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CBER CMC BLA Review Memorandum

BLA STN 125874

**lunsotogene parvec-cwha
OTARMENI**

Reviewers

**Bo Liang, PhD, OTP/OGT/DGT1/GTB2
Mark Verdecia, PhD, OTP/OGT/DGT1/GTB1
Zhili Xu, PhD, OTP/OGT/DGT2/GTIB
Stella Lee, PhD, OTP/OGT/DGT2/GTB4
Zachary Mandell, PhD, OTP/OGT/DGT1/GTB3
Tania Rosen-Cheriyen, PhD, OTP/OGT/DGT1/GTB2
Meghna Thakur, PhD, OTP/OGT/DGT1/GTB3
Bizunesh Abere, PhD, OTP/OGT/DGT1/GTB1**

1. **BLA#:** STN 125874

2. **APPLICANT NAME AND LICENSE NUMBER**

Regeneron Pharmaceuticals, Inc.

License number: 1760

3. **PRODUCT NAME/PRODUCT TYPE**

- a. Non-proprietary/Proper/USAN: lunsotogene parvec-cwha
- b. Proprietary Name: OTARMENI
- c. Company codename: DB-OTO
- d. UNII Code: P6ZNU67HPU
- e. NDC Code (vial): 61755-062-00
NDC Code (barrier bag): 61755-062-99
NDC Code (carton): 61755-062-01
NDC Code (administration kit): 61755-062-11
- f. Chemical Abstract Service Name (registry number): 2907748-12-1

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

- a. Pharmacological category: Adeno-associated virus vector-based gene therapy
- b. Dosage form: Suspension for injection
- c. Strength/Potency: 3.0×10^{13} vector genome (vg)/mL
- d. Route of administration: Intracochlear injection
- e. Indication(s): For the treatment of pediatric and adult patients with severe-to-profound and profound sensorineural hearing loss (any frequency >90 dB HL) associated with molecularly confirmed biallelic variants in the *OTOF* gene, preserved outer hair cell function, and no prior cochlear implant in the same ear.

5. **MAJOR MILESTONES**

- a. Received: December 23, 2025
- b. Filed: February 21, 2026
- c. Mid-cycle communication: Not applicable for CNPV.
- d. Advisory Committee meeting: AC meeting was not held.
- e. Late-cycle communication: Not applicable for CNPV.
- f. CNPV Action date: April 22, 2026

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Bo Liang, PhD, OTP/OGT/DGT1/GTB2	Labeling, environmental assessment

Mark Verdecia, PhD, OTP/OGT/DGT1/GTB1	Analytical methods (vector genome titer and potency), validation of analytical methods, reference standard for potency, Drug Product batch analysis, Drug Product specification and justification of specification, and lot release protocol
Zhili Xu, PhD OTP/OGT/DGT2/GTIB	Analytical methods (b) (4) in-process (b) (4) validation of analytical methods, reference standards (not for potency), Drug Substance batch analysis, Drug Substance specification and justification of specification
Stella Lee, PhD, OTP/OGT/DGT2/GTB4	DS manufacturing process, process development, process characterization, and process validation
Zachary Mandell, PhD, OTP/OGT/DGT1/GTB3	DP manufacturing process, process development, process characterization, process validation, and shipping
Tania Rosen-Cheriyen, PhD, OTP/OGT/DGT1/GTB2	Comparability and leachables/extractables
Meghna Thakur, PhD, OTP/OGT/DGT1/GTB3	Drug Substance and Drug Product stability, in-use stability, device compatibility, clinical assays
Bizunesh Abere, PhD, OTP/OGT/DGT1/GTB1	Raw materials including (b) (4) reagents, components, etc., CCS, and adventitious agent risk (3.2.A.2 including viral clearance)
Yongwook Choi, PhD, CBER/OTP/OCTHT/DCT1	(b) (4) assay for (b) (4) in Drug Substance
Lauren Kokai, PhD, CBER/OTP/OCTHT/DCT2/TEB2	Product administration devices including the Vygon Premicath Catheter, syringes, syringe caps, needles, and syringe pumps
Johnny Lam, PhD, CBER/OTP/PSPS	Product administration devices including the Vygon Premicath Catheter, syringes, syringe caps, needles, and syringe pumps

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No ⁻¹)

Jillian Socea, Ph.D. and Jake Lindstrom, Ph.D. (CDRH/OPEQ/OHT3/DHT3C)	Infusion Pump - General Labeling Strategy, Essential Performance Requirements, Risk Analysis	Yes ^a
Sunny Park (CDRH/OPEQ/OHT1/DHTIB)	Device Sterility (Catheter and Administration Kit)	Yes
Joyce Lin (CDRH/OPEQ/OHT1/DHTIB)	Catheter Engineering - Bridging Study for Intracochlear Use	Yes
Hanniebey D. Wiyor, Ph.D. (CDRH/OPEQ/OHT3/DHT3C/TH T3C4)	Human Factors - URRR and Training Program	Yes (with comments/deficiencies addressed)

^a The CDRH/OHT3 reviewers (Socea and Lindstrom) recommended approval with postmarketing commitments and specific labeling modifications. CMC Device review team implemented the USPI labeling modifications in consultation with the Clinical and Labeling review team. The PMC commitment was not requested from the Applicant.

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
11/6/2025	125827/0	1 st CMC wave of pre-submission (rolling submission #1)
11/10/2025	125827/0.1	Response to 11/6/2025 IR #1
11/17/2025	125827/0.2	Response to 11/13/2025 IR #2, Response to 11/14/2025 IR #3
11/20/2025	125872/0.5	Response to 11/17/2025 IR #5 (DBSQC sterility testing)
11/25/2025	125827/0.6	2 nd CMC wave of pre-submission (rolling submission #3)
11/25/2025	125874/0.7	Response to 11/21/2025 IR #7
12/3/2025	125874/0.9	Response to 12/1/2025 IR #8
12/4/2025	125874/0.10	Response to 12/2/2025 IR #9
12/11/2025	125874/0.13	Response to 12/9/2025 IR #14
12/15/2025	125874/0.16	Response to 12/11/2025 IR #15
12/17/2025	125874/0.17	Response to CBER filing checklists
12/19/2026	125874/0.19	3 rd CMC wave of pre-submission (rolling submission #5)
12/22/2025	125874/0.20	Response to 12/18/2025 IR #18
12/23/2025	125874/0.23	Response to 12/19/2025 IRs #21 and 23
12/29/2025	125874/0.24	Response to 12/22/2025 IR #24
1/9/2026	125874/0.29	Response to 1/7/2026 IR #27
1/16/2026	125874/0.32	Response to 1/14/2026 IR #31
1/23/2026	125874/0.37	Response to 1/16/2026 IR #35
1/23/2026	125874/0.38	Response to 1/22/2026 IR #38
1/27/2026	125874/0.42	Response to 1/23/2026 IR #41
1/28/2026	125874/0.43	Response to 1/26/2026 IR #43
1/30/2026	125874/0.46	Response to 1/28/2026 IR #46
2/3/2026	125874/0.50	Response to 1/30/2026 IR #49

2/5/2026	125874/0.53	Response to 2/3/2026 IR #52
2/9/2026	125874/0.56	Response to 2/5/2026 IR #55
2/13/2026	125874/0.58	Response to 2/11/2026 IR #59
2/17/2026	125874/0.62	Response to 2/13/2026 IR #61
2/18/2026	125874/0.64	Response to 2/13/2026 IR #62
2/19/2026	125874/0.65	Response to 2/17/2026 IR #64
2/23/2026	125874/0.70	Response to 2/19/2026 IR #68
2/24/2026	125874/0.71	Response to 2/20/2026 IR #69
2/25/2026	125874/0.72	Response to 2/23/2026 IR #70
3/2/2026	125874/0.75	Response to 2/26/2026 IR #72
3/5/2026	125874/0.77	Response to 3/3/2026 IR #75
3/10/2026	125874/0.82	Response to 3/6/2026 IR #79
3/12/2026	125874/0.86	Response to 3/10/2026 IR #82
3/13/2026	125874/0.87	Response to 3/6/2026 IRs #62 and 43
3/18/2026	125874/0.89	Response to 3/16/2026 IR #84
3/18/2026	125874/0.90	Response to 3/10/2026 IR #70 (follow-up)
3/23/2026	125874/0.92	Response to 3/19/2026 IR #86
3/25/2026	125874/0.93	Response to 3/23/2026 IR #87
3/26/2026	125874/0.95	Response to 3/24/2026 IR #88
3/31/2026	125874/0.97	Response to 3/20/2026 PMRs/PMCs
4/1/2026	125874/0.100	Response to 4/1/2026 IR #91
4/7/2026	125874/0.103	Response to 4/6/2026 IR #92

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

DMF (b) (4)	(b) (4)	(b) (4)	Yes	(b) (4) information is provided as a component of the (b) (4) and reviewed by OGT. (b) (4) information was added to DMF (b) (4) in Amendment 58.
BB-MF (b) (4)	(b) (4)	Stopper	Yes	No DMF review is required. Information pertinent to container closure is provided in the BLA.
BB-MF (b) (4)	(b) (4)	(b) (4) vials	Yes	Information on sterile supply of (b) (4) vials. No DMF review is required. Information pertinent to container closure is provided in the BLA.
BB-MF (b) (4)	(b) (4)	Stopper	Yes	No DMF review is required. Information pertinent to container closure is provided in the BLA.
510K K941562	Becton, Dickenson and Company	BD 1 mL Luer-Lok Syringe	Yes	This is a component of the administration kit, which is reviewed by OTP device team and CDRH consults.
510K K980987	Becton, Dickenson and Company	BD 3 mL Luer-Lok Syringe	Yes	This is a component of the administration kit, which is reviewed by OTP device team and CDRH consults.
510K K021475	Becton, Dickenson and Company	BD Needle 21G 1/2IN	Yes	This is a component of the administration kit, which is reviewed by OTP device team and CDRH consults.
510K Exempt	Becton, Dickenson and Company	BD Syringe Caps	Yes	This is a component of the administration kit, which is reviewed by OTP device team and CDRH consults.

510K K954302 and K041468	Vygon Corporation	Primecath (b) (4)	Yes	This is a component of the administration kit, which is reviewed by OTP device team and CDRH consults.
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10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Based on the review of the information provided in the initial submission and the subsequent amendments received throughout the review period, the CMC review team concludes that the manufacturing and controls for lunstogene parvec-cwha (OTARMENI) are capable of yielding a product with consistent quality attributes deemed acceptable for commercial manufacturing under the BLA.

Description of the Product

OTARMENI contains dual adeno-associated virus serotype 1 (AAV1) vectors that recombine after administration. The recombined vector genome utilizes an engineered hair cell-specific promoter derived from regulatory elements of myosin 15 (*Myo15*) to drive complementary DNA (*cDNA*) expression of human *OTOF* transcript variant 5 encoding isoform e of the otoferlin protein (OTOF). The drug product is supplied as a sterile, frozen suspension containing two vectors, i.e., DB-OTO-3 and DB-OTO-5, (b) (4). The formulation is a phosphate buffer containing 10 mM sodium phosphate, 180 mM sodium chloride, 5% sucrose (w/v) and 0.001% poloxamer. The drug product is supplied in a 2 mL (b) (4) vial, contains no preservative, and must be stored frozen at -80 °C. After product thaw, each vial contains an extractable volume of 0.63 mL, for a single dose for one ear.

Regulatory Flexibilities

1. Acceptance of the commercial lot release acceptance criteria based on data from a small number of lots, considering the rare disease indication. This regulatory flexibility is exercised with adequate assurance of product safety and efficacy and the Applicant's commitment to re-assess all lot release acceptance criteria based on post-approval manufacturing experience. This approach aligns with FDA's January 11, 2026 announcement "Flexible Requirements for Cell and Gene Therapies to Advance Innovation".

2. Acceptance of a drug product shelf life longer than the time supported by the real-time stability data. Regulatory flexibility is exercised to allow conservative extrapolation beyond real-time stability data due to relevant supportive stability data from an engineering lot and clinical lots of different concentrations. This flexibility to set the shelf life for biologics aligns with FDA's draft Q1 guidance "Stability Testing of Drug Substances and Drug Products" dated June 2025.
3. Acceptance of drug product labeling and secondary packaging validation studies being conducted using (b) (4) vials, not the OTARMENI drug product, because the (b) (4) study can help to ensure that the product quality will be maintained during labeling and secondary packaging.
4. Acceptance of setting the (b) (4) acceptance limits in the drug product manufacturing process based on testing of a subset of quality attributes without potency. This regulatory flexibility is justified by temperature data, the current (b) (4) acceptance limits, stability data, our assessment of the potential risk to product potency, and the Applicant's commitment to conduct post-approval studies to re-assess the (b) (4) limits with a complete set of quality attributes, including potency.
5. Acceptance of validation of the (b) (4) assay for (b) (4) (b) (4) in drug substance without assessment of robustness. This flexibility is justified by the adequate assay performance in terms of accuracy, precision, linearity, specificity, and sensitivity for potency assurance when used in conjunction with the potency assay. The Applicant commits to assessing assay robustness in a post-approval study.
6. Acceptance of product potency assurance by measuring (b) (4) and examining the (b) (4) in the product. This flexibility is exercised because of the difficulty in developing a bioassay that directly measures the biological activity of otoferlin.

Manufacturing Summary

The two AAV1 vectors in OTARMENI are produced as separate drug substances using the same manufacturing process. They are subsequently (b) (4) to produce OTARMENI during the drug product manufacturing process. Each vector is produced by transient transfection of (b) (4) (b) (4) human embryonic kidney 293 cells (HEK 293) (b) (4) bioreactor. (b) (4)

(b) (4)

filtration. (b) (4) affinity chromatography, anion exchange chromatography, and (b) (4) filtration methods. (b) (4)

DB-OTO-3 or DB-OTO-5, which is stored (b) (4)

To manufacture OTARMENI drug product, (b) (4)

of 3.0×10^{13} vector genome/mL. (b) (4) filter sterilized and filled into 2 mL (b) (4) vials. The finished drug product vials are 100% visually inspected and frozen at -80°C . The frozen vials are shipped to a labeling and secondary packaging facility to complete the vial labeling and packaging prior to commercial distribution of OTARMENI drug product.

Manufacturing Control Strategy

The manufacturing process is controlled by (1) raw material and reagent qualification programs, (2) in-process monitoring and in-process control testing, (3) validation of the manufacturing process, and (4) validation of lot release and in-process test methods.

The manufacturer accepts raw materials based on in-coming acceptance tests and verification of raw material specifications. Suppliers are qualified and audited according to established supplier qualification programs. Raw materials derived from animals and humans are appropriately qualified to ensure the absence of microbial or viral contamination. In addition, methods including (b) (4)

are employed to remove potential microbial or vial contaminants.

The manufacturing process control strategy includes setting acceptable limits for process parameters and acceptance criteria for in-process and lot release tests to ensure product safety, identity, strength, purity, and potency. Lot release tests include quantitative assays for vector genome concentration, (b) (4), process- and product-related impurities, and potency. Potency is assured by quantification of the (b) (4)

All in-process and lot release assays are validated.

The Applicant performed process characterization studies using an innovative small-scale model that determined the critical process parameters (CPPs) for process

qualification and validation studies. Issues discovered with the model were resolved during interactive review.

Process Validation

Process validation included production of (b) (4) process performance qualification (PPQ) (b) (4) lots and (b) (4) PPQ drug product lots at the (b) (4) facility. Criticality of process parameters and quality attributes was determined by failure modes and effects analysis (FMEA) based on prior knowledge, manufacturing experience, and process understanding from development studies using small-scale models. The operation ranges for process parameters and quality attributes were established by process development and characterization studies.

Process parameters and quality attributes were monitored in each PPQ run. Selected process parameters were tightened to improve process control based on successful commercial-scale manufacturing experience. All (b) (4) PPQ runs and (b) (4) out of (b) (4) drug product PPQ runs were successful. (b) (4) drug product PPQ run failed due to vial crimp issue. The root cause has been identified. Corrective action and preventive action have been implemented and found effective. Sanitary processing capability was demonstrated by consistently meeting in-process (b) (4) acceptance criteria. Additional validation studies were also performed, including aseptic processing simulation, shipping validation, drug product labeling, and secondary packaging validation. Process consistency during routine commercial manufacturing will continue to be monitored and assessed post-approval according to an established continued process verification (CPV) plan.

Impurity Profile

Product-related and process-related impurities are monitored using in-process tests or lot release tests with acceptable limits. Product-related impurities include (b) (4)

Process related impurities, including (b) (4)

are monitored as lot release tests. Other potential process-related impurities – including the (b) (4)

– have demonstrated consistent and efficient clearance or are expected to be cleared based on clearance data for other residuals; therefore, these impurities are not monitored in the commercial manufacturing process.

Stability

(b) (4) drug product must be stored frozen at -80°C for long-term storage. The stability data supports a (b) (4) shelf life for the drug substance.

Drug product shelf life is set at 18 months based on extrapolation from 12 months of real-time stability data. OTARMENI is light sensitive; therefore, extended exposure to light should be limited during thawing, storage, and handling in clinic prior to administration.

Comparability

All 24 patients in clinical study DB-OTO-001 received product manufactured with the clinical manufacturing process. Several major differences are introduced in the commercial manufacturing process, including a (b) (4)

Compared to the clinical manufacturing process, the commercial manufacturing process (b) (4). The clinical and commercial manufacturing processes produce products with comparable attributes, including statistically equivalent (b) (4). Therefore, the commercial manufacturing process is comparable to the clinical manufacturing process.

Manufacturing Risk

The risk of product contamination with microbial and adventitious viral contaminants is minimized by i) ensuring adequate control of raw materials, especially those of biological origin used in generation of (b) (4) (b) (4), and product manufacturing; ii) testing of (b) (4) (b) (4) for microbials and adventitious viral agents; and iii) demonstrating robust viral clearance using (b) (4).

The risk of extractables and leachables that could originate from the product manufacturing process, container closure systems, and the administration device was analyzed. The analytical studies and the associated toxicology assessment were sufficient to demonstrate that the risk is negligible. In addition, a PMC is implemented to verify that (b) (4) from container closure system following a longer duration of storage are within the safety limits.

The risk of drug product bearing defects, e.g., with the damaged container closure system or flawed appearance, is controlled by a robust 100% visual inspection process and lot release testing. Vials with any defects, e.g., containing visible particulates or bearing physical damage, are rejected and investigated. The number and category of visual inspection rejects will be reported in the lot release protocol and reviewed by the FDA prior to commercial distribution.

Combination Product

OTARMENI and the Administration Kit are a cross-labeled combination product. The Administration Kit contains a 21-gauge needle (K021475), 1 mL syringe (K162081), 3 mL syringe (K182589), syringe cap (510(k) exempt), and Vygon Premicath® 1Fr/28G catheter (K954302/K041468). The Vygon Premicath® catheter, originally cleared for intravenous use, was bridged for intracochlear delivery through design verification testing reviewed and approved by CDRH/OHT1. The Administration Kit is packaged separately from the drug product vial due to different storage requirements and is labeled "USE ONLY WITH OTARMENI." Both packages bear National Drug Code numbers with the same labeler and product codes and include the United States Prescribing Information, which contains device-related instructions for use. OTARMENI administration also requires a syringe infusion pump, which is not included in the Administration Kit. The USPI employs a general labeling approach specifying required pump performance parameters (0.9 mL/hour flow rate, capability to infuse volumes as small as 0.2 mL, compatibility with 1 mL or 3 mL syringes) rather than designating specific pump models. This general labeling strategy was reviewed and approved by CDRH/OHT3.

B. RECOMMENDATION

I. APPROVAL

This Biological License Application (BLA) provides an adequate description of the manufacturing process and characterization of the drug product lunstogene parvec-cwha. The CMC review team has concluded that the manufacturing process and associated test methods and control measures can yield a product with consistent quality characteristics. This information, along with Post-Marketing Commitments (PMCs) from Regeneron Pharmaceuticals, Inc., satisfies the CMC requirements for biological product licensure per the provision of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products.

Post-Marketing Commitments (PMCs)

1. Regeneron commits to assessing (b) (4) from DB-OTO Drug Product (DP), stored at $\leq -80^{\circ}\text{C}$ for (b) (4) months, using adequately qualified assays. A final study report will be submitted in a "Postmarketing Study Commitment – DP (b) (4) Final Study Report" by December 31, 2027.

Final Study Report Submission Date: December 31, 2027

2. Regeneron commits to assessing the robustness of the (b) (4) lot release test for the (b) (4). A final study report will be submitted as a "Postmarketing Study Commitment – (b) (4) Robustness Assessment Final Study Report" by September 30, 2026.

Final Study Report Submission Date: September 30, 2026

3. Regeneron commits to conducting a study to re-evaluate the maximum (b) (4) [REDACTED] for DB-OTO Drug Product (DP) and Labeled Drug Product (LDP) manufacturing processes according to the study protocol outlined in VV-IOPS-190989 V:2.0 (Evaluation of the Maximum (b) (4) [REDACTED] for DB-OTO DP and LDP Manufacturing Processes). Regeneron will submit the study results as a "Postmarketing Study Commitment – (b) (4) [REDACTED] Final Study Report" by November 30, 2026.

Final Study Report Submission Date: November 30, 2026

4. Regeneron commits to implementing a drug product-specific assay control for the relative potency assay. The final study report will establish acceptance criteria for the assay control as part of potency assay suitability criteria and include updated standard operating procedure (SOP) that implements the assay control along with finalized system suitability criteria.

The study results, analysis of the data to support the assay control suitability criteria, and the updated relative potency assay SOP will be submitted as a "Postmarketing Study Commitment – Assay Control for Relative Potency Final Study Report" by May 31, 2026.

Final Study Report Submission Date: May 31, 2026

5. Regeneron commits to reassessing the acceptance criteria for release testing of lunsotogene parvec-cwha drug substance and drug product based on manufacturing experience and revising the acceptance criteria, if appropriate. A final acceptance criteria reassessment report will be submitted as a "Postmarketing Study Commitment – Re-assessment of Lot Release Acceptance Criteria Final Study Report" after CBER lot release of (b) (4) [REDACTED] drug product batches including PPQ lot(s) that are released for commercial distribution. If (b) (4) [REDACTED] commercial lots have not been manufactured by December 31, 2027, Regeneron will provide an updated timeline for reassessing the lot release acceptance criteria using (b) (4) [REDACTED] commercial lot data.

Final Study Report Submission Date: December 31, 2027

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Bo Liang, Staff Fellow; OTP/OGT/DGT1/GTB2	Concur	

Mark Verdecia, Biological Reviewer; OTP/OGT/DGT1/GTB1	Concur	
Zhili Xu, Biologist; OTP/OGT/DGT2/GTIB	Concur	
Stella Lee, Biologist; OTP/OGT/DGT2/GTB4	Concur	
Zachary Mandell, Staff Fellow; OTP/OGT/DGT1/GTB3	Concur	
Tania Rosen-Cheriyen, Staff Fellow; OTP/OGT/DGT1/GTB2	Concur	
Meghna Thakur, Staff Fellow; OTP/OGT/DGT1/GTB3	Concur	
Bizunesh Abere, Staff Fellow; OTP/OGT/DGT1/GTB1	Concur	
Anurag Sharma, Branch Chief; OTP/OGT/DGT1/GTB2	Concur	
Andrew Byrnes, Division Director; OTP/OGT/DGT1	Concur	
Denise Gavin, Office Director; OTP/OGT	Concur	

Review of CTD

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Module 3

3.2.S DRUG SUBSTANCE

(Reviewed by SL)

3.2.S.1.1 Nomenclature

Table 1 lists the nomenclature.

Table 1: Nomenclature (provided by Regeneron).

Type	Nomenclature
International Nonproprietary Name (INN)	lunsotogene parvec
United States Adopted Name (USAN)	lunsotogene parvec
Company or laboratory code for the drug substance	(b) (4)
Company or laboratory code for the drug product	DB-OTO
Chemical Abstracts Service (CAS) registry number	2907748-12-1

3.2.S.1.2 Structure

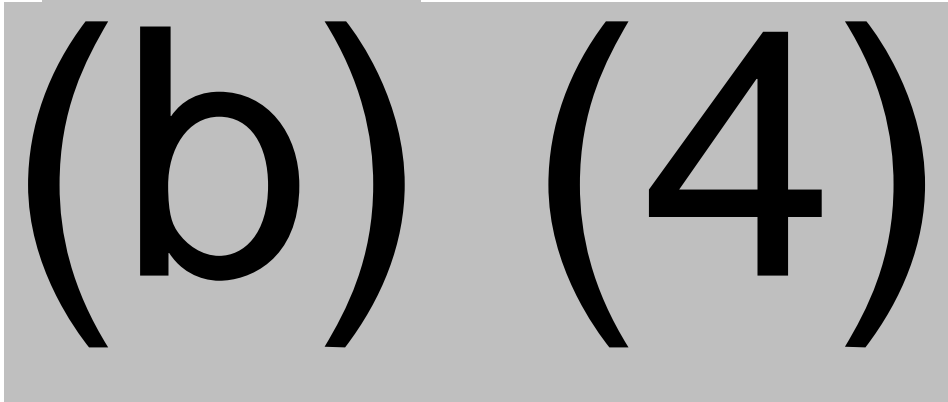


Lunsotogene parvec is a dual adeno-associated virus serotype 1 (AAV1)-based gene therapy product comprising two drug substances (DSs), (b) (4) to express human otoferlin (OTOF) protein (Figure 1). (b) (4)

Figure 1: DB-OTO is composed of two AAV1 vectors (provided by Regeneron).




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

(b) (4)



(b) (4)



3.2.P DRUG PRODUCT

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

(Reviewed by ZM)

The Drug Product (DP) is a sterile, frozen liquid suspension in an aqueous buffered solution (pH 7.3) containing (b) (4) each of DB-OTO-3 and DB-OTO-5, and excipients outlined in Table 62. DP is filled into 2 mL (b) (4) vials with elastomeric stoppers and aluminum seal caps, with a minimum fill volume of (b) (4)

(0.63 mL extractable (b) (4)). The solution is clear to slightly opalescent, colorless, and essentially free from visible particulates.. *Reviewer's Comments:* (b) (4)

Table 60: Nominal Composition of Drug Product Formulation (Provided by Regeneron).

Component	Function	Quality Standard	Drug Product Nominal Composition	Content per Vial ^a
DB-OTO-3	Active ingredient	Specification	(b) (4)	(b) (4)
DB-OTO-5			(b) (4)	(b) (4)
Sodium Phosphate, (b) (4)	Buffer	(b) (4)	(b) (4)	(b) (4)
(b) (4)		(b) (4)	(b) (4)	(b) (4)
Sodium Chloride	Stabilizer	(b) (4)	180 mM	6.62 mg
Sucrose		(b) (4)	5% (w/v)	31.5 mg
Poloxamer 188		(b) (4)	0.001% (w/v)	0.0063 mg
Water for Injection	Solvent	(b) (4)	QS	QS

^a Calculated based on the minimum extractable volume per vial.

(b) (4); QS, quantity sufficient; (b) (4); w/v, weight by volume

3.2.P.2 Pharmaceutical Development

(Reviewed by ZM)

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

(b) (4)

(b) (4)

(b) (4)

3.2.P.2.1.2 Excipients

A summary of each excipient and its function is shown in Table 60.

Reviewer's Comments: *These are standard excipients for a recombinant AAV product and are known to be compatible with the AAV1 capsid based on precedent from approved AAV1 products. The DB-OTO formulation closely mirrors (b) (4)*

DB-OTO uses sodium phosphate salts, 180 mM sodium chloride, and 5% w/v sucrose, which is consistent with (b) (4) and within typical ranges for other approved rAAV products including (b) (4) DB-OTO includes 0.001% poloxamer 188, which (b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The nonclinical, clinical, and commercial DP lots used the same dosage form, formulation excipients, and container closure system. The only significant difference was the (b) (4) which evolved throughout the product life cycle.

The DP formulation was refined between the clinical and commercial stages. Specifically, the (b) (4)

final commercial concentration of 3.0×10^{13} vg/mL. This adjustment was supported by stability data confirming that the (b) (4) titer is sufficient to meet all requirements for the commercial product.

Reviewer's Comments: *The formulation robustness study described below confirmed that the (b) (4) 3.0×10^{13} vg/mL does not adversely affect the compatibility of the (b) (4).*

The sponsor conducted a formulation robustness study using (b) (4)

Reviewer's Comments: *The parameters of the formulation robustness study support the DP specification and several formulation-related CPPs.*

An ongoing stability study evaluates each formulation under long-term storage and potential excursions during manufacturing, storage, and handling. After preparation,

formulations were characterized for baseline pH and (b) (4) then subjected to: long-term storage at -80°C for 12 months (data available to 6 months); accelerated storage at (b) (4) for one month (completed); and (b) (4) freeze/thaw cycles (completed). Quality attributes assessed include: Physical Form/Condition, Clarity, Color, pH, (b) (4), Vector Genome Titer (b) (4)

(b) (4) Poloxamer 188 (b) (4), and Particulate Matter (b) (4)

Reviewer's Comments: A concern is the (b) (4) Poloxamer 188 range (0.001 (b) (4) w/v), and in particular the risk of (b) (4) risk at (b) (4) Poloxamer 188 concentrations. This is mitigated by: 1) The sponsor (b) (4) 2) Multiple (b) (4)

Formulation Robustness at (b) (4)

Despite this statistical finding, the sponsor determined that the practical impact was negligible, as the observed changes did not exceed the inherent variability of the assays. A summary of the DOE results is provided in eCTD 3.2.P.2.2.

Reviewer's Comments: Statistical significance at (b) (4) likely reflects minor formulation effects amplified by accelerated degradation, not analytical variability as the sponsor suggests. Analytical noise wouldn't produce significance under only one condition. While this reveals a flaw in the sponsor's interpretation, the minimal effect magnitude makes their conclusion irrelevant.

Formulation Robustness at Freeze and Thaw: The DP demonstrated robustness to freeze/thaw stress across the range of formulation compositions evaluated. As detailed in the DOE analysis presented in eCTD 3.2.P.2.2, none of the variations resulted in a practically significant impact on stability relative to the control formulation.

Formulation Robustness at -80 °C: The long-term stability study at -80°C is ongoing, with data currently available up to the 3-month time point. Preliminary results from these data indicate that variations in formulation composition have no practically significant impact on drug product (DP) stability compared to the control formulation.

Reviewer's Comments: The completed accelerated and freeze-thaw portions of the study, combined with the favorable preliminary data from the ongoing long-term (-80°C) study, provide sufficient evidence to support the sponsor's selected formulation parameters.

3.2.P.2.2.2 Overages

There are no overages included in the formulation.

3.2.P.2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties of DB-OTO are described in Section eCTD 3.2.S.1.3 (General Information).

3.2.P.2.3 Manufacturing Process Development

The sponsor made several manufacturing changes when switching from clinical to commercial DP production, notably (b) (4)

An overview of DP manufacturing process changes, including potential quality impacts and justifications, is in Table 62. Please refer to Section 3.2.S.2.6 for assessment of the comparability of DP manufacturing process changes.

Table 62: Overview of DP Manufacturing Processes Changes (Based on Information Provided by Regeneron)

(b) (4)

(b) (4)

3.2.P.2.3.1 DP process development studies

The design and operating parameters of the commercial DP manufacturing process was informed through a set of manufacturing process development studies DP manufacturing process parameters are defined based on process development studies and PPQ runs. The DP process development studies are described below.

(b) (4)

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

3.2.P.2.4 Container Closure System

(Reviewed by BA)

Please refer to information under Section 3.2.P.7 Container Closure System.

L/E

(Reviewed by TRC)

Note: Please refer to section 3.2.P.2.3.2 Leachables and Extractables for E&L assessment on (b) (4) DP, based on how the Applicant has organized their information in the BLA.

3.2.P.2.5 Microbiological Attributes

(Reviewed by BA)

The DB-OTO DP is a sterile suspension manufactured by aseptic processing for intracochlear infusion. The DP is supplied in a single-dose 2 mL vial with 0.63 mL of extractable volume of suspension and contains no antimicrobial preservatives. As part of aseptic processing, the DP is (b) (4)

(b) (4) aseptically filled in a controlled environment using processes that has been validated. Manufacturing product contact components are received pre-sterilized and ready-to-use or are (b) (4) sterilized prior to use at (b) (4). Materials used in the DP manufacturing process (e.g., excipients, components) are (b) (4) grade, and additional testing for (b) (4) or (b) (4) may be performed in accordance with manufacturing site procedures (please see Section 3.2.P.4.1 Specifications of the BLA) prior to release for use in manufacturing. As part of the release process, DP is tested for sterility and bacterial endotoxin. *Please See DMPQ memo for further details on the microbial containment strategy.*

Container closure integrity testing (CCIT) is performed by (b) (4)

This is acceptable.

3.2.P.2.6 Compatibility

(Reviewed by MT)

A compatibility study was performed to examine the compatibility of DB-OTO DP with the intracochlear (IC) dosing apparatus materials using administration components representative of those provided in the commercial administration kit. The IC administration components tested in the compatibility studies are listed in Table 65.

Table 65: Components used in IC compatibility studies (based on information provided by Regeneron)

Component	Description
Syringe pump	(b) (4)
Catheter	(b) (4) Vygon Premicath® peripherally inserted central catheter Gauge/Length - 1 Fr/28 G, 30 cm Manufacturer's Reference Number - 1261.306
Syringes	BD Luer-Lok™ syringe, Polycarbonate, 1mL, Manufacturer Ref # 309628 BD Luer-Lok™ syringe, Polypropylene, 3mL, Manufacturer Ref # 309657
Needle	21-gauge, 1.5-inch, stainless-steel, BD Precision Glide™ needle, 305167
Syringe Cap	BD Luer-Lok™ syringe tip cap, Polypropylene, 305819

For IC compatibility study (b) (4)

The sampling plan is provided in Table 66.

Table 66: Sampling Plan for IC Compatibility Studies (provided by Regeneron)

(b) (4)

The acceptance criteria of the quality attributes tested in the compatibility study are defined by DB-OTO specifications in place at the time of testing. The results of the study are summarized in Table 67.

Table 67: IC Compatibility Results of DB-OTO (based on information provided by Regeneron)

(b) (4)

(b) (4)

Reviewer's Comments:

- In Amendment 20 dated 12/22/2025 in response to IR # 18 dated 2/18/2025, Regeneron clarified that the (b) (4) lot numbers indicated in the comparability report (b) (4) were internally assigned for tracking stability samples within the study and (b) (4) originate from PPQ lot (b) (4) which is fully representative of the commercial manufacturing process. No development lots were included in the in-use compatibility study. In addition, Regeneron submitted the compatibility study protocol and compatibility study report to the BLA.
- DB-OTO-DP remained stable across all timepoints (t=0, syringe storage, and delivered samples) with no meaningful changes in quality attributes.
- Some variability was observed in (b) (4) measurements; however, all values remained within the pre-defined acceptance criteria. The (b) (4) exhibited fluctuations likely due to variability in the (b) (4) measurements; however, the values remained well below the upper specification limit of (b) (4) indicating that product quality was maintained. Additionally, since the potency by (b) (4) remains stable and inherently measures (b) (4) data are not critical for demonstrating product quality.
- Both 1 mL polycarbonate and 3 mL polypropylene syringes are compatible with DB-OTO DP for intracochlear administration. Additionally, the Vygon Premicath® polyurethane catheter and both tested syringe pumps (b) (4) are compatible with DB-OTO DP when delivered at 0.9 mL/hour over 16 minutes.

- The compatibility studies support the in-use period and storage condition stated on the labeling.

Overall Reviewer's Assessment of Section 3.2.P.2:

- During the review process, several information requests were issued to clarify aspects of the pharmaceutical development program, including (b) (4) parameters, (b) (4) compatibility, and (b) (4) model justifications. These issues were adequately resolved through the information request process, with details of the questions and resolutions documented throughout this review memo and in the corresponding BLA amendments. The information provided in Section 3.2.P.2 is acceptable with several post-marketing commitment.
- The sponsors proposed (b) (4) were not sufficiently supported. To address this, we issued a series of IRs (IR #38 on 1/22/26, IR #46 on 1/28/26, IR #52 on 2/3/26, IR #59 on 2/11/26, and IR #70 on 2/23/26). These culminated in the sponsor's agreement to conduct post-marketing study under a PMC. The sponsor provided a study protocol to conduct under the PMC in Amendment 72. This study protocol was reviewed and was found to be acceptable.
- Overall (b) (4) assessment: Considering the (b) (4) analysis, methods and data collected so far, the PT reviewer's lack of concerns with the TRA, and the Applicant's PMC to evaluate real time (b) (4) content with DP stability samples stored over (b) (4) months, there are no further concerns with the (b) (4) evaluation.
- There are no further deficiencies that would result in a CRL.
- The device compatibility data is adequate to demonstrate the stability of DP when held in capped syringes for up to (b) (4) supporting the labeling instructions that DP should be administered within 4 hours of puncturing the vial.
- The compatibility studies support labeling instructions that the unpunctured thawed vials may be stored in the refrigerator for up to 24 h or at room temperature for up to 8 h; however, the vial should not be refrozen once thawed.

3.2.P.3 Manufacture

(Reviewed by ZM)

3.2.P.3.1 Manufacturer(s)

(Reviewed by ZM)

Table 68: DP manufacturer information (provided by Regeneron)

Site Name	Address	FEI Number	Specific Manufacturing Responsibilities or Type of Testing
(b) (4)	(b) (4)	(b) (4)	Manufacture and storage of DP. Testing of Appearance, pH, (b) (4), Bioburden, Endotoxin, (b) (4), Vector Genome Titer, (b) (4)

			(b) (4) Poloxamer 188
Regeneron Pharmaceuticals, Inc. ^b	(b) (4)		Release for distribution Testing of Extractable Volume, (b) (4)
(b) (4)			
(b) (4)			Testing of Container Closure Integrity
(b) (4)			Testing of Particulate Matter
(b) (4)			Testing of sterility
(b) (4)			Testing of Potency by (b) (4)
(b) (4)			Storage of (b) (4) DP
(b) (4)			Secondary packaging and labeling of DP

a Responsible for critical in-process, release and stability testing.

b Responsible for release and stability testing.

c Responsible for release testing only.

DP, drug product; FEI, FDA Establishment Identifier

Reviewer's Comments: (b) (4) is tested at both (b) (4) and Regeneron. Both sites are qualified with a completed co-validation (reviewed by DBSQC).

The storage location for (b) (4) and labeled DP was unclear. IRs #68 and #70 were issued on 2/19/26 and 2/23/26, respectively.

Amendment 70 dated 2/23/2026 stated (b) (4) DP is stored at (b) (4)

Amendment 72 dated 2/25/2026 stated: After labeling/packaging at (b) (4) dispositioned labeled DP ships to (b) (4) for clinical site distribution. The (b) (4) doesn't manufacture, test, or disposition LDP. This is acceptable. Since final disposition occurs before shipment, per FDA guidance the (b) (4) need not be listed on Form 356h or Module 3.

3.2.P.3.2 Batch Formula

(Reviewed by ZM)

Table 69: Batch Formula of Drug Product (Provided by Regeneron).

Component	Function	Reference to Quality Standard	Nominal Composition	Total Content per Vial ^a	Total Content per Representative Batch ^{ab}
DB-OTO-5	Active ingredient	Manufacturer's specification	(b) (4)	(b) (4)	(b) (4)
DB-OTO-3	Active ingredient	Manufacturer's specification	(b) (4)	(b) (4)	
Sodium Phosphate (b) (4)	Buffer	(b) (4)	(b) (4)		
Sodium Phosphate (b) (4)		(b) (4)	(b) (4)		
Sodium Chloride	Stabilizing agent	(b) (4)	180 mM	(b) (4)	
Sucrose	Stabilizing agent	(b) (4)	5% (w/v)	(b) (4)	
Poloxamer 188	Surfactant	(b) (4)	0.001% (w/v)	(b) (4)	
Water for Injection	Solvent	(b) (4)	QS	QS	QS

(b) (4)

(b) (4)

sufficient; (b) (4)

; w/v, weight by volume

QS, quantity

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

- The information provided in sections 3.2.P.3.1 and 3.2.P.3.2 is acceptable.
- IRs #68 and #70 were issued to clarify the storage location for (b) (4) and labeled drug product.
- There are no existing deficiencies.

3.2.P.3.3 Description of Manufacturing Process

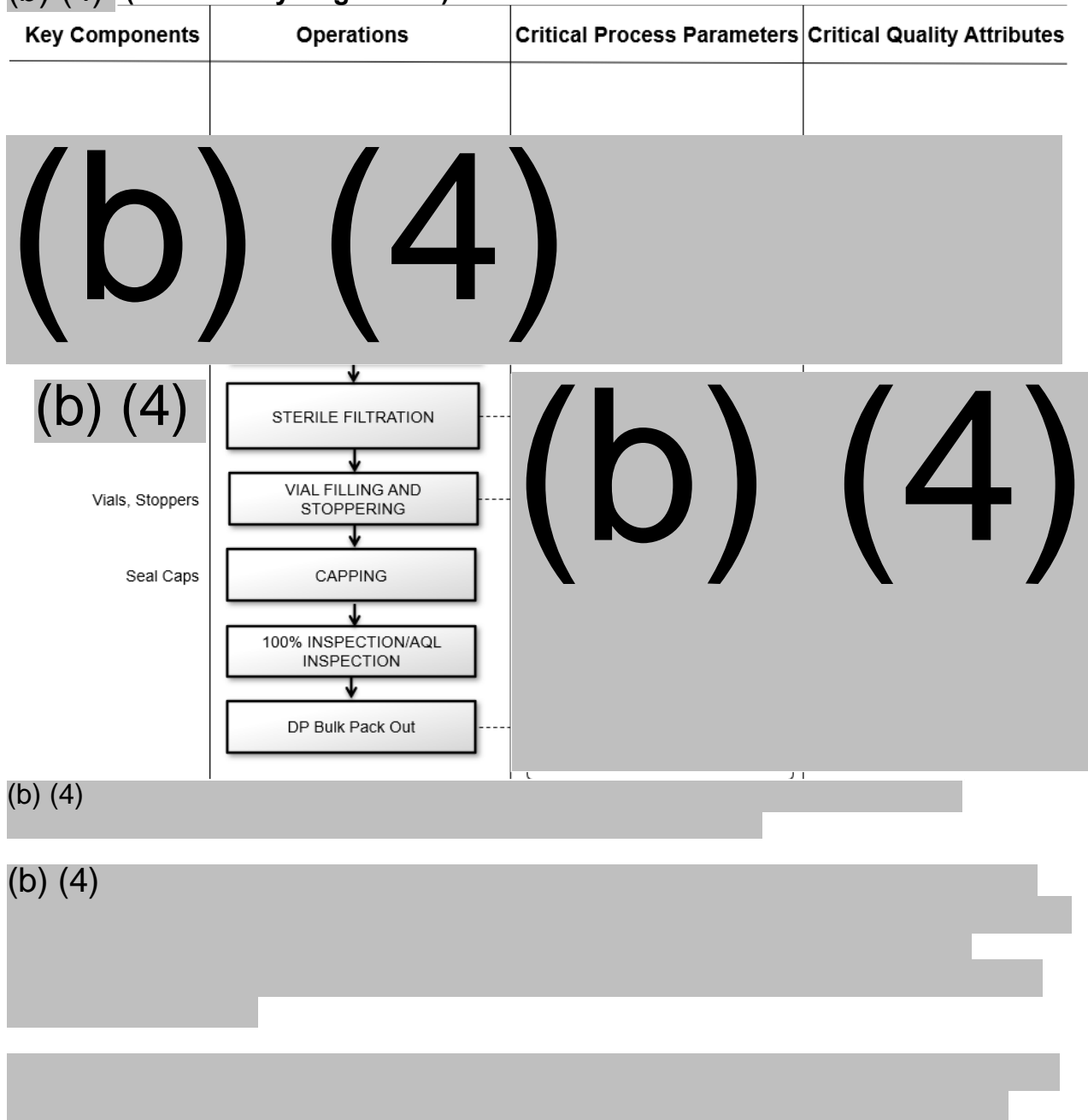
(Reviewed by ZM)

Each DP batch uses (b) (4) DB-OTO-3 DS batch and (b) (4) DB-OTO-5 DS batch, contingent on meeting release criteria. An autogenerated lot number tracks each DP batch, with

manufacture date recorded as the sterile filtration and vial filling date. All product-contact components are sterile, ready-to-use. 25 shows the DP manufacturing process flow.

Reviewer’s Comments: We noted a discrepancy between lot release protocol (VV-RIM-00453438-5.0) and other documentation regarding whether (b) (4) DS batches could be used per DP batch. IR #59 was issued. Amendment 58 confirmed (b) (4) batches of each DS are used and the lot release protocol was updated.

Figure 25: Flow Diagram of the DB-OTO Drug Product Manufacturing Process at (b) (4) (Provided by Regeneron).



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

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

(b) (4)

Sterile Filtration: (b) (4)

***Reviewer's Comments:** Additional details on the sterile filtration setup and operation can be found in the formulation robustness study in eCTD 3.2.P.2.3*

Aseptic Filling, Stoppering, and Capping: Sterile filling, stoppering, and sealing occurs in a Grade (b) (4) using an (b) (4) system. The DP solution is filled into sterile, ready to use vials using a (b) (4) are automatically performed in-process and are non-destructive. Vials and stoppers are received sterile and ready to use by the supplier. Capping activities occur within the (b) (4) under a Grade (b) (4) environment in a Grade (b) (4) room. Sterile, ready-to-use aluminum seals are crimped around the vial neck in accordance with the MBR.

***Reviewer's Comments:** Due to a crimping related CAPA, the crimping procedure was revised to include (b) (4) Additionally, a preventive maintenance schedule for crimping (b) (4) was established, along with (b) (4) for (b) (4) functionality.*

100% Inspection and AQL Inspection: Filled vials undergo 100% visual inspection by qualified operators for container, closure, product, and process defects. Defects are classified as: (1) Critical – harm potential or sterility concerns; (2) Major A – particles (b) (4) impacting SISPQ; (3) Major B – container impairments or quality

impacts; (4) Minor – cosmetic issues. Rejects are separated, classified, and documented.

Acceptance Quality Limits (AQL) inspection uses (b) (4). Lots exceeding limits are placed on hold, investigated, and may undergo 100% re-inspection. After AQL completion and QC sampling, and unlabeled vials are (b) (4) until shipment.

(b) (4)

Reviewer's Comments: In IR #82 (3/10/26), we requested the location where (b) (4) data is collected and documented during vial (b) (4) packaging, as we noticed that this monitoring activity is not reflected in the (b) (4) DP manufacturing MBR. In Amendment 86 dated 3/12/2026, the sponsor provided documentation illustrating that (b) (4) are monitored at this stage by recording time milestones (to the second) on Form (b) (4) 000062105 for each step of the pack-out process, calculating the elapsed time between steps to ensure material is not (b) (4) per event. The form includes a reconciliation section that totals the number of (b) (4) events exceeding (b) (4) and requires escalation to management if more than (b) (4) events occur or if any single event exceeds (b) (4). Additionally, the procedure requires a minimum (b) (4) event longer than (b) (4) to ensure the drug product returns to -80°C (b) (4). This is acceptable.

Reviewer's Comments: In IR #64 (2/17/26), we raised concerns about shipping unlabeled vials in labeled bags before final labeling, particularly regarding lot-to-lot Chain of Identity (COI) maintenance. Without vial identification during storage/shipment, there is increased risk of inadvertent lot commingling within bags or mislabeling during final labeling, potentially compromising traceability and patient safety during recalls or adverse event investigations. The sponsor's post-labeling DP identity test cannot distinguish between manufacturing lots or detect lot mix-ups. We requested: 1) detailed COI procedures with documentation or supportive data in the labeling PPQ protocol, 2) consideration of crimp/temporary mini labels per vial, and 3) clarification of the lot numbering system. The sponsor responded in Amendment 65 with the following information:

Regeneron declined to implement vial labeling, citing feasibility concerns and quality risks. Instead, the sponsor relies on physical segregation, container labeling hierarchy, lot traceability documentation, and procedural controls at each site to maintain COI.

1. Physical Segregation Approach: The sponsor's COI strategy relies primarily on physical segregation at multiple levels. (b) (4) DP lot ships to and is received at (b) (4) at a time, eliminating any possibility of inter-lot overlap during

handling or storage. At (b) (4), sealed barrier bags are stored in dedicated, access-restricted freezers secured with tamper-evident tags. At (b) (4), each lot is stored in (b) (4) freezers to maintain segregation throughout the manufacturing process.

2. Labeling Hierarchy:

(b) (4)

(b) (4), individual vials are labeled and cartons receive a unique 10-digit Regeneron LDP (Labeled Drug Product) number based on the item master number, assigned specifically for each packing and labeling activity. Vial labels include tradename, product name, NDC, storage conditions, manufacturer, barcode, product description, lot number, and expiry.

3. Lot Traceability System: Each (b) (4) DP lot is filled in a dedicated process run, and all (b) (4) vials from that run are placed exclusively (b) (4) associated with that same (b) (4) lot. The traceability system connects the (b) (4) DP lot number to the unique LDP number through the allocation process. (b) (4) are labeled with the Regeneron-assigned (b) (4) DP lot number, (b) (4) barrier bags (b) (4) DP lot number, ensuring clear identification and segregation of vials originating from a (b) (4). Both the Regeneron (b) (4) DP lot number and the Regeneron LDP lot number are documented in the (b) (4) packaging batch records and associated allocation documentation.

4. Procedural Controls by Site:


- At (b) (4), controls include line clearance forms and batch record controls during DP vial filling, room clearance forms during visual inspection and AQL, and verification procedures with GMP checklists during pack-out and shipping.
- At (b) (4), controls include verification of shipping paperwork upon receipt of (b) (4) DP from (b) (4), additional labeling for inventory traceability, and maintenance of (b) (4) integrity.
- At (b) (4), controls include receipt verification with discrepancy procedures, dedicated freezer storage at -80°C, material staging with (b) (4) label inspection, vial labeling with lot verification, and packaging with serialization and (b) (4) inspection.

Reviewer's Comments: This response is generally acceptable. We sent IR # 70 on 2/23/26 to follow-up on the specific standard operating procedure (SOP) numbers that govern all procedures designed to prevent commingling of vials from different drug product (DP) manufacturing lots and whether the sponsor maintains multiple manufactured (b) (4) DP lots in storage at the same time and location prior to shipment to (b) (4) for labeling. This second point is a minor issue, as the sponsor has specified that each lot is stored (b) (4) freezer. In Amendment 72, the sponsor provided the following information:

A summary of all procedural controls including work instructions (WI), batch records, SOPs and associated documentation which are used to prevent commingling of vials from different DP lots is provided in BLA Amendment 72. The documentation therein references reflect the current procedural process in effect during commercial manufacturing.

The following information illustrates how the Sponsor maintains control over multiple manufactured lots of (b) (4) DP that are stored concurrently at the same facility prior to shipment to (b) (4) for labeling.

(b) (4)

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Reviewer's Comments: We agree that the procedures at both (b) (4) demonstrate that while multiple lots may be held in a (b) (4) or area, strict segregation is sufficient to prevent commingling.

Vial Labeling and Secondary Packaging: Labeling and secondary packaging takes place in controlled non-classified areas at room temperature. Product temperature is maintained through the use of (b) (4) during the labeling and packaging activities. Prior to labeling and packaging, vials are stored at - 80 (b) (4) °C.

Reviewer's Comments: In submission VV-RIM-00431544, the sponsor confirmed that identity testing is performed on the DP after labeling and packaging operations are complete, per 21 CFR 610.14. Since the drug product specification includes two identity tests (b) (4), we issued IR #49 on 2/30/2026, to clarify which test is performed post-labeling. In Amendment 50, the sponsor specified that the (b) (4) test is conducted after labeling is complete. This is the more appropriate identity test and their answer is suitable.

(b) (4)

Packaged vials are stored at -80 (b) (4) °C until shipment to storage.

Reviewer's Comments: Although the sponsor originally intended to apply a tamper-evident seal to the carton after closure, this step was removed from the manufacturing process, as documented in Amendment 65 dated 2/19/2026. The sponsor justifies this change by explaining that the carton's slit-lock tuck closure provides adequate lid security, and that sufficient tamper evidence is provided by the (b) (4)-sealed barrier bag and the carton's integrated locking mechanism. We find this justification acceptable and concur that the modified packaging design provides adequate tamper evidence. DMPQ conducted a PLI of the labeling facility (b) (4). During labeling, operators removed vials from the (b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.3:

- The information provided in Section 3.2.P.3.3 is acceptable following resolution of multiple information requests.
- Several IRs were issued to address documentation, protocol clarity, and process controls for the drug product, all of which were subsequently resolved through amendments. Initial requests successfully clarified the location of manufacturing batch records (IR #38), confirmed the use of (b) (4) batches per drug product batch (IR #59), and specified that the (b) (4) test is performed post-labeling (IR #49). More substantive IRs addressed process integrity, specifically the risk of lot commingling for (b) (4) vials (IRs #64, #70) and the monitoring of (b) (4) during packaging (IR #82). The sponsor resolved these concerns by providing a comprehensive Chain of Identity strategy detailing physical segregation and procedural controls to prevent commingling, and by documenting a robust (b) (4) monitoring procedure that includes (b) (4) to ensure product temperature is maintained.

3.2.P.3.4 Controls of Critical Steps and Intermediates (Reviewed by ZM)

The overall process control strategy includes a formal program for managing critical steps and intermediates. This strategy, combined with final product release and stability testing, ensures the manufacturing process robustly and consistently produces DP that meets predetermined requirements for safety, identity, strength, purity, and quality (SISPQ).

Table 14 provides the framework for in-process controls (IPCs), detailing their classification, limit definitions, and the required response to excursions. The critical process parameters (CPPs) for each manufacturing operation are further described in the sections below.

Table 71: Critical Process Parameters and Quality Attributes for DP Manufacturing (FDA, CMC)

(b) (4)

(b) (4)

Non-Critical Process Parameters:

(b) (4)

(b) (4)

(b) (4)

Post-Fill Operations: Following aseptic filling and crimping, the DP undergoes labeling and secondary packaging with specific environmental controls. Unprotected exposure time to (b) (4) based on development studies demonstrating no impact on temperature and pH within this timeframe. These non-critical parameters complement the critical (b) (4) to ensure product integrity throughout the packaging process.

Overall Reviewer's Assessment of Section 3.2.P.3.4: The information provided in section 3.2.P.3.4 was reviewed and is acceptable as submitted.

3.2.P.3.5 Process Validation and/or Evaluation

(Reviewed by ZM)

Manufacturing Process Validation

To establish process consistency, the sponsor conducted a Process Performance Qualification (PPQ) study at the (b) (4) facility. (b) (4) lots were included in this PPQ study, as (b) (4) was invalidated due to a (b) (4) equipment malfunction that caused (b) (4) defects. The (b) (4) successful PPQ lots all produced DP that meets all pre-defined AC. In addition to this core study, the sponsor executed several supporting studies to establish allowable limits for time out of refrigeration, and to validate DP (b) (4), shipping, labeling, and aseptic processing. Furthermore, the sponsor has established a continuous process verification plan to ensure ongoing control. Table 72 provides details on the specific lots used across these comprehensive process validation and evaluation studies.

Reviewer's Comments: FDA does not set a required number of PPQ batches or require that there be (b) (4) successful PPQ runs. For this reason, we agree that (b) (4) successful PPQ runs is sufficient to confirm manufacturing process control.

Table 72: Process Performance Qualification Lot Summary (Provided by Regeneron).

(b) (4)

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(b) (4)

Labeling and Secondary Packaging Validation

The sponsor submitted a labeling Process Performance Qualification (PPQ) protocol in Amendment 65 (2/19/26). The PPQ protocol describes the execution of (b) (4) validation batches, each consisting of (b) (4) vials. To demonstrate that the commercial-scale process will consistently produce a finished product that meets all packing quality specifications, each vial will be labeled and packaged via the intended commercial process, which results in one labeled vial in one (b) (4)-sealed barrier bag with prescribing information and packaged in (b) (4) carton. These cartons are aggregated into shippers, which are then loaded into (b) (4) containers and palletized.

The protocol incorporates a stringent inspection and sampling strategy based on Acceptance Quality Limits (AQL). All units across the (b) (4) batches will undergo 100% inspection for critical defects. For the (b) (4)-unit batches, 100% inspection is required for all critical defects ((b) (4) AQL) at the vial, barrier bag, and carton levels, with (b) (4) units sampled for major (b) (4) AQL) and minor defects (b) (4) AQL). Acceptance criteria is (b) (4) defects accepted/(b) (4) reject for critical and major defects, and (b) (4) accepted/(b) (4) reject for minor defects. For shippers, (b) (4) per batch), and pallets (b) (4) per batch), 100% inspection is required with (b) (4) acceptance criteria. Key Packaging Quality Attributes include undamaged product, correct counts, print legibility and scannability, label adherence, bar code grade verification, and correct palletizing. The PPQ summary report was submitted on March 13, 2026. The summary report demonstrated that labeling PPQ for the commercial process was successfully completed across (b) (4) validation batches. During labeling of Batch (b) (4) the sponsor identified two major label defects (one crooked label and one wrinkled label), an extra carton was identified during (b) (4) and reached (b) (4) per an (b) (4). These resulted in one deviation (b) (4) #1269881). The resultant investigation attributed these issues to human factors and material distribution constraints within the (b) (4) during assembly. Corrective actions

were implemented, including improved material distribution and the (b) (4) to enhance operator ergonomics and temperature management. The effectiveness of these corrective actions was demonstrated in subsequent runs: Batch completed with zero critical, major, or minor defects, and Batch completed with only (b) (4) minor defect ((b) (4)). All acceptance criteria were met, and the commercial packaging process for Regeneron DB-OTO was deemed validated and ready for commercial use. Continued Process Verification (CPV) will be implemented for ongoing process monitoring.

The sponsor submitted the unexecuted labeling MBR in Amendment 90 (3/19/26).

Continuing Process Verification:

(Reviewed by ZM and SL)

Regeneron has established a comprehensive CPV program for both DS and DP manufacturing at (b) (4) documented primarily in procedures VV-IOPS-184901 (Process Performance Monitoring Plan, serving as the CPV protocol) and VV-IOPS-166625 (Trending of Release Data), which were provided in response to multiple Information Requests (IRs #14, #23, #41, and #69) after the sponsor initially failed to include detailed CPV monitoring plans in the original BLA submission. The program establishes monitoring strategies for IPMs across both DS and DP manufacturing, with every post-PPQ lot evaluated against established monitoring limits, trend reports generated every (b) (4) months, and a phased approach to statistical process control based on lot accumulation: statistical control limits ((b) (4) SD) for CPPs and CQAs are established at (b) (4) lots, re-evaluated at (b) (4) lots, and finalized at (b) (4) lots to ensure the process remains in a state of control. The release data trending component uses control charts with limits calculated based on the number of lots manufactured (warning limits at (b) (4) lots, static control limits at (b) (4) lots), applies Nelson trend rules to detect special causes of variation, conducts risk-based investigations through Notice of Monitoring Signal (NOMS) or laboratory investigation (GLIF), and documents trending in monthly and lot-by-lot release trend reports using multiple monitoring tools including control charts, run charts, and data tabulation with defined response requirements for deviations.

***Reviewer's Comments:** We found that this CPV approach provides adequate assurance of continued operation in the validated state for both DS and DP manufacturing processes.*

Overall Reviewer's Assessment of Section 3.2.P.3.5:

- ❑ *The information provided is acceptable*
- ❑ *The initial submission contained significant deficiencies, including the absence of labeling validation data and a detailed CPV plan. These were resolved through multiple IRs, which prompted the sponsor to submit the required validation protocols, reports, and CPV procedures. Additional IRs were necessary to clarify inconsistent batch numbering and to confirm the resolution of shipping deviations. Numerous*

manufacturing deviations during (b) (4) DP manufacturing PPQ, including the invalidation of (b) (4) lot and particulate contamination events, were addressed through internal investigations and corrective actions. This was deemed acceptable through several IRs and interactive review.

3.2.P.4 Control of Excipients

(Reviewed by BL)

3.2.P.4.1 Specifications

All excipients used in manufacture of DP are (b) (4) grade and tested in accordance with (b) (4) by suppliers. Representative COAs are provided in Section 3.2.R. In Amendment 20 received on 12/22/2025 in response to IR #18, Regeneron clarified that all incoming excipient lots are tested per (b) (4) prior to being released for DB-OTO product manufacturing. Additional (b) (4) tests are performed for selected excipients using relevant (b) (4) methods. In Amendment 20 dated 12/22/2025, Regeneron submitted their internal specifications for all incoming excipients. The internal specifications include the qualification requirements for incoming excipients, including information on the suppliers, catalogs, incoming inspection and Certificates of Analysis verification requirements, sampling plans, and the required in-house tests (Table 76 - Table 80). Tests for identity are included in the in-house testing plans for all excipients.

UNII for excipients are listed below:

Sodium phosphate, (b) (4)	(b) (4)
Sodium phosphate, (b) (4)	(b) (4)
Sodium chloride	451W47IQ8X
Sucrose	C151H8M554
Poloxamer 188	LQA7B6G8JG
Water	059QF0KO0R

Table 76: In-house tests for sodium phosphate. (b) (4)

(b) (4)

(b) (4)

Table 77: In-house tests for sodium phosphate,(b) (4)

(b) (4)

Table 78: In-house tests for sodium chloride

(b) (4)

(b) (4)

Table 79: In-house tests for sucrose

(b) (4)

(b) (4)

Table 80: In-house tests for Poloxamer 188

(b) (4)

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(b) (4)

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

All are (b) (4) methods.

3.2.P.4.4 Justification of Specifications

All are set based on (b) (4) acceptance limits.

3.2.P.4.5 Excipients of Human or Animal Origin

None

3.2.P.4.6 Novel Excipient

None

Overall Reviewer's Assessment of Section 3.2.P.4: Information on control of excipients is acceptable.

3.2.P.5 Control of Drug Product

(Reviewed by MV)

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

Drug Product Specifications

The Sponsor states that the same approach for setting the drug substance (DS) acceptance criteria was applied to set the drug product (DP) acceptance criteria. Furthermore, several tests and acceptance criteria were the same as the DS and were set using a pooled DS and DP data set and analysis. Tests in common are shown in Table 81.

Table 81: Drug Product Specifications in Common with Drug Substance (provided by Regeneron)

(b) (4)

(b) (4)

The drug product specifications for release and end of shelf-life are provided in Table 82.

Table 82: Specifications for Drug Product (based on information provided by Regeneron)

Test Parameter (Attribute)	Analytical Procedure	Proposed Acceptance Criteria	End of Shelf Life
Appearance: Physical Form/Condition	(b) (4)	Essentially free from visible particles	Same as release
Extractable Volume	(b) (4)	(b) (4) 0.63 minimum withdrawable content	Not tested
Sterility	(b) (4)	No growth	Not tested
Particulate Matter (b) (4)	(b) (4)	(b) (4)	Same as release
Particulate Matter (b) (4)	(b) (4)	(b) (4)	Same as release
(b) (4)	(b) (4)	(b) (4)	Not tested
Vector Genome Titer	(b) (4)	(b) (4)	Same as release
(b) (4)	(b) (4)	(b) (4) (b) (4)	Same as release
(b) (4)	(b) (4)	(b) (4)	Same as release
Potency (b) (4)	(b) (4)	(b) (4)	Same as release
Container Closure Integrity	(b) (4)	Not tested	No leak detected

Sterility

The DP acceptance criterion for sterility is set as no growth. Sterility is tested at DP release to ensure microbial control of the final product. Container closure integrity testing is performed in lieu of sterility as part of the stability testing program. Sterility will not change during product storage provided container closure integrity is maintained; therefore, sterility is not tested on stability. All GMP lots (PPQ^{(b) (4)}) showed no growth for sterility testing.

Reviewer's Comments: The proposed AC is acceptable.

Extractable Volume

The extractable volume acceptance criterion for the DP presentation is ^{(b) (4)} 0.63 minimum withdrawable content. The method for release and stability testing is based on (b) (4) methods (b) (4)

Reviewer's Comments: The proposed AC is acceptable.

(b) (4)

Reviewer's Comments: The proposed AC is acceptable.

Vector Genome Titer

Vg titer is tested at release and on stability for DP to ensure process consistency in formulating to the target concentration and to ensure material stability. There is no change in long-term stability. A summary of the statistical analysis (minimum and maximum results, mean, standard deviation and (b) (4) tolerance intervals) is provided in Table 83. Statistical analysis for vector genome titer was performed on ^{(b) (4)} results. Calculated tolerance intervals were (b) (4) for ease of interpretation.

Table 83: Vector Genome Titer Statistical Analysis for (b) (4) Drug Product (based on information provided by Regeneron)

(b) (4)

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re-evaluating specifications as additional manufacturing data became available and proposed using trending programs with statistical controls.

We rejected this justification in an information request (IR #68) on 2/19/2026, citing 21 CFR 211.160(b) and (b) (4) principles that critical quality attributes should be established based on clinical experience and manufacturing data rather than nonclinical studies. We noted that clinical experience only supported (b) (4) (b) (4)) and that Process Performance Qualification lots demonstrated a narrower range. We required Regeneron to revise the acceptance criteria of (b) (4)), representing a compromise that acknowledges limited manufacturing experience while ensuring adequate process control. In Amendment 70 dated 2/23/2026 in response to IR #68 Question 1, Regeneron agreed to the revised criteria, adjusted the associated critical process parameter action limit for (b) (4) and updated multiple submission sections accordingly. This is acceptable.

Potency

The potency of DB-OTO drug product is assessed using a (b) (4) assay, with results reported as percent relative potency compared to a reference standard. The acceptance criteria are set at (b) (4) relative potency for both release and end of shelf life.

DB-OTO drug product contains a (b) (4) of DB-OTO-5 and DB-OTO-3 drug substance. To generate a full-length, functional mRNA transcript, both vectors must co-transduce the target cells and undergo recombination. Because both vectors are required for this process to occur, potency by (b) (4) must be evaluated at the drug product level.

Potency is tested at drug product release and on stability to ensure potency is maintained throughout the end of shelf life, with samples compared to the reference standard to monitor consistency over time.

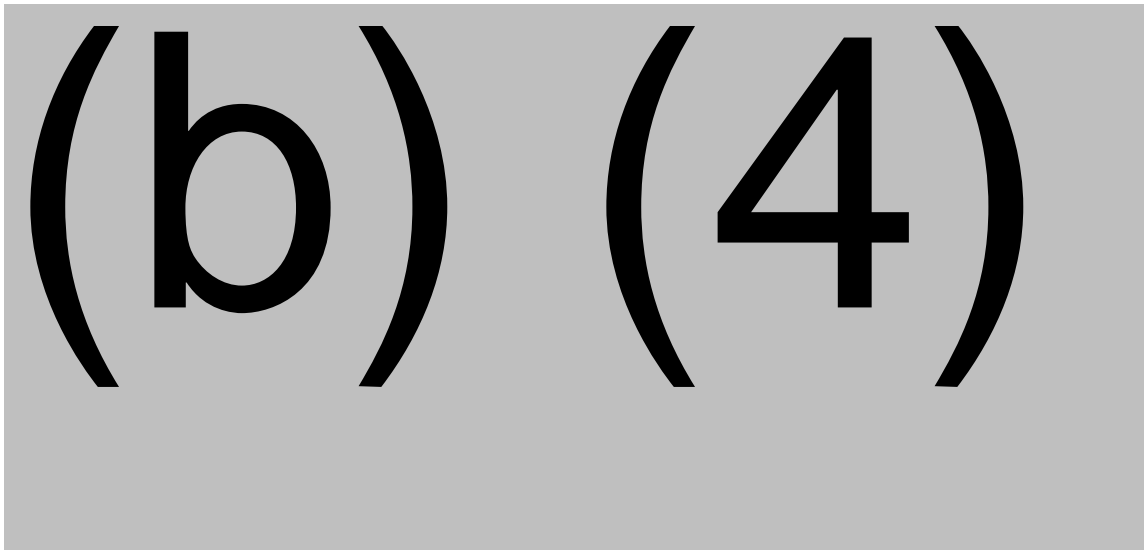
Table 84: Potency by (b) (4) Results for Drug Product (based on information provided by Regeneron)

(b) (4)

The acceptance criteria are based on manufacturing process capability. To supplement the limited dataset of (b) (4) P2-derived drug product lots (which showed results ranging

from (b) (4), historical data from P1-derived drug product lots tested as part of the P1:P2 comparability assessment were included in the statistical analysis. Poolability between the P1-derived and P2-derived datasets was confirmed using a Brown-Forsythe test for variance and a t-test for means, and comparability between P1 and P2 drug product has been established. The combined dataset of (b) (4) lots showed a minimum of (b) (4), maximum of (b) (4), geometric mean of (b) (4), and geometric coefficient of variation of (b) (4), with tolerance intervals of (b) (4). Since potency by (b) (4) does not change on long-term stability, the release and end of shelf-life acceptance criteria are aligned.


Figure 27: Drug Product Potency results for P2 lots (FDA, CMC)



The potency of all GMP lots (PPQ (b) (4)) was within the established acceptance criteria.

Reviewer's Comments: The proposed AC is acceptable.

(b) (4)



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(b) (4)

A follow up information request (IR #86) was sent on 3/19/2026 asking the Sponsor to formally incorporate the action limit into the drug product specifications and lot release protocol (LRP) to ensure consistent application and documentation. In amendment 92 dated 3/23/2026 the Sponsor agreed and updated the appropriate sections.

Particulate Matter

Particulate matter in the drug product is measured to ensure the safety of the filled product, with acceptance criteria set in accordance with (b) (4) methods for solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of less than 100 mL. The acceptance criteria, based on (b) (4) method (b) (4) specify that there should be no more than (b) (4) particles per container for particles (b) (4) and no more than (b) (4) particles per container for particles (b) (4). These same acceptance criteria apply at both release and end of shelf life.

Particulate matter is tested at drug product release and on stability because it may be impacted by the final container closure system and is considered a potential stability-indicating attribute. However, stability studies have shown no significant change in (b) (4) during long-term storage.

Appearance, pH, (b) (4), Endotoxin, (b) (4)

Poloxamer 188

See 3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

The majority of proposed acceptance criteria were acceptable as initially submitted, including sterility, extractable volume, (b) (4), potency by (b) (4), and particulate matter. However, deficiencies were identified for two critical quality attributes: vector genome titer (b) (4).

In IR #68 (2/19/2026) Regeneron was required to revise the vg titer AC to (b) (4). In Amendment 70 (2/23/2026), Regeneron agreed to the revised criteria and adjusted the associated critical process parameter action limit for (b) (4).

In IR #68 (2/19/2026) Regeneron was asked to narrow the drug product release specification for (b) (4) so that it appropriately reflects demonstrated manufacturing capability. In Amendment 70 (2/23/2026), Regeneron tightened the acceptance criteria from (b) (4) at both release and end-of-shelf-life, using a (b) (4) standard deviations approach based on PPQ lot data. In IR #84 (3/16/2026), Regeneron was asked to implement an action limit of (b) (4) to (b) (4), with measurements outside this limit triggering deviation reports and corrective action. In Amendment 89 (3/18/2026), Regeneron agreed to implement the requested action limit.

The drug product specifications are acceptable as amended following resolution through multiple information requests.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Potency assay

(Reviewed by MV)

Assay development: The method development report indicates that the assay was developed based on a draft protocol from (b) (4) which served as the foundation for the current validated method. The DB-OTO drug product contains a (b) (4) of DB-OTO-5 and DB-OTO-3 drug substances that must co-transduce target cells and undergo recombination to generate a full-length, functional mRNA transcript. This dual vector system requires both components to be present simultaneously for functional activity, making it inappropriate to assess potency on individual (b) (4) and necessitating the development of a drug product-specific potency assay.

Assay Summary: (b) (4)

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

The validation was adequately performed (b) (4) according to ICH guidelines in a cGMP environment. The method successfully met all acceptance criteria for specificity, linearity, accuracy, precision (repeatability and intermediate precision), robustness, (b) (4) potency level range. The assay is suitable for its intended purpose of assuring product potency through measurement of (b) (4) from the dual vector system.

Two deficiencies were identified and resolved during the review process. The first deficiency concerned system suitability criteria and was addressed through IR #79 dated 3/6/2026. The issue involved tolerance intervals that used (b) (4) confidence with (b) (4) coverage, which is wider than the preferred (b) (4) confidence with (b) (4) coverage. In Amendment 82 dated 3/11/2026, Regeneron provided a reassessment using (b) (4) confidence (b) (4) coverage intervals with additional release and stability data. This resulted in modest updates to some criteria, including tightening the reference standard (b) (4), adjusting the (b) (4), and modifying the (b) (4). Parameters showing no change or wider limits retained the current, more stringent criteria. This response was deemed acceptable.

The second deficiency addressed assay precision and variability through IR #49 dated 1/30/2026. The concern was that the reported (b) (4) for intermediate precision did not reflect actual variability observed during shipping validation (up to (b) (4) decrease) and stability testing ((b) (4) decrease). In Amendment 50 dated 2/3/2026, Regeneron clarified that no out-of-specification results occurred during routine lot release or long-term stability testing. While Regeneron adopted the recommendation to implement a drug product-specific assay control, they declined the suggestion for multiple independent assay runs. A post-marketing commitment was established whereby (b) (4) will be reassigned as the assay control once PPQ Lot (b) (4) becomes the primary reference standard, with study initiation planned for April 2026 and final report submission in May 2026. The acceptance criteria were established at (b) (4) relative potency based on tolerance interval analysis. This response and plan were found acceptable.

There are no remaining deficiencies that should be included in a complete response letter. All identified issues have been adequately addressed through amendments and post-marketing commitments.

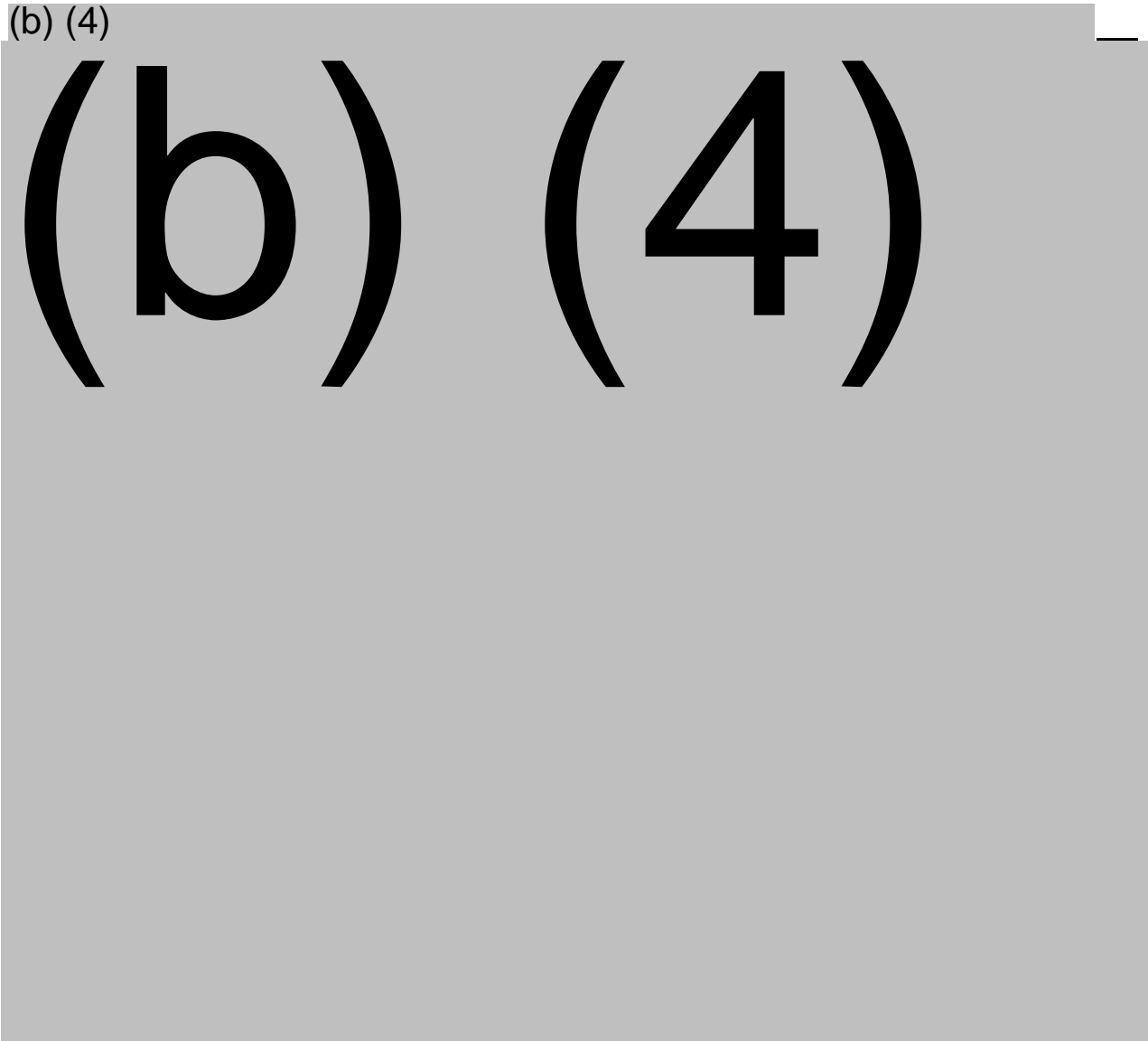
3.2.P.5.4 Batch Analyses

(Reviewed by MV)

The lots used in this analysis include (b) (4) Process 2 (P2) PPQ batches (b) (4) manufactured between (b) (4), and the DB-OTO-001 (CHORD) Phase 1/2 clinical trial, development lots (b) (4) for stability studies and (b) (4) validation. The Sponsor also provided information for historical lots manufactured using Process 1 (P1), including (b) (4) GMP


clinical batches (b) (4) a non-clinical toxicology batch, and an engineering batch.

(b) (4)




(b) (4)

(b) (4)



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



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

(b) (4)

(b) (4)

3.2.P.5.5 Characterization of Impurities

(Reviewed by MV)

Process-related impurities such as bioburden, endotoxin, particulates, and leachables are adequately controlled through validated aseptic manufacturing, sterile materials, environmental monitoring, and testing at multiple stages. Product-related impurities in the drug product are limited to those already present in the drug substance, as characterized in Section S.3.2 Impurities. The drug product manufacturing process, which consists of (b) (4), (b) (4), and fill operations, does not introduce new impurities or alter the existing impurity profile.

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

The information provided is acceptable. Impurities in the drug product are adequately controlled.

3.2.P.6 Reference Standards or Materials

(Reviewed by MV)

The DB-OTO reference standards program utilized (b) (4)

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

(b) (4)

Table 93: Results of Statistical Analysis of the (b) (4)

(provided by
Regeneron)

(b) (4)

Reviewer's Comments: We noted the absence of a comprehensive protocol for qualifying and bridging future reference standards throughout the product's commercial lifecycle to control potential drift in potency, while maintaining linkage to clinical trial material and pivotal study lots. We also noted that the (b) (4) potency assay uses (b) (4) replicates for comparing (b) (4)

On 2/26/2026 an information request (IR #72) was sent to Regeneron asking them to provide a detailed protocol addressing source material selection criteria, manufacturing processes for preparing reference standard lots, container closure systems, storage conditions, expiration dating strategies, and specifications for quantitative assays including the number of replicates and justification for replicate selection, as well as methodology for establishing reported values from multiple test results. Regeneron was also asked to perform a formal statistical analysis demonstrating that (b) (4) replicates provide adequate power to detect a (b) (4) difference in potency, or alternatively, justification of what magnitude of difference is considered clinically relevant with demonstration of adequate power for that threshold, including confirmation that this sample size sufficiently establishes equivalence within the (b) (4) acceptance range with appropriate statistical confidence. Finally, we requested that Regeneron explain how the equivalence testing against clinical lot (b) (4), which yielded a (b) (4)

confidence interval of (b) (4), factors into the assigned value, and why no correction factor is applied when this confidence interval excludes (b) (4), potentially suggesting (b) (4) is systematically lower in potency than the clinical material.

In Amendment 75 dated 3/2/2026 in response to IR #72 Question 1, part a sent on 2/26/2026, Regeneron responded that future reference standard qualification is governed by SOP VV-IOPS-173897, which describes the comprehensive processes for selection, preparation, qualification, performance and suitability monitoring, inventory management, and retirement of product. This SOP works in conjunction with the product-specific RS specification provided in Section P.6, Table 2, and future RS qualification will use the same specification and acceptance criteria as the current RS. Regarding source material and manufacturing, Regeneron stated that only DB-OTO drug product (DP) lots meeting release specification acceptance criteria can be used to create future reference standards. The manufacturing process will remain consistent with the current primary RS, with DP lots manufactured according to the commercial manufacturing process and (b) (4) for RS purposes. Each DP lot will be tested against release specifications, and the future RS will be tested against the qualification testing panel included in Section P.6. For replicate testing, Regeneron indicated that (b) (4) replicates will be performed for (b) (4), with the arithmetic average of the (b) (4) replicates compared to acceptance criteria. For the (b) (4) potency assay, (b) (4) replicates will be performed, and the geometric mean value will be calculated with a (b) (4) criterion. To prevent future reference standards from differing by more than (b) (4) from pivotal clinical study materials, the (b) (4) assay acceptance criteria require that the qualification average falls between (b) (4) and the (b) (4) confidence interval remains between (b) (4).

Regeneron also provided a detailed statistical analysis of the sample size as requested in Question 1, part b. To determine the validity of the analysis we requested a statistical consult from the statistics reviewer Hu-Hsiang Wu on 3/3/2026 via e-mail. The review was completed on 3/12/2026 and Regeneron's response was found to be acceptable. As stated by the FDA statistics reviewer, "the Applicant used equivalence test instead of a significance test for difference. Unlike conventional significance tests for difference, the equivalence test procedure does not rely on failing to reject a null hypothesis to infer similarity—a result that can occur simply due to small sample sizes. Rather, it tests whether the effect is statistically contained within pre-specified equivalence margin, meaning the inference is explicitly about equivalence with respect to the defined equivalence margin." The reviewer also stated, the the (b) (4) GCV is considered small for cell-based assays, the (b) (4) CI of RP (current vs historical RS) is (b) (4) which suggests a small estimated reduction (b) (4), and the (b) (4) CI of RP (current vs (b) (4), and historical vs (b) (4)) look similar, which suggests that current RS works like historical RS on testing P1 DP lot."

In response to Question 1, part c, Regeneron clarified that (b) (4) is assigned a value of (b) (4) relative potency for use in the (b) (4) potency assay. Traceability to clinical material is maintained through the qualification process, which established equivalency between (b) (4) and the pivotal clinical lot. The

equivalency testing yielded a (b) (4) confidence interval (CI) of (b) (4), which met the predefined acceptance criteria of (b) (4). Regarding why no correction factor was applied despite the (b) (4) CI excluding (b) (4), Regeneron explained that when (b) (4) falls within the (b) (4) CI, the relative potency of the new primary RS is considered indistinguishable from (b) (4), and no action is taken. If the (b) (4) CI does not include (b) (4), the relative potency value is compared against all previous primary RS values back to the pivotal clinical reference material to assess cumulative drift. Any candidate resulting in cumulative drift exceeding (b) (4) relative potency is considered unsuitable for use as a primary RS, ensuring that systematic differences do not accumulate over time.

On 3/23/2026, an information request was sent to Regeneron regarding their reference standard qualification strategy for the (b) (4) potency assay for DB-OTO. Two concerns about their proposed approach were raised. First, we found that the (b) (4) equivalence range is too wide to ensure adequate control of reference standard drift over the commercial lifecycle. Therefore, we requested that Regeneron revise their protocol to use a (b) (4) equivalence margin and re-assess the number of tests needed to achieve adequate power. In Amendment 87 dated 3/25/2026, Regeneron committed to implementing a (b) (4) equivalence range for future reference standards. Section 3.2.P.6 Reference Standards and internal specifications have been updated accordingly. Second, we found Regeneron's approach for assigning relative potency values to reference standards inappropriate in cases where the (b) (4) confidence interval excludes (b) (4). We informed Regeneron that when statistical evidence indicates the reference standard potency differs from (b) (4), they should assign the actual measured mean value as the relative potency rather than defaulting to (b) (4). Alternatively, they may use a different lot as reference material if that lot includes (b) (4) in the (b) (4) confidence interval. In Amendment 87 dated 3/25/2026, Regeneron confirmed that when the (b) (4) confidence interval excludes (b) (4), a correction factor will be applied based on the actual measured geomean relative potency value rather than defaulting to (b) (4). The Sponsor will continue to compare values against all previous primary reference standards back to pivotal clinical material to assess cumulative drift, ensuring that assigned relative potency values accurately reflect measured assay performance while maintaining oversight of potency consistency over the commercial lifecycle. Section 3.2.P.6 Reference Standards has been updated to reflect this revised approach.

Overall Reviewer's assessment of Section 3.2.P.6

Several deficiencies were identified, including a lack of a comprehensive protocol for qualifying future reference standards while controlling potency drift and maintaining linkage to clinical material; insufficient justification for (b) (4) replicates in the (b) (4) potency assay; and unclear rationale for not applying a correction factor when equivalence testing against pivotal clinical lot (b) (4) yielded a (b) (4) CI of (b) (4) excluding (b) (4).

IR #72 (February 26, 2026) requested a detailed qualification protocol, statistical justification for the (b) (4)-replicate approach, and explanation of the assigned value methodology. Regeneron's response (Amendment 75, March 2, 2026) provided SOP

VV-IOPS-173897 for future reference standard qualification, replicate testing specifications (b) (4) replicates for (b) (4) replicates for (b) (4) potency with (b) (4) and acceptance criteria requiring qualification averages and (b) (4) CI between (b) (4) to prevent drift exceeding (b) (4) from pivotal clinical material. The equivalence test appropriately assesses whether effects fall within pre-specified margins, and the (b) (4) GCV with (b) (4) CI of (b) (4) suggests only (b) (4) reduction. Regeneron clarified that (b) (4) is assigned (b) (4) relative potency; when the (b) (4) CI excludes (b) (4), cumulative drift is assessed against all previous reference standards back to pivotal clinical material, with candidates exceeding (b) (4) drift deemed unsuitable.

However, two additional concerns were raised in a subsequent information request (March 23, 2026): the (b) (4) equivalence range was deemed too wide for adequate drift control, and the approach of defaulting to (b) (4) relative potency when the (b) (4) CI excludes (b) (4) was considered inappropriate. In Amendment 87 (March 25, 2026), Regeneron committed to implementing a narrower (b) (4) equivalence range and applying correction factors based on actual measured geomean relative potency values when the (b) (4) CI excludes (b) (4), rather than defaulting to (b) (4). These revisions were acceptable.

3.2.P.7 Container Closure System

(Reviewed by BA)

The drug product (DP) primary container closure system (CCS) consists of a 2 mL (b) (4) vial made from (b) (4) 13 mm chlorobutyl elastomeric stopper with (b) (4) coating, and a 13 mm lacquered aluminum seal with a blue flip-off button. Details of the primary packaging components, including supplier names and drug master file references, are provided in Table 94 below.

- The vials are sterilized by (b) (4) and are ready-to-use.
- The stoppers are sterilized by (b) (4)
- The flip-off seals are sterilized by (b) (4)

Table 94: Primary Container Closure System (based on information provided by Regeneron)

Component	(b) (4)	(b) (4)	Manufacturer Name	Description	Drug Master File ^a
Vial	(b) (4)	(b) (4)	(b) (4)	2 mL vial (b) (4) (b) (4)	DMF (b) (4) (b) (4)
Stopper	(b) (4)	(b) (4)	(b) (4)	13 mm (b) (4), gray, chlorobutyl elastomeric stopper (b) (4) coating	DMF STN (b) (4) (b) (4)

Seal	(b) (4)	(b) (4)	13 mm aluminum seal, blue flip-off button	N/A (non-product contact)
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^a The (b) (4) vial is manufactured by (b) (4) under DMF (b) (4). The vial is supplied sterile by (b) (4) under DMF (b) (4).

^b There are two part numbers for the vials as the product may be supplied in different packaging configurations.

There is no difference in actual product characteristics.

DMF, drug master file; (b) (4)

The suitability as the DP CCS was assessed based on the physicochemical properties per (b) (4) for the vial and (b) (4) for the stopper, and biocompatibility per (b) (4) provided by the vendor and leachable and extractable studies performed by the Applicant (please refer Section 3.2.P.2.3.2 Leachables and Extractables in this memo).

The vials used in CCS do not provide protection from light. Light protection is provided by the secondary packaging (an opaque, cardboard carton) and CCS durability is demonstrated through shipping validation (please refer to Section 3.2.P.3.5 Process Validation and/or Evaluation – shipping validation and DMPQ review memo).

The DP is stored at -80°C (b) (4) and the compatibility of the CCS is demonstrated by long-term stability data as detailed in Section S.8. Stability.

Secondary Packaging

The labelled DP vials are placed into a labelled barrier bag and (b) (4) sealed. The sealed barrier bag is placed into a carton with literature insert(s) placed on top. The carton is closed and visually inspected.

- Barrier bag: (b) (4)
- Opaque cardboard carton to provide light protection for DP.

Reviewer's Comments: Incoming material specifications and representative CoAs for the vials, stopper, and seal are included in the BLA, have been reviewed and found to be acceptable. In Amendment 16 dated 12/15/2025 in response to IR #15 sent on 12/11/2025, the Applicant added part numbers to the vial, stopper and seal to match those used in PPQ runs shown in Section 3.2.P.3.5 Table 5-2 of the P2 Fill Finish Process PPQ Protocol (vv-rim-00451054). In Amendment 89 dated 03/18/2026 in response to IR #84 sent on 03/16/2026, the Applicant provided a native PDF file of the CoA for the (b) (4) seal Cap and the quality of the document was found acceptable.

Overall, the CCS maintains integrity over the stability time points tested, as demonstrated by container closure integrity testing (please refer to Section 3.2.P.8 Stability reviewed by Dr. Meghna Thakur). (b) (4) is identified as a risk specific to (b) (4) vials during (b) (4) shipping and barrier bags are demonstrated to effectively mitigate pH maintenance. The Applicant assessed the impact of (b) (4) storage on DB-OTO pH and evaluated effectiveness of barrier bags in preventing pH shifts from (b) (4). Study was performed using (b) (4) (identical formulation matrix as DB-OTO, pH 7.3) filled into 2 mL (b) (4) vials, stoppered, sealed, frozen at -80°C for two shipping scenarios: 1) DP to LDP (b) (4) to packing site; (b) (4) DP vials in (b) (4),

sealed in barrier bags and placed in (b) (4) shippers, and 2) LDP to Clinic: individual DP units sealed in barrier bags, placed in individual carton boxes, placed in (b) (4) shippers. In both DP-to-LDP and LDP-to-clinic shipping scenarios pH (b) (4) to (b) (4) after (b) (4) days at (b) (4) without barrier bag. pH is maintained within specification with barrier bag and the (b) (4) days (b) (4). Additionally, shipping validation demonstrated that barrier bags are essential for physical protection during shipping. Photostability data demonstrated that the vials used in DP CCS do not provide protection from light. Light protection for DP is provided by the secondary packaging (an opaque, cardboard carton).

Upon review of Amendment 42 dated 01/27/2026 in response to IR #41 sent on 01/23/2026, qualification information for assessment of (b) (4) from DB-OTO DP by (b) (4) method was found missing intermediate precision among all other evaluated qualification parameters. In Amendment 58 in response to IR #59 sent on 02/11/2026, the Applicant clarified that intermediate precision was not performed for the DB-OTO matrix for the (b) (4) method qualified at Regeneron. The Applicant commits to assessing (b) (4) from DB-OTO DP, stored at (b) (4) (end of proposed shelf-life), using fully qualified assays, and submitting a final real-time DP (b) (4) study report as a PMC by June 30, 2032. Please refer to Section 3.2.P.2.3.2 (b) (4) in this review memo for further information on the assessment of (b) (4) in DP CCS.

Overall Reviewer's Assessment of Section 3.2.P.7:

- ❑ The information provided regarding the DS CCS is acceptable to support CCS suitability for DS storage and shipping.
- ❑ CCS (b) (4): While the Applicant had not performed the (b) (4) assessment appropriately for the CCS as they used accelerated conditions instead of real time conditions and some of their assays were not adequately qualified, they committed to collecting real time (b) (4) data from the DP stability samples at (b) (4) months and would submit the data as a PAS. Please see section 3.2.P.2.3.2 (b) (4) for additional information on this aspect. No further issues.

3.2.P.8 Stability

(Reviewed by MT)

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

The stability studies were performed on both Process 1 (Pre-change) and Process 2 (Post-change) batches of DB-OTO DP under three conditions: (1) long-term storage at -80 (b) (4) °C, (2) accelerated conditions at (b) (4) and (3) (b) (4) conditions at (b) (4). In addition, photostability and (b) (4) studies were performed on selected lots. The list of batches and stability studies are summarized in Table 95.

Table 95: Summary of DP Stability Batches and Stability Studies (based on information provided by Regeneron)

(b) (4)

(b) (4)

Acceptance criteria implemented for the long-term stability studies for the DP are provided in Table 96.

Table 96: DP Stability Specifications (based on information provided by Regeneron)

Test	Method Description	Acceptance Criteria
Appearance (color, clarity, visible particles)	(b) (4)	Clear to slightly opalescent, colorless, essentially free from visible particles
pH	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Vector Genome Titer	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Poloxamer 188	(b) (4)	0.001 (b) (4) (% w/v)
Potency by (b) (4)	(b) (4)	(b) (4)
Container Closure Integrity	(b) (4)	(b) (4)

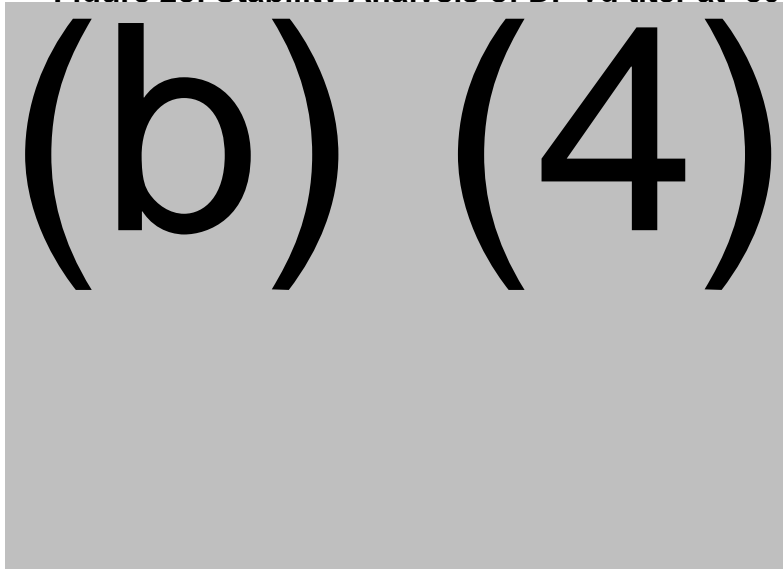
Long-term Stability Study

Stability data at the long-term storage condition are provided for (b) (4) DP lots, including (b) (4) P2 lots and (b) (4) P1 lots. The Applicant proposes a shelf-life of (b) (4) months based on the stability data. No significant changes were observed in pH, (b) (4), appearance, (b) (4), particulate matter, or Poloxamer 188. The results for the other quality attributes are discussed below:

Vector Genome Titer

We performed statistical analysis as described in (b) (4) on all DP lots, as shown in Figure 28. The best model accepted at the significance level of (b) (4) was different (b) (4), and the confidence bound of any batch does not cross the lower shelf-life specification limit of (b) (4). Process 2 PPQ lot (b) (4) was excluded from the analysis due to availability of only the initial time point. Data are available for (b) (4) P1 lots for (b) (4) 12 months; however, only (b) (4) of these lots is formulated at (b) (4) whereas the other (b) (4) lots were formulated at a higher titer. Process 2 lots are vialled at 3×10^{13} vg/mL except the development lot (b) (4) which is vialled at higher concentration (b) (4).

Figure 28: Stability Analysis of DP vs titer at -80°C (FDA, CMC)



(b) (4)

(b) (4)

(b) (4)

Potency by (b) (4)

Potency was assessed as part of the stability protocol for lots manufactured using Process 2. As shown in Figure 30, only (b) (4) P2 development lot (b) (4) has been tested for 12 months, and no downward trend is observed. There was (b) (4) reduction in relative potency for (b) (4) PPQ lots ((b) (4)) at the 3-month time point, however the values at 6-month time point provided late in the review cycle (13Feb2026) showed a restoration in potency. No significant changes in potency were observed for PPQ lot (b) (4) at any time point. Although there is variability in the potency values, the values remain within specification.

Figure 30: Stability Analysis of P2-derived DP Potency at -80°C (FDA, CMC)

(b) (4)

Reviewer's Comments:

The Applicant has proposed an initial shelf life of (b) (4) months based on stability data from (b) (4) Process 1-derived DP lots (b) (4) 12 months available) and a comparability assessment between Process 1 and Process 2-derived DP. However, only (b) (4) Process 2 development lot (formulated at higher concentration) has 12 months of stability data available, and the commercial Process 2 PPQ lots currently support only a 6-month shelf life. While Process 1 data can be supportive for shelf-life determination, several limitations exist: (1) Process 1 lots lack potency by (b) (4) data, a stability-indicating attribute; (2) the Process 1 lot with the most extensive stability data was formulated at a higher target concentration than the commercial product.

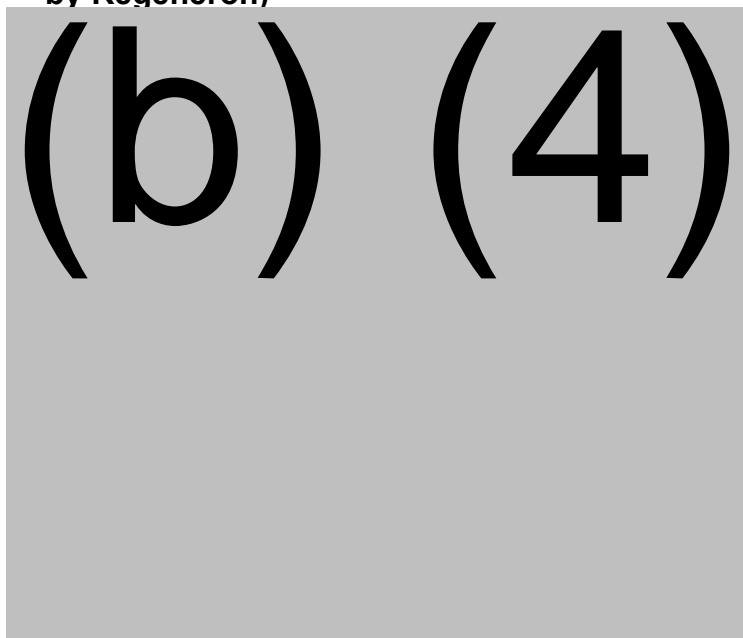
Additional Shelf-life justification

In amendment 77 dated 03/05/2026 in response to IR #75 dated 03/03/20026, the Applicant submitted additional justification and performed ANCOVA analysis with a (b) (4) significance level to evaluate stability trends for P1 and P2 DS, and P1 derived and P2-derived DP. Additionally, (b) (4) P1-derived DP lots were tested in the (b) (4) assay as part of method bridging study as representative of long-term stability trends. As shown in Table 97 and Figure 31 the P1 lots remain within the acceptance criteria.

**Table 97: Summary of P1-Derived (b) (4) Potency Results
(provided by Regeneron)**

(b) (4)

Figure 31: Stability Plot of P1-derived and P2-derived DP Potency Data (provided by Regeneron)



Reviewer's Comments: While the potency data provided to support shelf-life does not directly demonstrate stability due to lack of $t=0$, it indicates that the lots are potent at time points ranging from (b) (4) months. In addition, Applicant noted that the (b) (4) confidence intervals are expected to intersect specification AC at time points well beyond the proposed (b) (4) month shelf-life. However, this inference is not supported by real time data from primary stability batches and relies on extrapolation of stability data. Despite these limitations, regulatory flexibility may be offered given that the DP is stored frozen at -80°C in (b) (4) vials, no downward stability trends have been observed for critical quality attributes across all lots, and process comparability has been demonstrated. In accordance with the principles of draft (b) (4) guidance (b) (4) which limits extrapolation for complex biologics, a path forward can be offered to enhance regulatory flexibilities. Given the maximum available real-time data from a P2 stability lot is 12 months, a shelf-life of 18 months is the maximum appropriate, as this represents one-and-a-half times the duration of the available data as suggested in the guidance. Any future extension of DS or DP shelf-life can be submitted as a prior-approval supplement (PAS).

In Amendment 92 dated 3/23/2026 in response to IR #86 sent on 3/19/2026, the Applicant agreed to set the initial commercial shelf-life to 18 months for DP.

Accelerated Stability Study

(b) (4) DP lots manufactured using Process 2 and (b) (4) lot manufactured using Process 1 were tested for accelerated stability at (b) (4). In addition, (b) (4) Process 2 DP lot was tested for accelerated stability at (b) (4).

The sponsor performed degradation analysis of Process 1- and Process 2-derived DP at (b) (4). The attributes did not show a decreasing trend, with the exception of potency, which showed a moderate reduction over 3 months and all PPQ lots going out of specification at 6 months. In addition, some variability was observed in (b) (4) across lots; however, the values did not cross the lower specification limit.

The Process 2 development lot was also stored at (b) (4), and the attributes remained unchanged over 6 months, especially no change in % relative potency or vector genome titer was observed as shown in Table 98. Some variability in (b) (4) was noted; however, the results are inconclusive as the two vectors exhibited different trajectories. Nevertheless, the values remained above the lower specification limit throughout the 6-month period.

Table 98: Stability of Process 2 Development lot (b) (4) stored at (b) (4)
(based on information provided by Regeneron)

(b) (4)

Reviewer's Comments:

- In Amendment 30 dated 1/9/2026 in response to IR#27, dated 1/7/2026, Regeneron submitted updated stability plots containing a single linear regression line on each graph with (b) (4) confidence intervals as well as individual markers for each lot.
- Final stability data containing long term and accelerated storage conditions was provided on 2/13/2026. In amendment 70 dated 2/23/2026 in response to IR # 68 dated 2/19/2026, Applicant provided updated degradation profile plots for the

accelerated stability conditions (b) (4) including data from all lots. **Error! Reference source not found.**



- The accelerated stability studies indicate the DP remains stable at (b) (4) with some reduction in potency and (b) (4) for 3 months; however, storage at 6 months adversely impact product potency.
- Data from the development lot indicate that (b) (4) can be an alternative storage condition for up to 6 months with minimal impact on product quality and potency.

Freeze/thaw Stability

Freeze-thaw stability was only performed on (b) (4) (see section 3.2.S.7) and (b) (4) DP. (b) (4) can withstand (b) (4) freeze-thaw cycles without impacting product quality.

(b) (4) Stability Study

(b) (4)



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

(b) (4)

Photostability

To determine the photostability characteristics of the DB-OTO DP Lot (b) (4)

While all attributes underwent minimal changes when tested in the carton, (b) (4) reduction in potency was observed when the vial in the carton was compared to the (b) (4) covered vial; (b) (4)

Reviewer's Comments: Photostability studies show that the DP is sensitive to light exposure, and light exposure should be limited during storage. While changes in potency are observed in the marketing pack designated for use with the DP, the pack provides sufficient protection from light exposure overall, as determined by all the attributes remaining within specifications.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Stability studies for the ongoing stability lots will continue through up to either the (b) (4) -month time point in accordance with the stability protocol. Post approval, a minimum of (b) (4) lot of DP will be placed on long-term stability at the recommended storage condition of -80°C every year that manufactures such lots. The DP will be tested according to the protocol presented in Table 99 using validated methods.

Table 99: Post Post-Approval Stability Protocol for DB-OTO DP (provided by Regeneron)

Test	Test Interval (months)					
	0	3	6	9	12	18
Appearance	Release Data	X	X	X	X	X
pH		X	X	X	X	X
Particulate Matter		NR	X	NR	X	X
Vector Genome Titer		X	X	X	X	X
(b) (4)		X	X	X	X	X
(b) (4)		X	X	X	X	X
(b) (4)		X	X	X	X	X
(b) (4)		X	X	X	X	X

(b) (4)		X	X	X	X	X
Potency by (b) (4)		X	X	X	X	X
Container Closure Integrity	NR	NR	NR	NR	X	NR

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.8:

- The Applicant proposed a DP shelf life of (b) (4) months. However, the long-term stability data provided do not support a (b) (4) -month shelf life, as only (b) (4) manufactured using Process 2 has 12 months of available data. While (b) (4) lots manufactured using Process 1 have longer-term stability data ((b) (4) months), and stability trends support qualitative comparability between Process 1 and Process 2, these lots lack stability data on potency by (b) (4), which is one of the critical stability-indicating attributes, and the Process 1 lots were formulated at different target concentrations than the commercial Process 2 PPQ lots. Based on the available stability data from the commercial manufacturing process and extending regulatory flexibilities, a shelf life of 18 months will be assigned. Any extension beyond 18 months will require additional long-term stability data from Process 2 PPQ lots submitted as a PAS. Applicant agreed to set the initial commercial shelf-life to (b) (4) months for the DP.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

This section is reviewed by DMPQ reviewers, Carl Perez (OCBQ/DMPQ/MRB3) and Viviana Rairez (OCBQ/DMPQ/MRB2). Please refer to DMPQ review memo for details.

3.2.A.2 Adventitious Agents Safety Evaluation

(Reviewed by BA)

Control of potential adventitious agents (b) (4)

(b) (4))
in the (b) (4) relies on the use of non-animal derived raw materials in the production of DB-OTO (b) (4) DP. Please refer to Section 3.2.S.2.3 Control of Materials in this memo for the evaluation of adventitious agents safety in raw materials, biological starting materials, HEK 293 (b) (4) Section 3.2.S.2.4 Controls of Critical Steps and Intermediates in this memo for the evolution of adventitious agents safety in DB-OTO (b) (4), and Section 3.2.S.3.2 Impurities in this memo for evaluation of rcAAV in DB-OTO (b) (4).

(b) (4)

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(b) (4)

3.2.A.3 Novel Excipients

None

3.2.R Regional Information (USA)

Executed Batch Records

(Reviewed by BL)

The executed batch records of (b) (4) lots, including a (b) (4) , and (b) (4) DP lot ((b) (4) are submitted in Amendment 7. The unexecuted MBRs are also submitted in Amendment 7 dated 11/25/2025.

The unexecuted master batch record for the DP labeling and secondary packaging process is submitted in Amendment 90 dated 3/19/26.

Method Validation Package

(Reviewed by MV)

Method validation is described in sections 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures and 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.

Combination Products

(Reviewed by BL)

OTARMENI and the Administration Kit are a cross-labeled combination product. OTARMENI must be administered using the devices provided in the administration kit, including one Vygon Premicath® Catheter, one 1 mL syringe, one 3 mL syringe, and one syringe cap. OTARMENI and the Administration Kit are supplied in two different packages. The same United States Prescribing Information, which contains device-related instructions for use, is included in OTARMENI and Administration Kit packages. The syringe pump used for infusion is labeled in the USPI as general use and not part of the combination product. Device review is conducted by Lauren Kokai and Johnny Lam (OCTHT/OTP). Please refer to OCTHT review memo for device information. The device compatibility is documented in 3.2.P.2.6 Compatibility. It is concluded that the data from the device compatibility studies permitted the establishment of minimum required technical specifications for delivery device components for inclusion in the USPI to ensure safe and effective drug delivery.

Comparability Protocols

No comparability protocol is submitted.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

(Reviewed by BL)

The Applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25.20(l). The EA provided a risk assessment that follows the recommendations presented in CBER's Guidance for Industry ("Environmental Assessment of Human Drug and Biologics Applications" and "Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products"). The EA is based on the characteristics and pathology of the parental wildtype AAV1, the genetic modifications to AAV1, the product manufacturing process and control of the replication-competent AAV1, the non-clinical and nonclinical data on the potential toxicity of the AAV1 vector and *OTOF* transgene, vector biodistribution and shedding, the likelihood of transmission to animals and dissemination into the environment, the number of patients to be treated in the US, and product handling, preparation, administration, and disposal procedure in the clinic. Considering the non-pathogenic parental AAV1, the non-hazardous *OTOF* transgene controlled by a tissue limited promoter, the non-replicating and self-limiting nature of the engineered AAV1 vector, the low likelihood of transmission to animal or dissemination

into the environment, the limited number of patients to be treated due to the rarity of the disease, and the risk mitigation procedures in place at the manufacturing facility and the clinic, we conclude that the overall risk to the environment is negligible.

Based on the information in the EA, no significant environmental impacts are expected from the use of OTARMENI for the treatment of patients with congenital hearing loss due to *OTOF* mutations.

B. Reference Product Designation Request

(Reviewed by BL)

The Applicant has requested reference product exclusivity in section 1.3.5.3.

Reviewer's Comments: The Reference Product Exclusivity Period Determination Review form T-846.02 has not been prepared by review team. Reference product designation decision will be made post-approval.

C. Labeling Review

Full Prescribing Information (PI):

(Reviewed by BL)

The Established Pharmacologic Class (EPC) for Otarmeni is adeno-associated virus vector-based gene therapy. Product description in Section 11 DESCRIPTION is modified to be consistent with the EPC. After discussion with USPI labeling reviewer Afsha Amin and PT reviewer Kate Dabirsiaghi, Section 12.1 Mechanism of Action has been modified to i) remove the redundant product description that is already included in Section 11; ii) remove the claim of “hair cell specific” expression of otoferlin in inner hair cells, because expression is also observed in neuronal tissues; and iii) add a limitation that the expression of function otoferlin protein and restoration of synaptic transmission was only shown in mouse studies.

In Section 16 HOW SUPPLIED/STORAGE AND HANDLING, we asked the Applicant to include the NDC numbers for vial, carton, barrier bag and administration kit in the package content tables and add an instruction that the product should be thawed at room temperature. The PI also notes that the vial should be kept in the carton.

The product preparation and administration procedure in Section 2. DOSAGE AND ADMINISTRATION is supported by the device compatibility study as reviewed in 3.2.P.2.6 Compatibility. The PI indicates that thawed vials if not used immediately may be stored in the refrigerator for up to 24 hours or at room temperature for up to 8 hours. Product must be administered within 4 hours of puncturing the vial. The product should be infused with the catheter at a flow rate of 0.9 mL/hour. These steps were all tested under the worst-case conditions in the device compatibility study as detailed in section 3.2.P.2.6 Compatibility.

[Carton and Container Label:](#)

Figure 55. Blister carton provided by Regeneron.

Figure 34: Drug product vial label (provided by Regeneron)

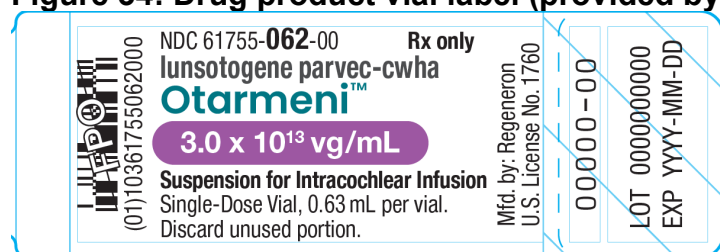
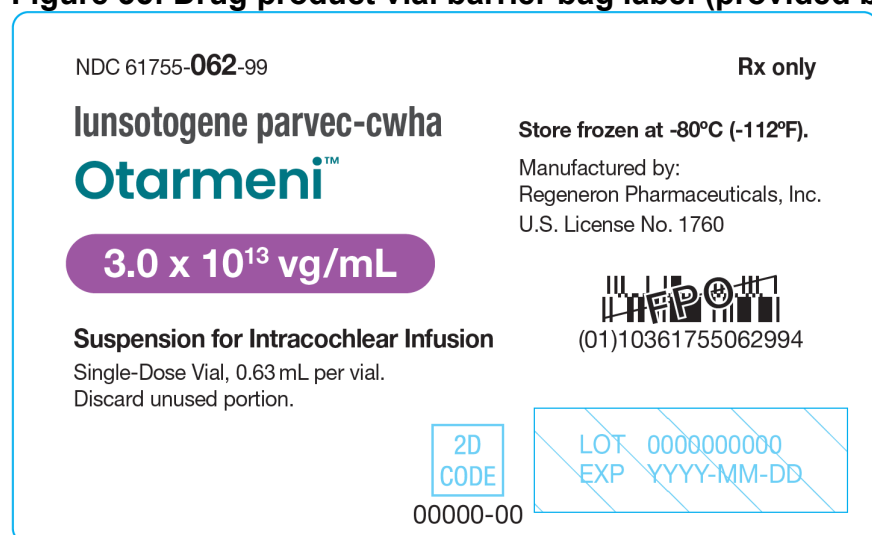


Figure 35: Drug product vial barrier bag label (provided by Regeneron)



Reviewer's Comments:

An intervening matter before the tradename was removed per IR #34 dated 1/16/2026. The revised labels with the intervening matter removed were submitted in Amendment 34 dated 1/20/2026. APLB considered the revised labels acceptable.

The content in the DP vial and package labels is acceptable.

DP container, DP package, and administration device kit package have different NDC numbers. In response to IR #60 dated 2/12/2026, Regeneron assigned a separate NDC code for the barrier bag in Amendment 61 dated 2/17/2026.

The administration device kit is provided in a separate package.

Reviewer's Comments: The content of device kit package label is acceptable. Refer to the device review memo for additional details.

Modules 4 and 5

qPCR assay for quantitation of DB-OTO DNA in human matrices
(reviewed by MT)

The qPCR assay was used for the quantitative determination of DB-OTO concentrations in human shedding matrices (feces, saliva (b) (4) and urine) and biodistribution (plasma [(b) (4)]). The assay is a (b) (4) qPCR method designed to (b) (4)

Assay Procedure



(b) (4)

Assay Validation

(b) (4)

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(b) (4)



(b) (4)

Reviewer's Comments:


(b) (4)



The approach is acceptable.

The qPCR assay is appropriately validated for detection and quantification of DB-OTO

(b) (4)




. The validation is sufficient to support the quantification of DB-OTO DNA in feces, plasma, saliva, and urine.

Cell-Based Assay for Detection of Neutralizing Antibodies Against AAV1 in Human Serum
Assay Description

(reviewed by MT)

This AAV1 neutralization assay was used in the pivotal study DB-OTO-001 and is performed and validated by (b) (4)



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