicant stated that the APS fills (b) (4) aseptic process conditions which included the GENGLYCOS DP manufacturing process and container closure system (CCS) i.e., (b) (4) Type (b) (4) glass vial, 20 mm chlorobutyl stopper, and plastic flip-off aluminum seal. The

applicant further stated that the (b) (4) was fixed across all production and that (b) (4) representative fill volume was selected for the (b) (4) vial configuration. Additionally, the applicant stated that the time limit for APS filling operations was considered when establishing the maximum limit for production. During the APS, each vial was filled with (b) (4) to a target volume of (b) (4) mL. Ultragenyx provided the inherent and corrective interventions performed during the APS in Table 24. Filled vials were (b) (4) followed by (b) (4) (b) (4) at each condition. Ultragenyx stated that vials were inspected for (b) (4) at the time of the (b) (4). Ultragenyx provided results for all (b) (4) APS runs in Table 22, which showed the following:

(b) (4)

Ultragenyx stated that (b) (4) was performed at the (b) (4) using following challenge organisms (b) (4)

In amendment STN 125858/0.12, Ultragenyx clarified that a critical reject is assigned to (b) (4)

The applicant also explained that the (b) (4) yield is calculated as follows:

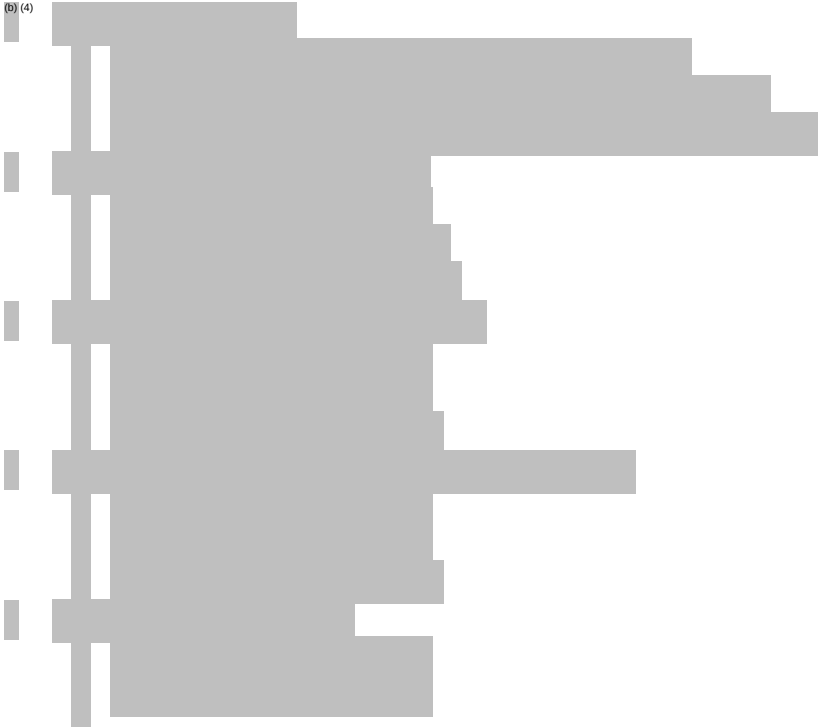
(b) (4)

In amendment STN 125858/0.12, Ultragenyx provided the following parameters used for the APS runs. The values in parentheses represent the corresponding parameters for routine (i.e., commercial scale) production of GENGLYCOS DP:

(b) (4)

In amendment STN 125858/0.12, Ultragenyx provided the type of EM performed, the number and location of samples, acceptance criteria, and results. The following EM action limits – same as those established during EM performance qualification (EMPQ) – were met following resolution of deviations:

(b) (4)



The following is a high-level summary of deviations observed during the APS and submitted in amendment STN 125858/0.12.

(b) (4)



(b) (4)

The remaining deviations were mostly documentation-related; CAPAs were initiated to revise the relevant documents.

Reviewer's comment: The information provided regarding APS appears acceptable. The APS study appears to have been performed in accordance with industry standard, including incorporating interventions and evaluation of parameters used during routine manufacturing of GENGLYCOS DP. The results of the APS study met the acceptance criteria, which demonstrating the facility is capable of aseptically manufacturing the DP. Ultragenyx's assessment of the deviations appears acceptable.

Shipping Validation

Ultragenyx stated that GENGLYCOS DP is shipped frozen ($\leq -60^{\circ}\text{C}$) in a temperature-controlled (b) (4) shipper from the DP manufacturing site (Ultragenyx Bedford, MA) to commercial packaging, labeling, and storage sites: (b) (4)

In amendment STN 125858/0.12, Ultragenyx clarified that the (b) (4) facility in (b) (4) is not intended to serve as a commercial packaging and labeling facility for GENGLYCOS DP under this BLA; rather, it is intended to support commercial shipping for global markets outside of the United States.

The shipping validation studies (reported in document VV-33559) were performed using (b) (4)

6 pages have been determined to be not releasable: (b)(4)

(b) (4). The shipping validation results met the predefined acceptance criteria, demonstrating that the shipper for GENGLYCOS DP is capable of maintain a temperature of $\leq -60^{\circ}\text{C}$ as required for the product, and the container closure integrity is maintained throughout the proposed shipping lane.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Ultragenyx provided the proposed lot release specifications for GENGLYCOS in Table 1., which included the following:

- Endotoxin (b) (4)
- Sterility (b) (4) Negative (no growth)
- CCIT by (b) (4) (b) (4) method: Meets requirements (b) (4)

Note: CCIT results are for stability testing.

3.2.P.5.3 Validation of Analytical Procedures – Container Closure Integrity

Ultragenyx explained that during the CCIT of GENGLYCOS DP, the filled vials are

(b) (4)

Ultragenyx stated that validation of the CCIT method was performed using (b) (4) vials containing (b) (4) mL of GENGLYCOS DP (lot (b) (4)). The following parameters were evaluated during the method validation:

(b) (4)

(b) (4)

(b) (4)

3.2.P.5.4 Batch Analyses

Ultragenyx provided the batch analyses of (b) (4) GENGLYSIS PPQ batches and (b) (4) engineering (Engin.) stability (b) (4) that were manufactured at the Ultragenyx Bedford, MA facility using the proposed commercial manufacturing process, (b) (4). The following are the details of the batches:

(b) (4)

The results for all the batches met the acceptance criteria for sterility (b) (4) negative (no growth) and endotoxin (b) (4)

Reviewer's comment: The information provided appears acceptable. All tests results for sterility and endotoxin met the release specifications for all batches. The data appear to support consistent manufacture of sterile GENGLYCOS DP at the Ultragenyx Pharmaceutical Inc. facility.

3.2.P.7 Container Closure System

The primary CCS of GENGLYCOS DP consists of a (b) (4) (8 mL) Type (b) (4) clear borosilicate glass vial, a 20 mm grey chlorobutyl rubber stopper, and an aluminum seal.

The vials are supplied by (b) (4) located in (b) (4) Ultragenyx stated that the vials meet the current (b) (4) (b) (4) Type (b) (4) glass requirements. The applicant provided a schematic drawing of the vial (Figure 1). Vials are received sterile and ready-to-use. In amendment

STN 125858/0.12, Ultragenyx clarified that vials are sterilized using (b) (4) in accordance with an established sterilization process to achieve a sterility assurance limit (SAL) of (b) (4). The applicant stated that each lot is verified for compliance based on the CoC provided by the vendor and that incoming testing is performed onsite in accordance with established material specifications. Ultragenyx provided the vial specifications with acceptance criteria in Table 2. The CoC specifications include sterility (b) (4) (no growth) and bacterial endotoxin (b) (4). Incoming testing includes visual inspection for defects, labels, and material identity. In amendment STN 125858/0.12, Ultragenyx provided the critical defects categorized as critical, major, and minor as well as the AQL – (b) (4), (b) (4), (b) (4) respectively – of the defects for each category.

The stoppers are supplied by (b) (4) located in (b) (4). The chlorobutyl rubber stopper has an (b) (4) (b) (4) on the product contact surface and a (b) (4) on the non-product contact surface. The applicant stated that the stoppers meet the current (b) (4) requirements for Type^{(b) (4)} elastomeric closures. Ultragenyx provided a schematic drawing of the stopper (Figure 2). The stoppers are received clean, (b) (4) -sterilized, and ready-to-use. Ultragenyx stated that stoppers are inspected and released for use based on verification of supplier's CoA and incoming testing. Ultragenyx provided the stopper specifications with acceptance criteria in Table 3. The CoA specifications included bacterial endotoxin (b) (4) with acceptance criteria for the (b) (4) that varies based on the (b) (4). Incoming controls include visual inspection for defects, labels, and material identity. In amendment STN 125858/0.12, Ultragenyx provided the critical defects categorized as critical, major, and minor, as well as the AQL – (b) (4), (b) (4), (b) (4) respectively – of the defects for each category.

The aluminum seal with a green polypropylene plastic flip-off cap is supplied by (b) (4). Ultragenyx provided a schematic drawing of the seal was provided (Figure 3). The seals are received clean, (b) (4) sterilized, and ready-to-use. Ultragenyx stated that seals are inspected and released for use based on review of the supplier's certificate of quality and certificate of (b) (4). Ultragenyx provided the seal specifications with acceptance criteria in Table 4. The certificate specifications included bioburden (b) (4) (b) (4). Incoming controls include visual inspection for defects, labels, and material identity.

Secondary packaging for labeled vials consists of a vial tray containing the required quantity of vials per patient. The tray is placed in a printed carton along with a folded package leaflet and is then tamper-sealed. Each carton is coded with the patient weight band, vial quantity, lot number, expiration date, and serialization information.

Reviewer's comment: The information provided on the primary CCS for GENGLYCOS DP appears acceptable. The CCIT shipping validation results appear to demonstrate

the transport process from Ultragenyx to the storage/distribution site can maintain an integral CCS.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Ultragenyx proposed a shelf life of 24 months for GENGLYCOS DP when stored at $\leq -60^{\circ}\text{C}$. The applicant stated that ongoing and planned studies will further confirm and extend the shelf life to a maximum of (b) (4) months.

Ultragenyx provided the long-term stability protocol and specifications in Table 2 which includes CCIT (b) (4) (b) (4) method. CCIT is evaluated at time point (b) (4) (i.e., (b) (4)) and (b) (4) thereafter, including at the time (b) (4) . The acceptance criterion for CCIT is meets requirements of (b) (4) .

To support the microbial control of the DP during proposed shelf life, Ultragenyx submitted CCIT stability data for product manufactured under (b) (4) different processes ((b) (4)) and stored at $\leq -60^{\circ}\text{C}$.

In Tables 6, 11, and 13, the acceptance criteria for CCIT (b) (4) (b) (4) is (b) (4) . However, the results for the initial CCIT of GENGLYCOS DP lots (b) (4) (PPQ 1), (b) (4) (PPQ 2), and (b) (4) (PPQ 3) were reported as (b) (4) . In amendment STN 125858/0.12, Ultragenyx clarified that the criterion of (b) (4) applied to the initial CCIT of the PPQ lots represents the method's LOQ, as the results were below this limit. Therefore, the results were still demonstrated to be within the acceptance criterion

of (b) (4).

In amendment STN 125858/0.41, Ultragenyx provided additional stability data for other drug products from similar programs (b) (4) manufactured at GTMF using (b) (4)

In Table 2, Ultragenyx provided CCIT results from GENGLYCOS, (b) (4) lots, which the applicant stated were GTMF-manufactured drug product lots. The CCIT results at the 24-month time point for (b) (4) GENGLYCOS developmental (b) (4) DP (b) (4) (b) (4) met the acceptance criteria (b) (4). Additionally, CCIT results at 12-month time point for (b) (4) GMT-manufactured lots, including (b) (4) GENGLYCOS PPQ lots, met the acceptance criteria. Ultragenyx stated that it will continue to generate and monitor long-term stability and CCIT data through (b) (4) months per the stability protocols.

Reviewer's comment: While CCIT data at the end of the proposed shelf life (24 months) from (b) (4) lots manufactured using the commercial process would demonstrate manufacturing consistency and provide a higher confidence that the container closure system will maintain its integrity – and therefore the drug product's sterility – throughout the entirety of the proposed shelf life, there is evidence from CCIT data from a GENGLYCOS development (b) (4) that provide that sterility of GENGLYCOS DP appears to be maintained throughout the proposed 24-month shelf life under the intended storage condition of $\leq -60^{\circ}\text{C}$. This sterility assurance is further supported, in part, by stability data from (b) (4) GENGLYCOS PPQ lots manufactured according to the commercial process, though that data extends only to 12 months.

Also, the CCIT from the (b) (4) GENGLYCOS PPQ lots at 12-months were performed post-shipping and post-thawing. Therefore, the passing CCIT results demonstrate storage at -60°C did not negatively affect the integrity of the container closure system to ensure the drug product's sterility.

Assessment of the product-specific attributes of the stability data from the for the purpose of establishing the shelf life of GENGLYCOS DP is deferred to OTP.

3.2.A APPENDICES**3.2.A.1 Facilities and Equipment****Facilities Table**

Facility: Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	CMO
Ultragenyx Pharmaceutical Inc. 170 Middlesex Turnpike Bedford, MA 01730 FEI: 3025268614 • DS manufacture • DS storage • DP manufacture • Cell Bank storage • Plasmid storage	Inspection	Yes	Yes	No
Ultragenyx Pharmaceutical Inc. 150 Presidential Way Woburn, MA 01801 FEI: 3023224237 • DS release and stability testing • DP release and stability testing • Cell bank stability testing	Inspection	Yes	Yes	No
(b) (4) FEI: (b) (4) • DS release testing • DP release and stability testing	Waiver	Yes	Yes	Yes
(b) (4) FEI: (b) (4) • DP primary/secondary labeling • DP storage and distribution	Waiver	No	Yes	Yes

Facility: Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	CMO
(b) (4) [REDACTED] FEI: (b) (4) • DS release testing	Not required	No	Yes	Yes
(b) (4) [REDACTED] FEI: (b) (4) • DS release testing	Not required	No	Yes	Yes
(b) (4) [REDACTED] FEI: (b) (4) • Cell bank manufacturing • Cell bank testing • Cell bank storage • (b) (4) cell bank testing • Plasmid testing	Not required	No	Yes	Yes
(b) (4) [REDACTED] FEI: (b) (4) • Cell bank testing	Not required	No	Yes	Yes
(b) (4) [REDACTED] FEI: (b) (4) • Cell bank testing	Not required	No	Yes	Yes

Facility: Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	CMO
(b) (4) [REDACTED] FEI: (b) (4) • Cell bank testing	Not required	No	Yes	Yes
(b) (4) [REDACTED] FEI: (b) (4) • Cell bank storage • (b) (4) cell bank storage • Plasmid storage	Not required	No	Yes	Yes
(b) (4) [REDACTED] FEI: (b) (4) • (b) (4) cell bank (b) (4) manufacture and storage • (b) (4) cell bank testing • Plasmid manufacture, testing, and storage	Not required	No	Yes	Yes
(b) (4) [REDACTED] FEI: (b) (4) • (b) (4) cell bank ((b) (4) [REDACTED] manufacture and storage	Not required	No	Yes	Yes
(b) (4) [REDACTED] FEI: (b) (4) • (b) (4) cell bank testing	Not required	No	Yes	Yes

Acronym key: DP – drug product; DS – drug substance

In amendment STN 125858/0.9, Ultragenyx explained that (b) (4) was (b) (4)

Facility Design

Ultragenyx Pharmaceutical Inc. located at 170 Middlesex Turnpike Bedford, MA, also known as the Gene Therapy Manufacturing Facility (GTMF), is a multi-product manufacturing facility that manufactures AAV-based gene therapy products.

The GTMF (approximately 112,000 ft²) is a (b) (4)-level, single building; manufacturing areas are located on Levels (b) (4), with a (b) (4) between the (b) (4) levels. Ultragenyx provided a list of manufacturing rooms and supports areas in Tables 5 and 6. The critical rooms used to manufacture GENGLYCOS are summarized below.

Level (b) (4) DS manufacturing (Suite (b) (4) and supporting areas

Room and classification	Description/use
(b) (4)	(b) (4)

Level (b) (4) DP manufacturing suite

Room and classification	Description/use
(b) (4)	(b) (4)

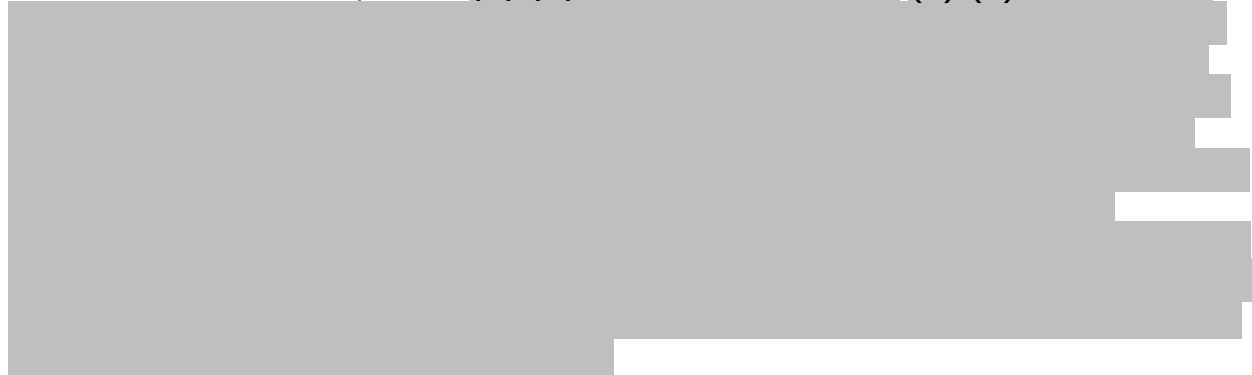
Reviewer's comment: The information provided regarding the description of the manufacturing areas appears acceptable. The cleanroom classifications appear appropriate for their respective manufacturing operations.

Flow Diagrams

Personnel: Personnel enter the manufacturing areas through the (b) (4) rooms (b) (4), proceed to a (b) (4) (b) (4) and into the (b) (4) rooms (Grade (b) (4)). After (b) (4), personnel enter Level (b) (4) hallway (Grade (b) (4)) or Level (b) (4) hallway (Grade (b) (4)). (b) (4) flow of personnel is employed in rooms used for (b) (4) production (Room (b) (4)) (Room (b) (4)) DS (b) (4) (Room (b) (4)) (Room (b) (4)), and vial fill (Room (b) (4)) flow of personnel is employed in rooms free of (b) (4) or (b) (4) products including (b) (4) (Room (b) (4)) (Room (b) (4)) (Room (b) (4)), and supporting areas (Rooms (b) (4)). Ultragenyx stated that a (b) (4) management space (Room (b) (4)) utilizes a combination of (b) (4) (b) (4) flow depending on activities being performed. Personnel airlocks are used for movement between rooms. Personnel exiting the DS production area utilize the (b) (4) corridor (Room (b) (4)) to access the (b) (4) room (Room (b) (4)). Personnel entry into (b) (4) room (b) (4), Grade (b) (4) is through (b) (4) grade airlocks from Grade (b) (4) to Grade (b) (4) and Grade (b) (4) to Grade (b) (4) within Rooms (b) (4). Exit from the (b) (4) room is via a separate airlock (Room (b) (4)). Entry to the vial fill room (Room (b) (4)), Grade (b) (4) is through a dedicated airlock (Room (b) (4)), Grade (b) (4).

Materials and equipment: Materials and equipment intended for use are transported through airlocks that are segregated from personnel airlocks. On Level (b) (4) (DS manufacturing areas), separate airlocks are designated for clean incoming materials (Rooms (b) (4)) and for manufacturing (b) (4) exiting the facility (Rooms (b) (4)). (b) (4) airlocks are located on the (b) (4) to the incoming material airlocks. On Level (b) (4) DP formulation and fill areas), a (b) (4) material (b) (4) airlock (Room (b) (4)) is utilized. The applicant justified this (b) (4) design on the basis that the product processed in the (b) (4) and vial fill areas presents a low risk of introducing contaminants.

Product: Transfer of DS product (b) (4) (b) (4)



Waste: Ultragenyx stated that all solid waste is placed into double-bagged biohazardous

waste containers. Solid waste from Level (b) (4) (DS manufacturing and supporting areas) exits the manufacturing rooms through material airlocks to the return corridor (Room (b) (4)), passes through the material exit airlock (Room (b) (4)), and is staged in a dedicated area (Room (b) (4)) adjacent to the warehouse. The solid waste is then disposed of through a dock (Room (b) (4)) dedicated to vendor waste management. Solid waste from Level (b) (4) (DP (b) (4) and fill) exits the manufacturing rooms through the material airlock (Room (b) (4)) to the facility hallway (Room (b) (4)). The waste is then transported to Level (b) (4) (Room (b) (4)) for staging in Room (b) (4). Ultragenyx also stated that liquid waste is collected using a dedicated system designed to prevent backflow and is subsequently (b) (4).

Floor diagrams for room classification of the manufacturing areas indicate that (b) (4) airflow is from areas of (b) (4) classified areas. In amendment STN 125858/0.12, Ultragenyx stated that the (b) (4) scheme for the facility meets the following design parameters:

(b) (4)

Reviewer's comment: Ultragenyx provided narratives and diagrams for the flow of personnel, materials and equipment, product, and waste. The flows appear to indicate an orderly movement of personnel as well as transfer of materials, product, and waste. The flows to and from the critical DS manufacturing room are (b) (4) through dedicated airlocks. Personnel movement and material/equipment transfer to the manufacturing areas through airlocks is (b) (4)

Different gowning levels are required through the (b) (4) airlocks before entering Grade (b) (4) area. The information provided appears acceptable.

Contamination controls

The manufacture of GENGYCOS includes the use of (b) (4), a (b) (4), which presents a high intrinsic biosafety risk. Ultragenyx stated that a contamination control strategy (CCS) was established based on risk assessments (SOP VV-11225, "Multi-Product Manufacturing Risk Management Strategy at GTMF") to develop multi-product controls for the facility. The applicant further stated the risk assessment evaluated the potential cross-contamination failure modes associated with the following: products and platforms; design of facilities, utilities, and equipment; processes; and controls. Ultragenyx also stated that critical containment controls, as well as engineering and procedural controls, are employed to prevent contamination and cross-contamination during concurrent manufacturing and to prevent the release of biologically active agents (e.g., AAV, (b) (4)) into the surrounding environment.

Ultragenyx provided the following critical containment controls:

- (b) (4)

(b) (4)

Ultragenyx provided the following engineering and procedural controls:

(b) (4)

(b) (4)

Reviewer's comment: The controls in place, which include (b) (4), (b) (4), (b) (4), and other measures listed above to mitigate contamination risks appear acceptable and were evaluated during the April 2026 PLI of Ultragenyx.

Facility cleaning and disinfectant effectiveness studies

Ultragenyx stated that facility surfaces are smooth, non-shedding, and cleanable, and infrastructure components (e.g., light fixtures, ventilation covers) are designed to minimize recesses. The applicant provided an overview of the cleaning procedures and referenced the applicable SOP (GTMF SOP VV-15616) for the cleaning process. The following agents used for facility cleaning, disinfection, and sanitization were provided in Table 11.

- (b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

Reviewer's comment: The information provided to date appears acceptable. The results of the efficacy studies indicate that the disinfectants used in the facility met the efficacy acceptance criteria according to consensus standards. The frequency of cleaning and disinfection performed on each of the surfaces in the manufacturing areas appear acceptable.

Utilities

Water for Injection (WFI)

WFI is generated from (b) (4)

(b) (4)

Ultragenyx stated that the WFI generation and distribution systems are routinely sampled for (b) (4).

Documentation for the WFI system including qualification was provided in Appendix 1: Utilities and Support Systems. Figure 1 illustrated the WFI system, including WFI flow and routine sampling points. Ultragenyx stated that installation and operation qualification (IOQ) of the WFI system was executed by a vendor and Ultragenyx. Ultragenyx performed the performance qualification (PQ) of the system. Table 14 listed the protocols used to qualify the components of the WFI system, including the (b) (4)

In Table 15, Ultragenyx provided the IOQ parameters with acceptance criteria assessed by the vendor (external) including tests for (b) (4)

Ultragenyx stated that there were no validation issues with impact to the qualification observed during the execution of the protocol.

In Table 16, Ultragenyx provided the IOQ parameters with acceptance criteria assessed by Ultragenyx (internal) including verification of: (b) (4)

Ultragenyx stated that all acceptance criteria listed in the internally executed IOQ protocols were successfully met following the resolution of validation issues.

IOQ results from the different protocols were provided in Tables 17, 19, 20, 21, 23, 24, 26, 27, 28, and 29. The results indicated that all tested parameters passed the defined acceptance criteria.

In Table 18, Ultragenyx provided a summary of validation issues encountered during the execution of IOQ protocol VV-19286, including root cause and corrective actions. The validation issues were related to equipment errors arising from system configuration and incorrect parts. Ultragenyx re-executed system verification activities following equipment replacement.

In Table 22, Ultragenyx provided a summary of two validation issues encountered during the execution of IOQ protocol VV-19892. The issues were incorrect documentation and instrument alarm configurations. The applicant identified the root causes to be a system configuration error and incorrect definition of the alarms. The

respective systems were revised, and the parameters were retested and passed.

In Table 25, Ultragenyx provided a summary of two validation issues encountered during the execution of the IOQ protocol VV-20020. (b) (4)

(b) (4). Ultragenyx stated that the changes were tested and documented.

Reviewer's comment: The information provided for the IOQ of WFI system appears acceptable. The results for the IOQ met the predefined acceptance criteria. The resolution of the issues encountered during the IOQ appears acceptable.

Prior to executing the PQ of the WFI system, Ultragenyx executed a WFI (b) (4) Study Sampling Protocol (VV-16589), to provide baseline data to assess the (b) (4) cycle frequency for the (b) (4) WFI (b) (4). The applicant stated that data from the study demonstrated that WFI (b) (4) acceptance criteria were met when a (b) (4) cycle was run on a (b) (4). Ultragenyx stated that in practice the system is (b) (4) (b) (4).

Ultragenyx executed the PQ of the WFI in (b) (4) phases:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

5 pages have been determined to be not releasable: (b)(4)

(b) (4)

Reviewer's comment: The acceptance criteria for the PQ appear to be in accordance with (b) (4) for WFI. The root causes of validation issues related to (b) (4) exceeding the respective acceptance criteria appear to have been identified and resolved appropriately. However, the issue related to (b) (4) identified in recovered (b) (4) samples during PQ — though most of these samples met PQ acceptance criteria — does not appear to have been fully resolved by the conclusion of the PQ phase. Ultragenyx relied on routine EM data to support qualification of the WFI system, as described below.

(b) (4) data collected: May 03, 2023 – September 30, 2025

In Table 46, Ultragenyx provided routine sampling results for (b) (4) and excursion rates. (b) (4) excursions were observed at the following sample locations during this timeframe (May 03, 2023 – September 30, 2025):

Sample Location	# of Excursion / Total # of Sample	Excursion rate (%)
(b) (4)	(b) (4)	(b) (4)

In Tables 48 and 49, Ultragenyx provided the excursion rates for utility locations at (b) (4) excursions in (b) (4) samples) and in cleanroom (b) (4) excursions in (b) (4) samples).

Microbial Identification: May 03, 2023 – September 30, 2025

In Table 47, Ultragenyx provided the microbial identification for all non-zero (b) (4) results from WFI sample collection for routine monitoring. The following list presents microorganisms identified from May 03, 2023 to September 30, 2025:

(b) (4)

In amendment STN 125858/0.18, Ultragenyx provided a summary for an investigation (deviation QE-003470) of the (b) (4) that occurred at sample location WFI (b) (4) indicated above. The applicant identified the likely root cause as environmental conditions surrounding the sample location. Specifically, the applicant explained that the sample location is within an uncontrolled space supplied with unfiltered air and open to an interstitial area, which may have contributed to sample contamination. Ultragenyx stated that no additional excursions have been observed at this sample location during routine WFI monitoring conducted from May 2023 to April 2026.

Ultragenyx provided the following CAPAs created to reinforce contamination control:

(b) (4)

(b) (4)

In amendment STN 125858/0.18, Ultragenyx stated that changes implemented under CAPA-003547, CAPA-003587, and CAPA-003588 were limited to WFI sampling sites located in uncontrolled, non-classified utility areas that are used solely for system monitoring purposes and are not connected to or used as manufacturing POU. The applicant identified these locations and stated that changes under these CAPAs

(b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

The applicant explained that to strengthen reliability and microbial controls, routine (b) (4) WFI (b) (4) was implemented for all WFI sample

(b) (4) located in the non-classified, noncontrolled utility spaces in Rooms (b) (4)

The applicant clarified that (b) (4) of manufacturing POU is not performed as part of routine manufacturing activities or routine WFI monitoring sample collection.

In amendment STN 125858/0.18, Ultragenyx explained that the (b) (4) requirements at the POU are different for (b) (4) sampling for routine WFI monitoring and manufacturing operations as follows:

(b) (4)

In amendment STN 125858/0.18, Ultragenyx noted that the discrepancy in the (b) (4) time was identified during the April 2026 PLI of the facility, which resulted in the issuance of a Form FDA 483 Observation. In amendment STN 125858/0.18, Ultragenyx stated that to address the discrepancy, the (b) (4) requirements for the (b) (4) sampling for routine WFI monitoring were revised under Change Control QE-008145 to align with the manufacturing current practice (i.e., (b) (4))

The applicant stated that the revised sampling procedure, VV-15109 version 13.0 became effective April 26, 2026.

In amendment STN 125858/0.18, Ultragenyx clarified that CAPA-001224, CAPA-001225, and CAPA-001226 (associated with deviation QE-003487), as well as CAPA-002320, CAPA-002321, and CAPA-002346 (associated with deviation QE-005180), did not have established effective checks. Instead, effectiveness for these CAPAs was assessed through routine EM and trending procedures. In amendment STN 125858/0.18, Table 10, Ultragenyx provided the effectiveness checks' documentation for the remaining 10 CAPAs listed in Part 1.2.6 (WFI Conclusion) of Section 3.2.A.1, Appendix 1. The effectiveness checks evaluated sustained control of WFI quality

through repeated facility walkthroughs and trend evaluations of (b) (4) sample data. Ultragenyx stated that sustained control has been demonstrated to date as there has been no (b) (4) recovery between September 24, 2025 and April 18, 2026. (Note: these CAPAs are not associated with WFI-(b) (4) for (b) (4))

Reviewer's comment: (b) (4) excursions and (b) (4) recoveries were identified during WFI qualification and routine monitoring; however, the CAPAs implemented in response appear to provide adequate mitigation, as supported by routine monitoring data from the most recent sampling period – September 24, 2025 to April 18, 2026. The totality of data supporting the WFI quality at the facility was evaluated during the April 2026 PLI.

Routine monitoring of WFI

Ultragenyx provided the following sampling frequency for routine WFI monitoring:

(b) (4)

In Table 45, Ultragenyx listed the following action limits for routine monitoring at POUs in Grade (b) (4) and Grade (b) (4) areas:

(b) (4)

Reviewer's comment: The information provided regarding routine WFI monitoring appears acceptable. Routine monitoring appears to include an assessment at all POUs and at a reasonable frequency. The actions limits are in accordance with industry standards (b) (4) Monitoring data from the water systems was evaluated during the PLI.

Clean Steam

Clean steam is used for (b) (4) equipment. Ultragenyx stated that a (b) (4) clean steam distribution system is not required, as (b) (4) (b) (4) (b) (4) The applicant submitted the clean steam qualification as part of the (b) (4) qualification documentation.

In Table 50, Ultragenyx provided the sample location (i.e., (b) (4)) used to collect samples during PQ and routine clean steam monitoring. The samples were/are tested for (b) (4) in accordance with per (b) (4) WFI quality requirements. The applicant stated that testing for (b) (4)

(b) (4) is performed during periodic requalification.

The specification for clean steam testing includes the following acceptance criteria:

(b) (4)

Reviewer's comment: The acceptance criteria for assessing clean steam quality appear acceptable.

Carbon Dioxide System

Ultragenyx provided a flow diagram and description of the carbon dioxide (CO₂) system

(b) (4)

In Tables 52 and 54, Ultragenyx provided the parameters that were assessed during the IOQ of the CO₂ system to verify that the system met all physical and functional requirements. All parameters met the acceptance criteria including the verification of (b) (4)

(b) (4) In Table 53, Ultragenyx provided a summary of (b) (4) IOQ validation issues: (b) (4) (b) (4)

Ultragenyx stated that sample locations for the CO₂ system PQ were selected based on the Carbon Dioxide Sampling Risk Management Plan (VV-16470). Using a risk-based (b) (4) approach, Ultragenyx identified the POU sampling points as well as sampling at the (b) (4) of the CO₂ distribution system. The applicant justified the (b) (4) approach was appropriate as the CO₂ system is (b) (4), and POU (b) (4) installed on equipment before CO₂ enters manufacturing mitigates risk. During the PQ, (b) (4) samples were collected on (b) (4) (b) (4) days for each sampling site.

Ultragenyx provided PQ sample locations, sampling frequency, tests, and acceptance criteria in Table 55. In addition to sampling at the (b) (4) of the CO₂ distribution system, POU sample locations included rooms utilized to manufacture (b) (4) (e.g., (b) (4))

(b) (4)). The acceptance criteria for PQ as well as routine monitoring were established based on the room classification in which the port resides as well as the process parameter requirements. In Table 55, Ultragenyx provided CO₂ acceptance criteria as follows:

(b) (4)

In Tables 57, 58, and 59, Ultragenyx provided the PQ results which showed that data for (b) (4) met the acceptance criteria for all samples collected at all sample locations. The applicant stated that no validation issues impacting the acceptance criteria were observed.

Routine CO₂ monitoring is performed (b) (4) for (b) (4) at the (b) (4) of the (b) (4) (Grade (b) (4)). Ultragenyx stated that (b) (4) testing were excluded from routine monitoring to mitigate a contamination risk and provided the justification as an absence of (b) (4) generating components and the presence of (b) (4) at each POU. The action limits for (b) (4) applied during routine monitoring are based on the room classification where the port is located as well as the process parameter requirements. In Tables 61 and 62, Ultragenyx provided result summary for routine CO₂ monitoring at (b) (4) sample locations for samples collected from October 2023 to September 2025. The data showed no excursions during this timeframe.

***Reviewer's comment:** The information provided regarding the qualification and routine monitoring of CO₂ appears acceptable. The routine monitoring locations and frequency, which the applicant established based on risk assessment, appear acceptable. The action limits which are based on environmental classification of the POU appear acceptable. Data from routine monitoring of the CO₂ systems was evaluated during the PLI.*

Oxygen

Ultragenyx provided the flow diagram and description of the oxygen (O₂) system (b) (4). The O₂, purchased from a qualified supplier, is stored as a (b) (4). O₂ is distributed throughout the facility as O₂ (b) (4). The O₂ distribution system consists of (b) (4).

(b) (4)

In Tables 64 and 66, Ultragenyx provided the parameters that were assessed during the IOQ of the O₂ system to verify that the system met all physical and functional requirements. All parameters met the acceptance criteria including the verification of (b) (4)

In Table 65, Ultragenyx provided a summary of an IOQ validation issue: (b) (4) (b) (4) (b) (4) (b) (4). Ultragenyx resolved the validation issue by (b) (4) (b) (4) with (b) (4) (b) (4) (b) (4).

Ultragenyx stated that sample locations for O₂ PQ were identified according to a sampling risk management plan in VV-16471. The locations included O₂ (b) (4)

In Tables 67 and 68, Ultragenyx provided a testing plan for the PQ study including sample locations, tests performed (b) (4) acceptance criteria, and sampling frequency (b) (4) samples each on (b) (4) different days). The POU tested included rooms utilized to manufacture (b) (4) (e.g., (b) (4)). In Tables 67 and 68, Ultragenyx provided O₂ acceptance criteria including:

(b) (4)

In Tables 70, 71, and 72, Ultragenyx provided PQ results which showed that results for (b) (4) met the acceptance criteria for all samples collected at all sample locations. The applicant stated that no validation issues impacting the acceptance criteria were observed.

Routine monitoring of O₂ is performed (b) (4) for (b) (4) which are in Grade (b) (4). Ultragenyx stated that (b) (4) testing were excluded from routine monitoring to mitigate a contamination risk due to the absence of (b) (4) generating components and the presence of (b) (4) at each POU. The action limit for (b) (4) applied during routine monitoring are based on the acceptance criteria established during PQ. Ultragenyx provided a summary of the results for routine monitoring at (b) (4) sample locations from June 2023 to third quarter in 2025 in Tables 74 and 75. The data showed no excursions during this timeframe.

Reviewer's comment: The information provided regarding the qualification and routine

monitoring of O₂ appears acceptable. The routine monitoring locations and frequency, which the applicant established based on a risk assessment, appear acceptable. The action limits which are based on environmental classification of the POU (Grade (b) (4)) appear acceptable. Data for the routine monitoring of the O₂ systems was evaluated during the April 2026 PLI.

Process Air

Ultragenyx stated that (b) (4) process air (PA) is used for applications in which there may be product- or process-contact, such as for (b) (4). Ultragenyx provided the flow diagram and description of the PA system. PA is generated on site by (b) (4).

The PA system includes (b) (4) to individual pieces of process equipment.

In Table 77, Ultragenyx provided the parameters that were assessed during the IOQ of the PA system to verify that the system met user requirements specification. All parameters met the acceptance criteria including the verification (b) (4).

(b) (4) As summarized in Table 78, Ultragenyx identified two IOQ validation issues:

Ultragenyx stated that sample locations for the PA system PQ were selected based on the Process Air Sampling Risk Management Plan (VV-16391). Using a risk-based (b) (4) approach, Ultragenyx identified sample locations to include the (b) (4) of each (b) (4) as well as (b) (4) locations for (b) (4). The applicant explained that the (b) (4) approach was appropriate as the PA system is (b) (4) mitigates risk. During the PQ, (b) (4) samples were collected on (b) (4) separate days for each sampling site.

Ultragenyx provided PA PQ sample locations, sampling frequency, tests and acceptance criteria in Table 79. The applicant stated that acceptance criteria for the PQ as well as routine monitoring action limits were established based on the room classification in which the port resides as well as the process parameter requirements. The PA acceptance criteria listed in Table 79 included:

(b) (4)

- (b) (4)

Ultragenyx provided a summary of the PQ results in Tables 81, 82, and 83 which showed that results for (b) (4) met the acceptance criteria for all samples collected at all sample locations, except at sample locations. At sample location (b) (4) out of (b) (4) samples failed the (b) (4) test. At sample location (b) (4) there were failures for (b) (4) of (b) (4) samples), (b) (4) of (b) (4) samples), and (b) (4) of (b) (4) samples).

In Table 84, Ultragenyx provided a summary of five validation issues observed during the PQ of PA under protocol VV-18013. A high-level summary of the investigation of the issues is documented below:

(b) (4)

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)



Reviewer's comment: The change of the sampling location from (b) (4) was made to mitigate the repeated failures in the PA quality supplied to the (b) (4). Although sampling location (b) (4) may not be entirely representative of the PA supplied to the (b) (4), PA is used for (b) (4). In consideration of the non-product contact use of the PA, the information provided for PA qualification including the resolution of the other validation issues appears acceptable to support the qualification of the utility.

PA System Changes

Ultragenyx executed additional IQ, OQ, and PQ of the PA system following modifications required by two change controls.

(b) (4)



Each change (QE-004572 and QE-006094) was qualified using a distinct protocol (VV-30904 and VV-40122, respectively). Ultragenyx provided a summary of the PQ testing requirements, sampling dates, number of samples (b) (4) samples each on (b) (4) different days), and results in Tables 85 – 94. Protocol VV-30904 required sampling at location (b) (4), which replaced the previous sampling point, (b) (4). The results

showed that samples from all locations met the acceptance criteria for (b) (4). Ultragenyx stated that no validation issues were observed during the execution of the two protocols.

In amendment STN 125858/0.18, Ultragenyx clarified that (b) (4) monitoring at all (b) (4) sample locations was required during the PA qualification conducted under protocol VV-30904. This requirement was based on the fact that (b) (4) had been previously qualified under protocol VV-18013, and the data had demonstrated equivalency between (b) (4) monitoring. (b) (4) monitoring at location (b) (4) was conducted during PQ protocol VV-30904.

Routine Monitoring of PA

Routine testing of PA includes (b) (4) monitoring. The action limits are the same as the acceptance criteria utilized during PQ. In Table 95, Ultragenyx outlined the PA sampling locations and indicated that testing is performed at either a (b) (4) frequency, depending on the sample type and location.

In Tables 96 – 101, Ultragenyx provided summaries of routine monitoring data collected between October 2023 and September 2025. The data indicated that there were four (b) (4) excursions at sample location (b) (4) and (b) (4) excursion at (b) (4). Ultragenyx stated that the excursions were documented under quality records QE-005444, QE-006119, and QE-006262 (b) (4), and QE-004111 (b) (4). In amendment STN 125858/0.18, Ultragenyx clarified that (b) (4) monitoring data were not collected between October 2023 and September 2025, as continuous monitoring was provided by the (b) (4). Ultragenyx stated that, based on the successful PQ results under protocol VV-18013 – demonstrated consistency between the (b) (4) testing across the validated operating range – a risk-based decision was made to rely exclusively on the continuously monitoring (b) (4) for ongoing process monitoring.

Ultragenyx stated that an investigation of the (b) (4) excursions was conducted under deviation QE-006119 after noting a trend, and no root cause was identified. The applicant explained that sample location (b) (4) is within an uncontrolled utility space, and environmental factors were considered a potential contributing cause since the room was not routinely cleaned. Ultragenyx identified the root cause for the (b) (4) excursion to be potential environmental ingress of (b) (4) into the (b) (4). Additionally, the applicant identified an unconfirmed laboratory error in the sampling method for (b) (4). In response to the (b) (4) failures, Ultragenyx implemented the following CAPAs (verbatim):

(b) (4)

(b) (4)

Ultragenyx implemented other changes including changing the PA requirement for (b) (4) from (b) (4) to meet (b) (4) specifications and upgrading the sample site limits for (b) (4) to Grade (b) (4) in-operation standards. The applicant stated that since implementing the CAPAs, site enhancements, and change controls, (b) (4) excursions have not been observed. Specifically, results for (b) (4) from (b) (4) sampling of the PA distribution system from May 2025 through December 2025 have exceeded action limits.

In amendment STN 125858/0.18, Ultragenyx explained that an assessment was conducted to (b) (4) the PA requirement for (b) (4). The assessment included potential (b) (4) sources (e.g., (b) (4)) their likelihood of presence, detectability, and potential impact. The assessment concluded that (b) (4) levels consistent with (b) (4) do not pose an unacceptable risk to product quality or patient safety when combined with the facility's engineered filtration, monitoring, and controls.

Reviewer's comment: The information provided for the routine monitoring of PA systems appears acceptable. Ultragenyx's decision to rely on (b) (4) (b) (4) monitoring based on their comparison of (b) (4) monitoring appears acceptable. The change in the PA requirement for (b) (4) from (b) (4) appears acceptable. The (b) (4) (b) (4) (b) (4) (b) (4) provide assurance that the PA is of acceptable quality.

Heating, Ventilation, and Air Conditioning (HVAC)

The HVAC system consists of (b) (4) air handling units (AHUs) that support the manufacturing areas. (b) (4) AHUs serve the DS and central services areas while the DP manufacturing and GMP warehouses are served by (b) (4) AHUs each. Additionally, there are (b) (4) AHUs that serve areas like offices, mechanical areas, and ancillary spaces. Ultragenyx provided diagrams illustrating the areas served by the AHUs. Ultragenyx stated that air changes/hour (ACH) are based in room/area classification as follows:

- Grade (b) (4)
- Grade (b) (4)
- Grade (b) (4)
- (b) (4) (b) (4) (b) (4) ACH

Ultragenyx stated that the AHU zones are not mixed, and the exhaust system is segregated by air handling zone and type of exhaust stream. Additionally, exhaust air from Rooms (b) (4) and (b) (4) passes through HEPA filters prior to being discharged to the atmosphere due to the potential presence

(b) (4)

Ultragenyx provided the AHU, rooms served, room grade, room design ACH, and percentage of recirculated air for the AHUs. Below is a summary of the AHUs and critical rooms served by each.

AHU	Room served / operations, and Grade	Air type (% recirculation)
-----	-------------------------------------	----------------------------

(b) (4)

Ultragenyx provided pressurization schemes for the manufacturing room and stated that

the scheme for the facility meets the following design parameters (verbatim):

(b) (4)

Ultragenyx classified the HVAC system into (b) (4) categories which governed the validation strategy.

(b) (4)

Ultragenyx commissioned AHUs and associated ancillary mechanical systems (e.g., (b) (4)) in accordance with approved user requirements specifications (URS) and design documentation. The following activities conducted on the (b) (4) AHUs passed the acceptance criteria as provided in Table 8:

(b) (4)

HEPA filters were commissioned and qualified as part of the facility qualification.

Ultragenyx provided the following activities and indicated that the acceptance criteria were met in Table 9 – 13:

(b) (4)

Ultragenyx reported one HVAC qualification issue (VV-17543-DEV-003 (VV-18571): The (b) (4) for Room (b) (4), Grade (b) (4) did not meet the acceptance criterion of (b) (4). The applicant explained that this requirement was a general user requirement, the intent of which was to identify the ideal ACH target for each area to minimize (b) (4) throughout each classified area. Ultragenyx stated that the (b) (4) between Room (b) (4) (designed as a (b) (4) room) and the (b) (4) adjacent rooms met the targeted room (b) (4) specifications. Ultragenyx further stated that Room (b) (4) met the (b) (4) specifications (maximum (b) (4)). The applicant concluded that no further corrective actions were required, as Room (b) (4) met the ACH range specified in (b) (4) (i.e., (b) (4) ACH for Grade (b) (4) areas), and the (b) (4) and (b) (4) test results were within acceptable limits.

Environmental monitoring performance qualification (EMPQ)

Ultragenyx performed environmental monitoring performance qualification (EMPQ) studies in 2023 and 2025. Additionally, the applicant submitted interim and routine EM data to support the facility EM program.

2023 EMPQ studies (b) (4)

The studies were performed under separate protocols, one for each functional area: DS, DP, Central Services, Raw Materials, and (b) (4). The results were assessed against acceptance criteria. Ultragenyx stated that risk assessment VV-14325 “Environmental Monitoring Performance Qualification Site Location Risk Assessment” was performed to identify sample locations for the initial EMPQ, and a modified Hazard Analysis and Critical Control Point approach was applied to determine the risk score of the sample locations. The applicant indicated that (b) (4) FDA Aseptic Processing Guidance, and (b) (4) were used. Ultragenyx stated that the EMPQ acceptance criteria (action limits) were based on (b) (4) requirements as follows:

4 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

2023 EMPQ of Raw Material area (b) (4)

The EMPQ was targeted for (b) (4) days of static testing and (b) (4) days of dynamic conditions. Ultragenyx provided a high-level summary of results for the EMPQ of the Raw Material area in Table 12 which showed no excursions were observed.

2023 EMPQ of (b) (4)

The EMPQ was targeted for (b) (4) days of each of the static and dynamic conditions. Ultragenyx provided a high-level summary of results for the EMPQ of the (b) (4) in Table 14 which showed no excursions were observed.

Reviewer's comment: The information provided for the EMPQ appears to not support the environment of the manufacturing environment due to extensive excursions including (b) (4) in Grade (b) (4) and Grade (b) (4) areas. Additional data to demonstrate environmental control in manufacturing areas and re-execution of the EMPQ is documented below.

2023 Interim EM Data (b) (4); i.e., (b) (4)

Ultragenyx stated that Protocol VV-20642 "GTMF Interim Routine Environmental Monitoring Protocol" was utilized to bridge the initial site EMPQ sampling plans and the final routine EM program. According to the applicant, a risk-based reduction of sample sites occurred based on EMPQ data. Grade (b) (4) sample locations were not changed and Grade (b) (4) sample sites were minimally reduced while Grade (b) (4) and Grade (b) (4) sample locations were reduced by approximately 50% and 75%, respectively. During the interim EM, action limits were based on the EMPQ acceptance criteria (action limits), and alert limits were set at (b) (4) of the action limits (Tables 15-16). Additionally, the personnel monitoring limits ((b) (4), in operation) were set as follows:

- Grade (b) (4) Action limits (b) (4)
- Grade (b) (4) Action limits (b) (4) Alert limits (b) (4)

2023 Interim EM of DS area

Ultragenyx provided the excursions observed during the interim EM of the DS area in Table 18 which included:

(b) (4)

Ultragenyx stated that the Grade (b) (4) excursion was investigated under quality event QE-003472 and was identified as *Staphylococcus genus*. The root cause was personnel. According to the applicant, the subsequent sample collection yielded passing results and there has been no repeat of the excursion.

2023 Interim EM of DP area

Ultragenyx provided the excursions observed during the interim EM of the DP area in

(b) (4)

2023 Interim EM of Central Services area

Ultragenyx provided the excursions observed during the interim EM of the Central Services area in Table 20 which included:

(b) (4)

2023 Interim EM of Raw Materials area

Results provided in Table 21 showed that no excursions were observed during the interim EM of the Raw Materials area.

While the Ultragenyx did not provide any excursions, the applicant stated that excursions during the interim EM program were investigated per SOP VV-14266 "Excursion Investigation and Response Procedure for EM and Critical Utilities" to determine the root cause and CAPA. The applicant stated that remediation cleaning was performed (as needed) prior to additional sampling, subsequent results would demonstrate effectiveness of remediation cleaning and/or CAPA (where applicable), and repeat occurrences would be considered a trend and require additional investigation. According to Ultragenyx, occurrences of (b) (4) were predominantly observed in Grade (b) (4) areas in locations that are adjacent to CNC areas and have a higher flow of incoming materials.

Reviewer's comment: The information provided for the EMPQ appears to not support the manufacturing environment due to extensive excursions including (b) (4) (b) (4) in Grade (b) (4) and Grade (b) (4) areas. Additional data to demonstrate that manufacturing areas are operated under a state of environmental control is provided below.

2023 – 2025 Routine EM Data (October 01, 2023 – October 2025, (b) (4)

Based on the results of the interim EM, Ultragenyx developed 'Routine Environmental Monitoring Risk Assessment for GTMF' (VV-24699) and initiated the routine monitoring program under SOP VV-13759, "Environmental and Utility Monitoring Program for UGT GTMF."

2023 – 2025 Routine EM of DS area

Ultragenyx provided the excursions observed during the routine EM of the DS area in Tables 22 – 24 as follows:

(b) (4)

Ultragenyx stated that an excursion was observed in the DS (b) (4) (Grade (b) (4)). The investigation of the event (QE-005806) did not identify a root cause. According to the applicant, there was no impact on the product as the (b) (4) was not in use during the timeframe of the excursion. Ultragenyx stated that no further action was taken as there was no trend observed with (b) (4).

2023 – 2025 Routine EM of DP area

Ultragenyx provided the excursions observed during the routine EM of the DP area in Tables 25 – 27 as follows

(b) (4)

Ultragenyx stated that the three excursions that occurred in Grade (b) (4) areas were all observed in the (b) (4) and were investigated under quality records QE-005571, QE-006529, and QE-005188. The probable root cause of QE-005517 was reported as aseptic technique. According to the applicant, no process activities were being performed during the timeframe of the EM, and no further action was taken as there was no trend observed at the location. The probable root cause of QE-006529 and QE-005188 was reported as material transfer within the (b) (4). The applicant stated that the excursions occurred (b) (4), (b) (4), (b) (4), and there were no other subsequent recoveries as part of (b) (4) operations; therefore, there was no impact on the (b) (4) process.

2023 – 2025 Routine EM of Central Services area

Ultragenyx provided the excursions observed during the routine EM of the Central Services area in Tables 28 – 30 which included:

(b) (4)

(b) (4)

2023 – 2025 Routine EM of Raw Material area

Ultragenyx provided the excursions observed during the routine EM of the Raw Material area in Tables 31 – 33 which indicated that there were no excursions.

2023 – 2025 Routine EM: microbial identification

According to Ultragenyx, microbial identification is required for all viable excursions and for any growth in Grades (b) (4) areas (i.e., per SOP VV-11923 (b) (4)).

Microbial identification data are trended on a (b) (4) basis. In Table 34, Ultragenyx provided the organisms identified at the DS area in (b) (4) . A total of 38 different organisms were identified within this time period, including one mold (*Chaetomium*); the majority were human-skin-associated flora.

2025 EMPQ Studies (b) (4))

Ultragenyx stated that the EMPQ for the DS, DP, and Central Services areas were repeated after the following site changes were made:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2025 EMPQ of DS area (b) (4)

According to summary report (VV-43185) for protocol VV-43182, the EMPQ was performed with a target testing of (b) (4) under static conditions and (b) (4) days under dynamic conditions. Extended sampling was extended for (b) (4) (b) (4) under each static and dynamic condition at specific locations due to the presence of (b) (4) (b) (4). Ultragenyx stated that dynamic testing was performed under normal operational use conditions including routine disinfection, and the activities were simulated.

In Tables 42 – 45, Ultragenyx provided a high-level summary of results for the EMPQ of the DS area. The results indicated that all results for (b) (4) (b) (4) samples from Grade (b) (4) and Grade (b) (4) areas were below the action limits. Ultragenyx stated that six validation issues were observed during the execution of the protocol. In Table 46, Ultragenyx provided a summary of the DS EMPQ

validation issues stemming from the identification of (b) (4) undesirable organisms in Grade (b) (4) and Grade (b) (4) areas. A brief summary of these validation issues as well as other issues with potential to impact the study are documented below:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2025 EMPQ of DP area (b) (4)

According to summary report (VV-43184) for protocol VV-43180, the EMPQ was performed with a target testing of (b) (4) under static conditions and (b) (4) days under dynamic conditions. Extended sampling was conducted for (b) (4) under dynamic conditions for specific locations due to the presence of (b) (4)

In Tables 48 – 51, Ultragenyx provided a high-level summary of results for the EMPQ of the DP area. The results indicated that all results for (b) (4) samples from Grades (b) (4) areas were below the action limits. Ultragenyx stated that there were nine validation issues observed during the execution of the protocol. In Table 52, Ultragenyx provided a summary of the DP validation issues stemming from the identification of (b) (4) undesirable organisms in the Grade (b) (4) areas, and the other validation issues were provided in the report. A brief summary of these validation issues as well as other issues with potential to impact the study are documented below:

(b) (4)

2025 EMPQ of Central Services area (b) (4)

According to the summary report (VV-43186) for protocol VV-43183, the EMPQ was performed. The EMPQ was performed with a target testing of (b) (4) (b) (4) under static conditions and (b) (4) days under dynamic conditions. Extended sampling was extended for (b) (4) under each static and dynamic condition at specific locations due to the presence of (b) (4).

In Tables 54 – 51, Ultragenyx provided a high-level summary of results for the EMPQ of the Central Services area. The results indicated that all results for (b) (4) samples from Grades (b) (4)

areas were below the action limits. Ultragenyx stated that there were eight validation issues observed during the execution of the protocol. In Table 57, the applicant provided a summary of the Central Service EMPQ validation issues due to undesirable organisms in Grade ^{(b) (4)} areas. A brief summary of these validation issues as well as other issues with potential to impact the study is documented below.

(b) (4)



(b) (4)



(b) (4)

In amendment STN 125858/0.18, Ultragenyx clarified that remedial cleanings are unplanned cleanings that were conducted in response to the undesirable organism recoveries, performed in accordance with the pre-approved protocol procedures VV-43172 and VV-43051. These cleanings were fully documented in room and equipment cleaning logbooks. The applicant explained that additional environmental samples were collected only after the completion of remedial cleanings to verify the effectiveness of the remediation actions. Ultragenyx stated that these remedial samples, which were considered as supplemental samples, did not count toward or replace samples required to satisfy the number of monitoring days per the EMPQ protocol. For each of the validation issues that required remedial cleaning, the applicant provided the dates for the sequence of events (i.e., initial sample collection, sample incubation and (b) (4), identification of validation issue, remedial cleaning, remediation sample, and (b) (4) of remediation samples). Ultragenyx clarified that, in accordance SOP VV-15616 (Cleaning and Sanitization of Classified and CNC Spaces in the GTMF), cleaning with a sporicidal agent is required if (b) (4) is observed.

In amendment STN 125858/0.14, Ultragenyx clarified that only validation issues related to the recovery of undesirable organisms identified during the execution of the 2025 EMPQ were submitted in the BLA. However, the applicant provided a summary of other validations issues in Table 3 of amendment STN 125858/0.14. These validation issues pertain to incorrect documentation (eight validation issues), quality alarms (one validation issue), and duplicate sampling (one validation issue). Three validation issues due to missing entries in documents and protocol error had impact on the qualification. Re-sampling for the two events were performed on different days. Additionally, validation issue VV-44088 (VV-43180-DEV-007) was opened due to a missing page containing original (b) (4) printouts was identified as potential data integrity, and deviation QE-007275 was opened leading to change control QE-004094.

2025 EMPQ of Raw Material area (b) (4)

The report of the 2025 EMPQ of the Raw Material area was submitted in amendment STN 125858/0.14. The EMPQ was executed for (b) (4) (b) (4) under static conditions and for (b) (4) days under dynamic conditions. (b) (4) (b) (4) of sampling under dynamic conditions was executed at specific locations due to presence of (b) (4) (b) (4) (see validation issue discussed below). All samples for monitoring (b) (4) in Grades (b) (4) and (b) (4) areas under static and dynamic conditions were below the action limits, as documented in Table 7.

Ultragenyx reported two validation issues: one attributable to protocol generation and the other to (b) (4) recovery. An (b) (4) sample collected from Room (b) (4) (Raw Material (b) (4) Grade (b) (4) yielded (b) (4) however, the results remained below action limits. Remedial cleaning was subsequently performed, and the area was resampled and results met action level limits with no objectionable organisms identified.

Reviewer's comment: During the 2025 EMPQ studies, all predefined acceptance criteria were met, including microbial results that were within established limits. The applicant noted that the recovery of (b) (4) and objectionable organisms did not negate the EMPQ study results, as all prospective criteria were satisfied. Remedial cleaning and subsequent resampling were conducted to address deviations associated with the recovery of (b) (4) and objectionable organisms. However, because this remedial cleaning was non-routine and unplanned, it may not be representative of a typical EMPQ study. Of note, sporicidal cleaning is performed in accordance with the facility's cleaning SOP when (b) (4) is observed during routine EM.

In amendment STN 125858/0.14, Ultragenyx clarified that the 2025 EMPQ study did not include Grade (b) (4) and Grade (b) (4) areas as these areas were qualified during the initial 2023 EMPQ study. The applicant explained that during the 2023 EMPQ study, these areas were evaluated under static and dynamic conditions, and all acceptance criteria were met and all validation issues were resolved. Ultragenyx further noted that an agreement was reached with the FDA to exclude these areas during a Type A meeting held September 4, 2025 (Meeting ID: 21793).

2025 Interim EM (November 09, 2025, start)

Ultragenyx stated that following the completion of the 2025 EMPQ sampling and testing EM will be conducted under an interim monitoring period per, VV-43421. According to the applicant, the ongoing EM activities follow the previously approved sampling plans utilized during the 2023–2025 routine EM program (per SOP VV-13759). Ultragenyx stated that sample locations for the interim EM were reduced from the full complement of EMPQ sample sites in alignment with the same reduction principles applied for interim monitoring in 2023. Action limits will be based on the acceptance criteria for the 2025 EMPQ with alert limits being half of the action limits (also provided in Tables 59 – 61). Additionally, the personnel monitoring limits applied during the 2023 interim EM and 2023 – 2025 routine (also provided in Table 62) will be applied.

In amendment STN 125858/0.18, Ultragenyx provided a comparison of the sample locations used during the 2025 EMPQ study and the 2025 interim EM along with justifications for selection of each EM sample location. The applicant explained that the sampling locations implemented during the interim EM period were aligned with the preexisting sampling maps in place prior to the initiation of the 2025 EMPQ study to ensure continued environmental oversight during data assessment and finalization of 2025 EMPQ executed protocols.

Ultragenyx stated that no (b) (4) recoveries have been identified in any controlled or

classified area since completion of EMPQ sampling and the initiation of interim routine monitoring in November 2025. Trend reports for the interim routine EM period conducted from November 2025 through (b) (4) were submitted in amendment STN 1258585/0.18.

In amendment STN 1258585/0.24, Ultragenyx provided (b) (4) 2026 routine EM trend reports. Ultragenyx stated that no adverse trends were identified. The reports showed the following findings for the monitored areas:

- Fill line: No alert or action level excursions were generated. No growth was recovered.
- DP area: No action level excursions were observed. Two alert level excursions were noted. Additionally, one instance of an undesirable organism – *Bacillus licheniformis*, spore-forming bacterium commonly found in soil – was recovered. Microbial identification of other recovered organisms indicated that the isolates are commonly associated with human microflora and soil.
- DS area: One action level excursion – (b) (4) – was observed. Three instances of an undesirable organism were recovered. The undesirable organisms were spore-forming bacteria commonly found in the environment. Microbial identification of other recovered (b) (4) indicated that the isolates are commonly associated with human microflora and environment.
- Central Services area: No action or alert level excursions were observed, and no undesirable organism were recovered. Microbial identification of other recovered organisms was consistent with those recovered in the DS area.
- Raw Material area: No action or alert level excursions were observed, and no microbial growth was recovered.

Reviewer's comment: Based on a review of all EMPQ data generated from the studies described above, the information provided for the facility EMPQ appears acceptable. All sampled locations met the prospective acceptance criteria established in accordance with industry standards. The resolution of the validation issues identified during the EMPQ execution appears acceptable. The routine EM limits are appropriate to ensure that the manufacturing environment meets the required environmental classification for the manufacture of GENGLYCOS.

Although EM limits were met for the data submitted in support of the EMPQ, the frequency of (b) (4) recovered in Grade (b) (4) and Grade (b) (4) areas still presents a risk of (b) (4) transfer to Grade (b) (4) and potentially Grade (b) (4) manufacturing areas (b) (7)(E), (b) (5)

(b) (4)

Equipment Process Equipment

Ultragenyx provided a list the major equipment and instruments used to manufacture GENGLYCOS in Tables 7 – 10 of Section 3.2.A.1 Facilities and Equipment. The applicant also referenced the single-use equipment and components provided in

Section 3.2.S.2.3 Control of Materials – Raw Materials. The information provided in Tables 7 – 10 included equipment description, identification number, location (room), process step, and if product contact. The filling system ((b) (4)) for filling, stoppering, and crimping vials was the only product contact equipment provided on the list. The critical equipment includes the following and the process step used:

- (b) (4)
- Freezers, (b) (4) – storage
 - Refrigerators, 2 to 8°C – storage
 - (b) (4)

Single-use components were provided in Table 5 of Section 3.2.S.2.3 Control of Materials – Raw Materials. In amendment STN 125858/0.21, Ultragenyx provided additional information on the single-use (disposable) equipment and components. The applicant provided the material(s) of construction and indicated whether the components are received clean, sanitized, and/or sterile. (b) (4) components are received as sterile, and (b) (4) components (b) (4) used during the (b) (4) step to manufacture DS are received clean. Of these (b) (4) components, the (b) (4) is additionally cleaned using the (b) (4) and the (b) (4) used for (b) (4) undergo a (b) (4) as defined in the batch record.

Equipment Qualification

Information on equipment qualification and cleaning was provided in Appendix 3 of Section 3.2.A.1 Facilities and Equipment. This memo summarizes the qualification results of the major equipment used to manufacture GENGLYCOS.

(b) (4)



(b) (4)



29 pages have been determined to be not releasable: (b)(4)

3.2.R REGIONAL INFORMATION

3.2 Post-Approval Change Management Protocol for DP (b) (4)

Ultragenyx submitted a post-approval change management protocol (PACMP) to (b) (4) of GENGLYCOS DP (b) (4) (b) (4) as proposed in the BLA to (b) (4). Based on a risk assessment, Ultragenyx concluded that there is no change to the manufacturing process systems/equipment, process single-use assemblies/consumables, process and analytical control strategy, or routine sampling/testing. The risk assessment included the following elements, with corresponding supporting information for the proposed (b) (4).

Ultragenyx stated that the DP lots manufactured at the proposed (b) (4) will be tested in accordance with the lot release specifications provided in Module 3.2.P.5.1 – Specifications and will be placed on long-term stability and tested in accordance with the protocol provided in Module 3.2.P.8.2 – Post-Approval Stability Protocol and Stability Commitment.

In amendment STN 125858/0.21, Ultragenyx stated that the (b) (4) (b) (4)
(b) (4) (b) (4) (b) (4) (b) (4). In amendment STN 125858/0.26,
Ultragenyx clarified that, similar to the routine manufacturing process described in the
BLA, (b) (4) (b) (4) (b) (4) consisting of (b) (4) (b) (4) (b) (4) (b) (4)
(b) (4). The applicant stated that the (b) (4)

Ultragenyx proposed to submit data of the executed PACMP as a CBE-30. In amendment STN 125858/0.48, Ultragenyx agreed with CBER's determination that the results of the PACMP should be submitted as a Prior Approval Supplement, and that the applicant may request an expedited review if there is an urgency for (b) (4)

Reviewer's comment: The information provided appears acceptable. There are no changes to the manufacturing process steps and equipment. The information on the filter validation appear acceptable to support the manufacture of a (b) (4) DP. The proposed reporting category of a Prior Approval Supplement appears acceptable.