

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: BLA STN 125858/0

From: Jing Lin, Ph.D., RAC
Laboratory of Biochemistry, Virology, and Immunochemistry (LBVI)
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

Through: Muhammad Shahabuddin, Ph.D.
Lab Chief, LBVI/DBSQC/OCBQ/CBER

Maryna Eichelberger, Ph.D.
Division Director, DBSQC/OCBQ/CBER

Product: GENGLYCOS (pariglasgene breca-parvovec)

Applicant: Ultragenyx Pharmaceuticals, Inc.

Subject: Review of analytical method, Capsid Identity by (b) (4), used for lot release of GENGLYCOS (b) (4) drug product

Recommendation: Approval

Summary:

Ultragenyx Pharmaceuticals, Inc. (Ultragenyx) submitted an original Biologics License Application (BLA) STN 125858/0 on December 23, 2025, for GENGLYCOS. The following analytical method used for lot release of GENGLYCOS (b) (4) drug product (DP) was reviewed:

1. Capsid Identity by (b) (4).

Conclusion:

The Capsid Identity by (b) (4) method was described in sufficient detail and validated for its intended use. The data provided demonstrated that the method is suitable for GENGLYCOS (b) (4) DP lot release testing.

Documents Reviewed:

Information in sections of the original submission that describe control of (b) (4) DP (3.2.S.4 and 3.2.P.5, respectively), including descriptions of (b) (4) DP specifications, analytical procedures of (b) (4) DP and validation of analytical procedures were reviewed. In addition, response to Information Request (IR) received on March 5, 2026, in Amendment 125823/0.9 was also reviewed.

Background:

GENGLYCOS (pariglasgene brecaparvovec, DTX401, AAV8G6PC, AAV8GSDIa) is a non-replicating, recombinant adeno-associated virus (rAAV) serotype 8 viral vector encoding a codon-optimized human glucose-6-phosphatase- α (hG6PCco) gene, also referred to as AAV8G6Pase. GENGLYCOS is intended for the treatment of Glycogen Storage Disease Type Ia (GSDIa), a rare, serious, and potentially life-threatening disease due to an inborn error of carbohydrate metabolism caused by pathogenic biallelic variants of the G6PC gene encoding the catalytic enzyme, glucose-6-phosphatase (G6Pase). Patients with GSDIa have deficient G6Pase enzyme and therefore have minimal ability to release glucose from stored glycogen or to generate glucose de novo, putting them at risk for severe hypoglycemia during periods of fasting between meals and during the night. By delivering a functional copy of the G6PC gene to hepatocytes, GENGLYCOS is designed to restore the production of normally functioning G6Pase in the liver. GENGLYCOS has received multiple FDA designations, including Orphan Drug, Fast Track, Regenerative Medicine Advanced Therapy (RMAT), and Rare Pediatric Disease.

AAV is a small, non-pathogenic, replication-deficient virus characterized by a single-stranded DNA (ssDNA) genome encapsulated within an icosahedral protein capsid shell. To date, 13 naturally occurring AAV serotypes have been identified, each characterized by a distinct capsid amino acid sequence that confers serotype specific tissue tropism and receptor binding properties. Among these, seven serotypes, AAV1, AAV2, AAV3, AAV5, AAV6, AAV8, and AAV9, represent the most studied and clinically relevant AAV serotypes widely used in gene therapy research and development.

(b) (4)



GENGLYCOS is manufactured at Ultragenyx Pharmaceutical Inc.'s Gene Therapy Manufacturing Facility (GTMF) in Bedford, Massachusetts, a dedicated facility that produces both AAV8- and AAV9-based gene therapy products, making specific and robust serotype identity testing an essential component of the quality control strategy for GENGLYCOS (b) (4) DP.

The manufacturing process of GENGLYCOS DS involves (b) (4)



(b) (4)

The manufacturing process of GENGLYCOS DP consists of (b) (4) aseptic filling and visual inspection. The GENGLYCOS DP is a clear, colorless suspension with a target concentration of 3×10^{13} GC/mL in formulation buffer (20 mM Tris, 200 mM NaCl, (b) (4) MgCl₂, 0.01% (w/v) Poloxamer 188, pH (b) (4)). The sterile filtered DP is filled into vials to achieve target fill volume of (b) (4) mL and store at $\leq -60^{\circ}\text{C}$ until distribution. DP is thawed at room temperature and then aseptically diluted in sterile saline for intravenous (IV) infusion. The recommended dose of GENGLYCOS is 1.0×10^{13} GC/kg body weight, administered as a single IV infusion. Multiple vials of GENGLYCOS DP are used for each dose based on the product's concentration and subject's weight.

Review:

1. Capsid Identity by (b) (4)

Introduction

(b) (4)

Method

(b) (4)

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

(b) (4)



Conclusion

The method is well described and validated. The data generated within this validation demonstrate that all acceptance criteria were met for all evaluated parameters. The test method is therefore suitable for its intended purpose of identifying AAV8 capsid for lot release of GENGLYCO (b) (4) DP.