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**CBER/DMPQ CMC/Facility BLA Review Memorandum**

**BLA STN 125874/0**

**Lunsotogene Parvec [DB-OTO]**

**OTARMENI**

**Viviana Ramirez, DMPQ**

**Reviewer**

**1. BLA#: STN 125874/0**

**2. APPLICANT NAME AND LICENSE NUMBER**

Name: Regeneron Pharmaceuticals, Inc.  
US License #: 1760

**3. PRODUCT NAME/PRODUCT TYPE**

Proper name: Lunsotogene Parvec [DB-OTO]  
Proprietary name: OTARMENI

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

- a. Pharmacological category: gene therapy
- b. Dosage form: injection
- c. Strength/Potency:  $3.0 \times 10^{13}$  vector genomes (vg)/mL
- d. Route of administration: Intracochlear Infusion
- e. Indication(s): for the treatment of patients with biallelic OTOF variant-associated hearing loss

**5. MAJOR MILESTONES**

- Application Receipt Date: December 19, 2026
- Filing Action: February 21, 2026
- PDUFA Action Due Date: April 22, 2026

**6. DMPQ CMC/FACILITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Viviana Ramirez, OCBQ/DMPQ/MRB2	Drug Substance, Drug Product, Facilities
Carl Perez, OCBQ/DMPQ/MRB3	Drug Substance, Drug Product, Facilities
Iryna Zubkova, OCBQ/DMPQ/ARB	DMPQ RPM
Christine Harman, OCBQ/DMPQ/MRB2	Team Lead, Secondary review

**7. SUBMISSION(S) REVIEWED**

Date Received	Submission	Sequence #	Comments/ Status
11/06/2025	125874/0.0	0001	Pre-Submission
11/19/2025	125874/0.3	0004	Response to CMC IR regarding testing laboratories
11/25/2025	125874/0.6	0007	Pre-Submission Wave 2: CMC data (except for validation and stability)
11/25/2025	125874/0.7	0008	Response to DMPQ IR regarding (b) (4) FEI correction and (b) (4) operations.
12/19/2025	125874/0.19	0019	Pre-Submission Wave 3: Shipping validation and stability

Date Received	Submission	Sequence #	Comments/ Status
02/03/2026	125874/0.50	0051	Response to OTP IR: Shipping Validation
02/05/2026	125874/0.51	0053	Response to DMPQ IR: DP PPQ Deviations and Shipping Validation
3/10/2026	125874/0.81	0082	Response to IR: Visual inspection, AQL and Particulate deviations
3/18/2026	125874/0.89	0090	Response to IR: Visual inspection deviations, CAPA effectiveness

**8. REFERENCED REGULATORY SUBMISSIONS (e.g., IND, BLA, 510K, Master File, etc.)**

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference
MF (b) (4)	(b) (4)	(b) (4)	Provided; no DMPQ review required
MF (b) (4)	(b) (4)	Facility and equipment information	Provided; reviewed in separate memo in support of this BLA
MF (b) (4)	(b) (4)	Packaging materials	Provided; no DMPQ review required
MF (b) (4)	(b) (4)		Provided; no DMPQ review required
MF (b) (4)	(b) (4)		Provided; no DMPQ review required
MF (b) (4)	(b) (4)		Provided; no DMPQ review required
MF (b) (4)	(b) (4)	Vials	Provided; no DMPQ review required
MF (b) (4)	(b) (4)		Provided; no DMPQ review required

**9. REVIEWER SUMMARY AND RECOMMENDATION**

**1) EXECUTIVE SUMMARY**

Regeneron Pharmaceuticals, Inc. (hereafter Regeneron) submitted documentation to BLA STN 125874/0 to support licensure of Lunsotogene Parvec [DB-OTO], an adenovirus-based gene therapy product indicated for the treatment of patients with biallelic OTOF variant-associated hearing loss.

CBER/DMPQ reviewed and evaluated the drug substance (DS) and drug product (DP) manufacturing processes, and the facilities proposed for use for the manufacture of DS and DP. Information evaluated and documented in this memo includes:

- Data to validate and support the consistency of the manufacturing process and product quality
- Facility information which includes contamination prevention measures, maintenance of controlled environments, and equipment used during the manufacturing process

As part of the BLA review, Pre-License Inspections (PLI) were conducted at the DP labeling facility (b) (4) from (b) (4). The PLI was documented in an establishment inspection report (EIR). At the conclusion of the PLI, an FDA Form 483 was issued on (b) (4) with one inspectional observation regarding control of primary labeling of DB-OTO final drug product and secondary packaging process. The firm responded on February 13, 2026. All inspectional 483 observations appear resolved; the PLI is classified as Voluntary Action Indicated (VAI).

Facility inspections for DS/DP manufacturing and DP testing facilities were waived based on the evaluations of the facilities' inspection histories and compliance status. The inspection waivers are documented in a separate inspection waiver memo.

## 2) RECOMMENDATION

Approval of the BLA is recommended with the following inspectional consideration:

- *To evaluate the efficiency of the visual inspection (VI) process and training of the VI operators to ensure that operators can effectively identify and reject defective vials including with particulates from the lot and to verify the effectiveness of the implemented CAPAs associated with the visual inspection process in mitigating future deviations relating to the visual inspection.*
- *To evaluate complaints and Biological Product Deviation Reports (BPDRs) related to any finding of particulates in distributed Lunsotogene Parvec [DB-OTO] Drug Product.*

Reference DP Visual Inspection section of this memo (starting on page 23) for further details of visual inspection process. CBER understands that the consideration may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

Below is a listing of the Drug Substance and Drug Product facilities to be included in the approval letter:

DS/DP manufacturing facility:

(b) (4) [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

Primary Labeling and Packaging:

(b) (4) [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

**I. SIGNATURE BLOCK**

<b>Reviewer/Title/Affiliation</b>	<b>Concurrence</b>	<b>Signature and Date</b>
Viviana Ramirez Consumer Safety Officer OCBQ/DMPQ/MRB2	Concur	
Christine Harman Acting Branch Chief OCBQ/DMPQ/MRB2	Concur	
CDR Donald Ertel Acting Division Director OCBQ/DMPQ	Concur	

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## BACKGROUND of SUBMISSION

DB-OTO is composed of two recombinant adeno-associated virus serotype 1 (rAAV1) vectors: DB-OTO-5, encoding the 5' component of the human isoform e otoferlin protein (OTOF) transcript variant 5; and DB-OTO-3, encoding the 3' component of human OTOF transcript variant 5. These two vectors were designed to recombine to form a functional OTOF transcript variant 5 expression cassette and functional human OTOF when co-transduced into the same target cell. DB-OTO is used for the treatment of patients with biallelic OTOF variant-associated hearing loss.

The Drug Product (DP) is a sterile frozen liquid suspension in an aqueous buffered solution, pH 7.3, containing (b) (4) DB-OTO-3, (b) (4) DB-OTO-5, 10 mM sodium phosphate, 180 mM sodium chloride, 5% (w/v) sucrose, and 0.001% (w/v) poloxamer 188. DP is filled into a 2 mL, (b) (4) vial with an elastomeric stopper and an aluminum seal cap.

### 3.2.S.2.5 Process Validation and/or Evaluation

## Description of the Manufacturing Process

The Drug Substance (DS) manufacturing steps, performed at (b) (4), include the following:

(b) (4)

Government	Percentage
Current government	85%
Previous government	15%

## Process Performance Qualification (PPQ)

The PPQ campaign was conducted at the (b) (4) facility by producing (b) (4) consecutive commercial-scale (b) (4) lots and (b) (4) consecutive commercial-scale (b) (4) lots. Each (b) (4) lot (b) (4) was (b) (4) DS lots. The following lot numbers were assigned per PPQ lot: for (b) (4)

The process steps that include in-process testing for (b) (4) with acceptance criteria (AC) are noted as follows:

(b) (4)

| (b) (4)

(b) (4)

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

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| (b) (4)

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| (b) (4)

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

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

| (b) (4)

(b) (4)

All testing results for all PPQ lots met the acceptance criteria.

During execution of the (b) (4) DS PPQ lots, a total of (b) (4) discrepancies and (b) (4) deviations occurred. There were (b) (4) major deviations and (b) (4) that were minor. The following deviations under DMPQ purview are summarized as follows:

(b) (4)

The other deviations under DMPQ purview were associated with documentation/entry errors, calibration failure and equipment malfunctions. All deviations were adequately investigated and addressed.

During execution of the (b) (4) DS PPQ lots, a total of (b) (4) discrepancies and (b) (4) deviations occurred. There were (b) (4) major deviations and (b) (4) that were minor.

Some of the deviations under DMPQ purview are summarized as follows:

(b) (4)

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Regeneron reported no impact to the PPQ runs and all above deviations. The other deviations under DMPQ purview were associated with documentation/entry errors, inadvertent operator errors, calibration failures and equipment malfunctions. All deviations were adequately investigated and addressed.

**Reviewer's Assessment:**

*All in-process (b) (4) testing and DS release testing results under DMPQ purview appear acceptable. Deviations that occurred during the PPQs were investigated and appear to be appropriately resolved.*

*The review of information not under DMPQ purview is deferred to Office of Therapeutic Products (OTP).*

**3.2.P.3.5 Process Validation and/or Evaluation**

**Description of the Manufacturing Process**

The DP manufacturing steps, performed at (b) (4), including the following:

(b) (4)

- Sterile Filtration
- Aseptic Filling, Stoppering and Capping
- 100% Visual Inspection and Acceptable Quality Level Inspection
- DP (b) (4) Pack Out

(b) (4)

(b) (4)

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).

### **Process Performance Qualification (PPQ)**

(b) (4) PPQ lots were manufactured under protocol at (b) (4) were considered (b) (4) consecutive successful executions. PPQ lot (b) (4) was invalidated due to an equipment malfunction involving the filler and relating to crimping issues. This malfunction was classified as an unforeseen, extrinsic factor unrelated to the manufacturing process. All steps prior to the equipment malfunction performed as intended and PPQ lot (b) (4) met all release acceptance criteria. Although PPQ (b) (4) lot was invalidated, the data was used to support (b) (4) studies and to challenge process durations. The list of PPQ runs is summarized in the following table.

PPQ Runs

(b) (4)

(b) (4)

The in-process testing is delineated in the following table:

(b) (4)

The DP release testing is delineated in the following table:

Parameter
Endotoxins (b) (4)
Sterility (AC: no growth)
Particulates-Visual Inspection (b) (4)

(b) (4)

Parameter
Container Closure Integrity Test (CCIT)

(b) (4)

<sup>1</sup> Refer to Deviation 1062383. PPQ Lot (b) (4) was deemed invalid and an additional PPQ run (PPQ Lot (b) (4)) was performed as a result.

A total of (b) (4) deviations ((b) (4) critical, (b) (4) major and (b) (4) minor). Deviations under DMPQ purview including deviations related to EM are summarized as follows:

(b) (4)


(b) (4)

(b) (4)



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(b) (4)



**Reviewer's Assessment:** PPQ Lots (b) (4) were successful. PPQ lot (b) (4) was invalidated and the investigation was adequately addressed. All in-process (b) (4) testing (b) (4) and DP release testing results under DMPQ purview appear acceptable. Deviations that occurred during the PPQs were investigated and appear to be appropriately resolved. The review of information not under DMPQ purview is deferred to OTP.

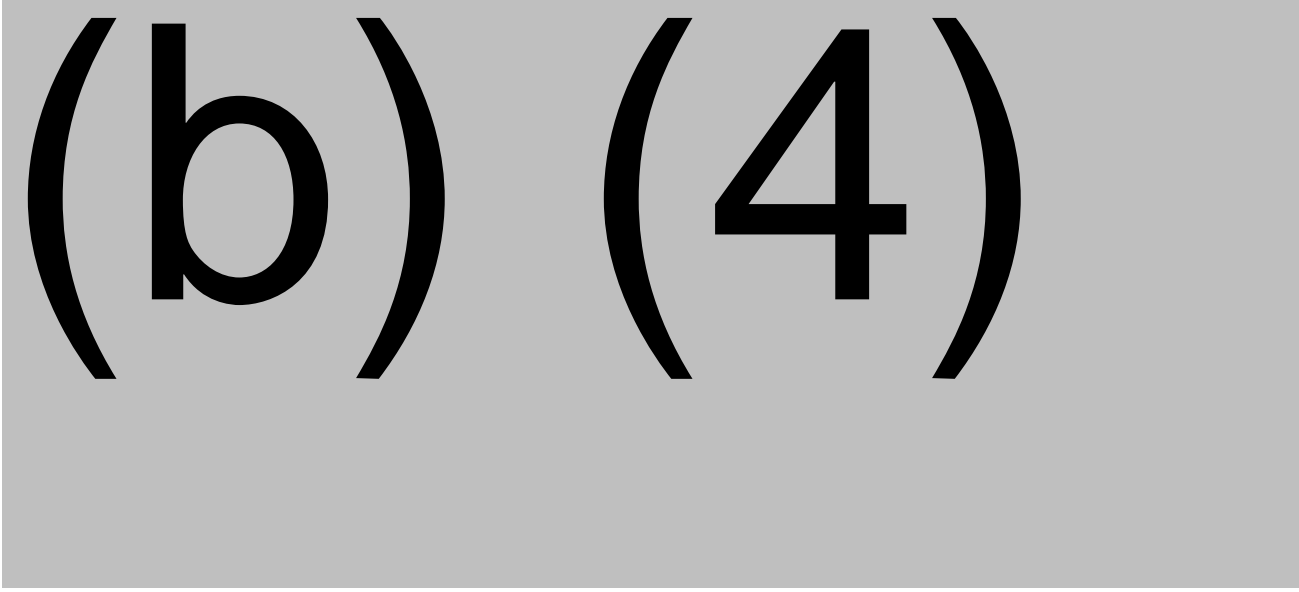
CCIT is reviewed in section 3.7 Container Closure System and appears acceptable. Visual inspection and AQL are reviewed in the Visual Inspection section below.

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(b) (4)

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(b) (4)

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(b) (4)

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### Process Hold Time and Time out of Refrigeration (TOR)

Process hold times, (b) (4) contact times, and time out of refrigeration was validated to demonstrate microbial and biochemical control during the DP manufacturing process while challenging the maximum process durations for the fill finish operations. Target hold times selected for the studies were based on estimated routine manufacturing times, allotting for an extension suitable for unplanned deviations related to manufacturing, equipment, or testing.

(b) (4)

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(b) (4)

Bar Index	Relative Length (Estimated % of Max)
1	100%
2	85%
3	75%
4	55%
5	95%
6	60%
7	90%
8	100%

(b) (4) testing associated with process duration are as follows:

(b) (4)

**Reviewer's Assessment:** The hold time and TOR studies support the selected hold times. All (b) (4) assessments met acceptance criteria. The review of information not under DMPQ purview is deferred to OTP.

### Aseptic Process Simulation (APS)


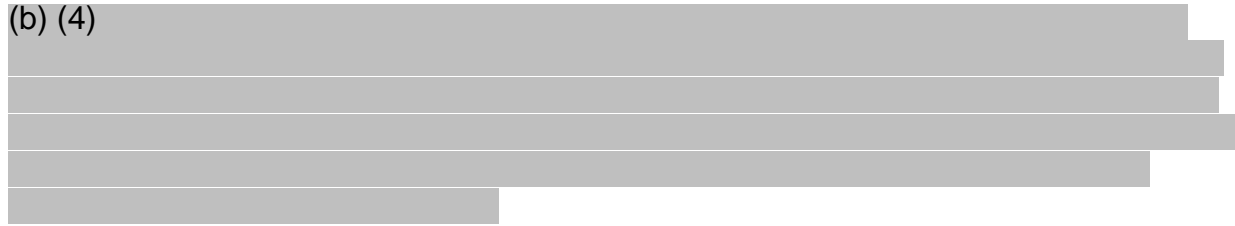
Aseptic filling operations on the (b) (4) were qualified through at least (b) (4) media fill runs (b) (4) currently used on the filling: 2 mL vial with 13 mm opening (b) (4)

The following factors are considered for the media fill runs:

[illegible]

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(b) (4)





### Visual Inspection

After filling operations, sealed vials are 100% visually inspected by trained and qualified operators in accordance with the firm's standard operating procedure. Vials were inspected for defects in the container closure, product (e.g., particulates) and other process handling defects.

Defective vials are documented by reject category and reject limits are defined:

- Critical defects (b) (4)   

- Major A (b) (4)   
  

- Major B (b) (4)   

- Minor (b) (4) 

After visual inspection, samples are taken from the acceptable DP vials for Acceptance Quality Limit (AQL) inspection in accordance with (b) (4) 

Vials identified with defects during the AQL inspection process are categorized by defect type and compared to the established AQL. Subsequently, the accepted filled DP vials are bulk packaged into boxes for long term storage at  -80 °C. If an initial AQL does not pass, an additional 100% visual inspection is conducted and an investigation is required to determine the root cause of the reject rates being exceeded. The second visual inspection is conducted to effectively remove any remaining defects and this is confirmed via the second AQL passing.

During AQL for PPQ (b) (4) a critical defect (b) (4) particulates) and 2 major defects (b) (4) particulates) were observed which exceeded the acceptable level, resulting in a failed AQL inspection (Deviation 1053407 and Deviation 1053416 discussed in the DP PPQ section). The (b) (4) vials were rejected. An additional 100% visual inspection was completed, in which (b) (4) vials were rejected for (b) (4) particulates, and a second AQL inspection under tightened level III conditions was performed and passed.

During 100% visual inspection of PPQ Lot (b) (4) a closure defect related to crimping was observed (refer to Deviation 1062383 in the DP PPQ section). Visual inspection was paused for PPQ (b) (4) once the crimping defect was identified at which point (b) (4) vials had been inspected and of those (b) (4) vials inspected, (b) (4) were rejected. After completion of the PPQ (b) (4) fill, the remaining (b) (4) vials were inspected of which (b) (4) vials were rejected. An additional 100% visual inspection of the (b) (4) vials prior to the pause were inspected and (b) (4) vials were rejected. The affected vials were segregated, and the remaining vials passed AQL inspection.

During the 100% visual inspection of PPQ Lot (b) (4) a total of (b) (4) vials with (b) (4) particulates were identified, exceeding the acceptable threshold. Subsequently, an AQL inspection was performed, during which (b) (4) vials containing (b) (4) particulates were observed and rejected. Following the AQL failure, a second 100% visual inspection was conducted, identifying (b) (4) vials with (b) (4) particulates. These vials were segregated and rejected. A second AQL inspection was conducted and passed (refer to Deviation 1084150 in the DP PPQ section). An investigation was conducted to determine potential root causes for the intrinsic particles seen in visual inspections of PPQ lots (b) (4)

Potential root cause was identified as the type of (b) (4) used to clean the (b) (4) and (b) (4) area, the type of (b) (4) known to shed, and lack of specific guidance in procedures regarding (b) (4) and proper (b) (4) techniques for (b) (4). A CAPA was initiated to revise procedures, establish a Facility Particle Library, and require identification testing for all particulate rejects for (b) (4). Additional actions included elimination of the problematic (b) (4), procedural clarification of aseptic handling practices, and implementation of (b) (4).

The visual inspection results are delineated in the table below.

Table 4: PPQ Visual Inspection Results

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



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(b) (4)

In response to an IR, additional information was provided in amendment STN 125874/0.81 (eCTD 0082) received 03/10/2026, that included additional details of the visual inspection deviations and corrective actions to address the presence of particulates, which were not effectively identified during the first round of the 100% visual inspection.

Deviation 1087937 investigated the reject limit of (b) (4) being exceeded for Major A defects during the visual inspection for PPQ (b) (4) Lot (b) (4). Both the first and second visual inspections exceeded this reject limit of Major A defects (b) (4). The first inspection rejected (b) (4) vials with Major defects (b) (4). A second visual inspection was performed and rejected (b) (4) vials with Major A (b) (4) particulate defects (b) (4).

Deviation 1084732 initiated to investigate the PPQ (b) (4) failed AQL limit. Investigation included interviews with operators who performed the first and second visual inspections. The interview identified inconsistency between the first and second visual inspections.

To address the inconsistency between the first and second visual inspections and to ensure all visual inspection performed are performed in a robust manner, the following corrective actions were implemented:

1. Updates to Standard Operating Procedure (SOP) 05.0112 for “Manual Visual Inspection of Filled Vials” that includes the following:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2. Updates to SOP 05.114 “Qualification of Personnel for Visual Inspection of Drug Product Vials” that includes

(b) (4)

(b) (4)

(b) (4)

3. Updated procedures to establish a baseline for types, sources and frequency of particulate matter observed to enable trend analysis and process improvement efforts.

Regarding the source of the particulates, Deviation 1084150 was initiated to investigate the root cause of the (b) (4) particles identified during the visual inspection of PPQ (b) (4). During PPQ (b) (4) a total of (b) (4) vials were rejected across both visual inspections and AQL due to (b) (4) particulate matter. The particulate matter was sent for analysis and identified as (b) (4).

A (b) (4) Root Cause Analysis was performed that addresses both deviation 1087937 and 1084150. Method and materials were identified as root causes. Materials that have the potential to shed particles were identified to be (b) (4) used for packaging parts; (b) (4) used during manual cleaning; and (b) (4) used for cleaning and preparation. The corrective actions to address the potential root causes of method and material included the following:

- Revision of the relevant procedure to require a deviation for all particle rejects identified during visual inspection and AQL. This action was closed on 08Dec2025.
- Revision of SOP 05.0112 “Manual Visual Inspection of Filled Vials” to define the initial handling of (b) (4) particles. This action was closed on 06Mar2026.
- Revision of SOP 05.1364 “Manual Cleaning of the Filler Parts at (b) (4) ensures removal of the ability to use (b) (4) preparation areas to prevent a potential source of particulates. This action was closed on 08Dec2025.
- Addition of instruction to SOP 05.1327 “Operation of the (b) (4) Filling System” that (b) (4) must be opened with (b) (4) and cannot be (b) (4) to ensure aseptic processing and prevent disruption of (b) (4). This action was closed on 08Dec2025.
- Addition of instruction to relevant procedure that after filler set up is completed, the (b) (4) must be thoroughly (b) (4) using approved (b) (4) to remove any potential particulates on the (b) (4). This action was closed on 08Dec2025.

In response to a follow-up IR regarding the corrective actions addressing the occurrences of particulates in the visual inspection and CAPA effectiveness, additional

details were provided in amendment STN 125874/0.89 (eCTD 0090) received 03/18/2026. The firm provided a complete listing all the CAPAs that were initiated and confirmed that effectiveness checks were initiated for CAPAs (1098613, 1098612) associated with updates to procedures used for the visual inspection qualification training and visual inspection process. These CAPAs are still active and are pending completion, April 7, 2026. Additionally, an effectiveness check will be evaluated upon closure of CAPA 1072770 (status ongoing), initiated to address recurrence of particulates, and includes revisions to procedures relating cleaning and operations of the (b) (4) filling system. The preventive actions in associate with CAPA 1072770 include removal of (b) (4) as the particulate source, clarifying instruction on the (b) (4) to reduce potential introduction of (b) (4) generated at this stage.

The firm also clarified that the impact and risk to product quality of PPQ lots regarding the presence of particulates, was assessed by both (b) (4) and Regeneron. The assessment determined there was no impact to product quality for the PPQ lots with visible particulates. This conclusion is based on the following:

- All vials containing particulates were separated and rejected from the batch.
- Batches passed the second tightened AQL Level III inspection with zero critical zero or major A defects.
- Release testing confirmed all PPQ lots passed appearance testing with results of "Clear to slightly opalescent colorless solution and essentially free from visible particulates" and passed particulate matter release testing.
- Regeneron Quality Assurance reviews and approves all deviations and CAPAs associated with a batch which includes an impact and risk analysis. QA determined the PPQ lots associated with the deviations could be dispositioned in accordance with applicable disposition procedures.

**Reviewer's Assessment:** *Several major deviations occurred during the visual inspection of PPQ lots, particularly PPQ (b) (4). Several information requests were issued relating to the deviations and corrective actions. Of major concern, is the inconsistency in identifying and removing defective vials containing particulates during the 100% visual inspection as the second visual inspection had removal of (b) (4) vials that were not identified during the first visual inspection. The firm provided details and clarifications to address major concerns associated with the visual inspection process and occurrence of particulates. The investigations and CAPAs appear adequate to address the identified root causes of the deviations. Of note, (b) (4) was issued an FDA-483 from a PLI conducted (b) (4) (b) (4) with an observation related to deficiencies in the visual inspection procedures and training. However, according to the FDA-483 response assessment, the identified issues were all addressed and corrected with the inspection classified as Voluntary Action Indicated (VAI).*

*Although the firm provided adequate responses to address the major concerns with the visual inspection, (b) (5)*

(b) (5)

### DP Vial Labeling and Packaging

Primary labeling/secondary packaging of final DP vials is performed at (b) (4). After receipt of unlabeled DP vials shipped from (b) (4), vials are (b) (4). After labeling/packaging completion and batch review and release by (b) (4), Regeneron, finished products are shipped using a validated shipper at -80 °C.

The labeling/packaging process at (b) (4) was evaluated by CBER/DMPQ in a (b) (4) PLI (see Establishment Inspection Report, (b) (4)). At the conclusion of the PLI, a one-item Form FDA 483 was issued to (b) (4), which consisted of four observations related to the labeling/packaging process. The firm responded to the observations, and the corrective actions were reviewed and found to be adequate (see FDA Form 483 response review memorandum, February 20, 2026). All inspectional issues were resolved, and the inspection was classified as voluntary action indicated (VAI).

### Labeling and Packaging PPQ

As a follow-up to FDA Form 483 Observation 1a citing the lack of a labeling and packaging process validation at (b) (4), the firm provided final PPQ summary report EVR-000833995 in Amendment 87 (BLA STN 125874/0.87 received March 13, 2026), summarizing the completed DB-OTO commercial labeling/packaging process validation. (b) (4) simulated labeling/packaging runs consisting of (b) (4) vials each were performed (b) (4) using materials representative of the commercial labeling/packaging process of DB-OTO final DP vials. In the labeling/packaging process, vials are labeled, placed in (b) (4) bags, sealed, and packed into a carton with the prescribing information. Packaging quality attributes were assessed for all vials, (b) (4), and cartons (e.g., undamaged product, correct product count, print legibility, label adherence, etc.). All acceptance criteria were met, with one deviation observed in Run (b) (4) (temperature excursion observed in (b) (4)), which resulted in a corrective action implementing a (b) (4) to improve to improve operator ergonomics and temperature control.

**Reviewer's Assessment:** All labeling and packaging PPQ acceptance criteria were met, with the one deviation appropriately resolved and determined to have no impact to the PPQ. The results of the PPQ demonstrate the commercial (b) (4) labeling/packaging process can consistently and accurately produce acceptable labeled/packaged final commercial DP product. The DP labeling/packaging PPQ appears acceptable.

### Primary Label Adherence Study

As a follow-up to FDA Form 483 Observation 1c referring to the lack of a label adherence study to demonstrate DP vial primary labels remain legible and adhered to the vial throughout the proposed shelf-life and storage conditions (b) (4) months at -80 °C), the firm provided label adherence study protocol REGN-PTL-19FEB2026, v2.0 in Amendment 87. The label adherence study is a real-time aging study evaluating the final commercial DP label and packaging components. The study will evaluate label legibility and adherence performance of (b) (4) total samples with clearly defined inspection and study acceptance criteria, with the following testing timepoints (b) (4) samples each timepoint): 0 days, 7 days, 14 days, 1 month, 3 months, 6 months, 9 months, 12 months, (b) (4) .

**Reviewer's Assessment:** In Amendment 66 (BLA STN 125874/0.66, received February 19, 2026), the firm indicated the label adherence study will be underway in March 2026. The label adherence study protocol appears adequately designed to evaluate the long-term stability and performance of the primary vial label when stored at -80 °C for (b) (4) months, which is more than the proposed shelf-life.

### Shipping Validation

The shipping validation consisted of several studies that included a transport simulation study for the (b) (4) DP and the Administration Kit, in addition to real-world transport studies for the (b) (4) DP, labeled drug product (LDP) and the Administration Kit.

### **Transport Simulation**

(b) (4) DP

The transport simulation qualification was conducted for DP (b) (4) load using a worst-case approach in terms of (b) (4) and continuous duration of exposure to (b) (4) transport.

The approach for Transport DP Simulation Qualification included the following:

Parameter	Approach	Testing Required
Study variables	(b) (4)	Full product release and CCI testing; Visual inspection
Shipment configuration	(b) (4)	Full product release and CCI testing; Visual inspection
Container evaluated	Vial, (b) (4) barrier bag	Full product release and CCI testing; Visual inspection

The transport simulation testing was considered worst-case when compared to real-world transport qualification for the following reasons:

- Transport simulation exposes the product to concurrent transport hazards for (b) (4) continuous (b) (4), which is longer than the estimated (b) (4) (b) (4) from the (b) (4) site to the pack/label site.
- Transport simulation testing is performed as a (b) (4) rather than a (b) (4) which exposes the product to more severe (b) (4).

The transport simulation qualification study was performed in accordance with FDA recognized standard (b) (4) (b) (4)

Transport simulation qualification was conducted in the following order:

(b) (4)

The testing conducted included full product release testing (appearance AC: Clear to slightly opalescent colorless solution and essentially free from visible particles), CCIT (AC: no leak detected) and visual inspection (AC: no obvious physical damage) and all passed acceptance criteria. Endotoxin and sterility testing were not performed as sterility results remain unchanged over time, provided the container closure remains intact.

Simulation studies were not performed with the LDP as the (b) (4) DP represented the worst-case packaging, using a (b) (4) configuration and thus results of these studies are used to support shipment of both DP and LDP. Real-world studies were conducted for both DP and LDP to evaluate the impact of the shipping conditions included increased distance, duration and handling events on the DP and LDP.

#### Administration kit

The intended kit components underwent design verification using worst-case simulated shipping conditions per (b) (4)

The approach for the Simulated Administration Kit Transport Qualification included the following:

Parameter	Approach	Testing Required
Study variables	(b) (4)	Design verification testing; Visual inspection of all packaging material and components
Shipment configuration	(b) (4)	Design verification testing; Visual inspection of all packaging material and components
Container evaluated	(b) (4)	Design verification testing; Visual inspection of all packaging material and components

The shipment configuration was (b) (4) shippers represent the distribution chain to the end users (ex. hospitals). The container included components, shipper and carton. The testing conducted included design verification testing and visual inspection of all packaging material and components.

Functional testing on the devices was performed after preconditioning the components through real-time aging and simulated shipping to represent a worst-case scenario for handling conditions. Simulated shipping preconditioning per FDA recognized standard, (b) (4), was conducted on the component kit in its packaging, comprised of all device components, assembled and packed into cartons and shippers.

The table below delineates the administration kit simulation shipping schedule sequence.

(b) (4)



**(b) (4)**

All functional design input requirements and acceptance criteria were verified through design verification testing to provide evidence that the kit components and delivery system perform as intended. Visual inspection of the packaging and individual components after simulated shipping passed with no failures, confirming that the components and secondary packaging were free from physical damage. A real world study was also performed to confirm that the packaging configuration adequately protects the kit components during transport.

### Real-World Transport Qualification

**(b) (4) DP**

The real-world transport qualification evaluated the performance of the product transport system through **(b) (4)** shipments, confirmed that the cold chain process was maintained throughout transport, and included inspection of the product for gross damage after shipment. The qualification route exposes product to increased distance, duration, and handling events as compared to anticipated commercial shipping routes. Product quality and CCIT are performed in accordance with the current effective specification at the time of testing to confirm the product quality is maintained under real-world transport conditions.

The approach for Real World **(b) (4)** DP Transport Qualification included the following:

Parameter	Approach	Testing Required
Study variables	<b>(b) (4)</b>	Full product release and CCI testing Visual inspection of all packaging material and vials Temperature review
Shipment configuration	<b>(b) (4)</b>	Full product release and CCI testing Visual inspection of all packaging material and vials Temperature review
Container evaluated	Vial, <b>(b) (4)</b> barrier bag <sup>a</sup> <b>(b) (4)</b>	Full product release and CCI testing Visual inspection of all packaging material and vials Temperature review

<sup>a</sup>All **(b) (4)** containing active product were enclosed in **(b) (4)** barrier bags for the first real-world qualification. During the real-world qualification addendum, all **(b) (4)** whether containing active product or **(b) (4)** material were enclosed in **(b) (4)** barrier bags. CCI, container closure integrity; **(b) (4)** DP, drug product; LDP, labeled drug product.

Real-world transport qualification for the (b) (4) DP was conducted using a combination of (b) (4) material using the primary container (vial), (b) (4), shippers and (b) (4) configuration intended for transport of commercial (b) (4) DP. (b) (4) material consisted of (b) (4) commercially representative vials. The use of (b) (4) vials as (b) (4) material is considered an equivalent or greater challenge in terms of (b) (4)

To ensure sufficient material for product quality and CCIT, (b) (4) minimum loads were shipped, arranged over (b) (4). The (b) (4) DP load configurations for the real-world study included maximum and minimum loads as detailed in the following table:

(b) (4)

[illegible]

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(b) (4)

(b) (4). Upon receipt of material for the real-world qualification, two deviations were identified: physical damage to the (b) (4) and failure to maintain temperature within the (b) (4). These deviations and actions are summarized as follows:

#### Physical damage deviation

The damage was identified during visual inspection of the maximum load. (b) (4) cracked (b) (4) were observed. The (b) (4) contained (b) (4) consisting of (b) (4). No damage was observed to the shippers and all (b) (4) containing active DP were free from damage. The root causes were identified as absence of (b) (4) barrier bags for (b) (4) and the unpacking/receipt process. All (b) (4) containing active DP were enclosed in (b) (4) barrier bags and showed no damage during inspection. No (b) (4) bags were utilized for the (b) (4) since it consisted of (b) (4) only; nonetheless, this appeared to affect the protection provided. An addendum to the qualification, delineated below, was executed using (b) (4) barrier bags, and no physical damage was observed, confirming this as a likely root cause. Regarding the unpacking and receipt process, (b) (4) containing (b) (4) were more difficult to remove from the shipper compared to (b) (4) with active DP, as the (b) (4) barrier bags were used for (b) (4) with active DP, which allowed for easier removal from the shipper. To remove (b) (4) containing filler material, the shipper had to be tilted, which allowed for (b) (4) to enter and penetrate the (b) (4).

To minimize damage during the receipt process, routine packing and transport will incorporate the use of (b) (4) barrier bags. The pack/label site is required to follow procedural guidelines, which include documenting any damage observed upon receipt, segregating damaged material, notifying the client within one business day, and ensuring that damaged vials are not further processed.

#### Temperature excursion deviation

Upon receipt of the (b) (4) shipment, it was found that the temperature monitoring devices located (b) (4) the shippers, (b) (4) of the pallets monitoring the temperature within the (b) (4) did not maintain the required temperature of (b) (4) throughout the shipment. During the unpacking process the following was observed:

(b) (4)

Despite the temperature excursion inside the shipper, impact to the product quality is considered low, support by research/development stability data indicating that DP remains stable at (b) (4) for up to (b) (4) months with no impact to product quality.

An investigation determined the root cause was attributed inadequate (b) (4) of the (b) (4) resulting from incorrect interpretation of procedures, insufficient training on (b) (4) (b) (4) process, inadequate equipment to perform (b) (4) and third party logistics provided not communicating temperature readings of (b) (4) every (b) (4) per procedure. The (b) (4) procedure was clarified and third party personnel were retrained prior to executing an addendum to the real-world transport qualification to ensure temperature maintenance during shipping.

#### Addendum To Real World Transport Qualification

An addendum to the real world transport (b) (4) DP qualification was executed to address the deviations summarized above. The addendum focused on the temperature maintenance and adequate product protection during transport. The addendum utilized (b) (4) maximum load, containing (b) (4) material only since the physical damage was observed solely at the maximum load. In addition, the maximum load represented a worst-case scenario in terms of temperature maintenance since the maximum load (b) (4) configuration provides less room for (b) (4) compared to the minimum load. The (b) (4) maximum load configuration, temperature monitoring devices location, and shipping route were the same as those described in the original qualification protocol.

The environmental temperature outside the (b) (4) ranged from (b) (4). Upon receipt, it was observed that both the (b) (4) and the (b) (4) failed to maintain the required temperature of (b) (4) for the full duration of the shipment; nonetheless, the internal temperature of the shippers was successfully maintained within the required -80°C (b) (4) (b) (4) temperature range for the duration of the shipment which was (b) (4).

Preliminary discussions with the third-party shipper identified malfunction as the root cause for the observed temperature excursion in both the (b) (4) and (b) (4). No physical damage to the shippers or (b) (4) was observed.

Additional information was provided in amendment STN 125874/0.50 (eCTD 0051) received 02/03/2026, in response to an IR sent for clarification on the shipping studies and the deviations noted during the real-world shipping. Regarding the third-party shipping company employed in the validation study, the applicant confirmed the same third-party shipping company may be used as well as other third-party shipping companies. The qualification of the shipping container is applicable to any shipping company provided that the same shipping qualified conditions are applied.

Regarding the temperature excursion failures that occurred during the Real-World Qualification studies, there were preliminary discussions with the third-party shipper that identified equipment malfunction as the root cause. Three investigations were launched as a result of the shipping validation deviations.

The first investigation looked at the (b) (4) shipment part of the validation and noted that the (b) (4) did not maintain (b) (4) temperatures during shipment. The root cause was identified to be that the (b) (4)

(b) (4) As a corrective action the (b) (4) was replaced. The (b) (4) was taken to the (b) (4) where it was confirmed that the (b) (4) on the (b) (4) was not (b) (4) properly, causing prolonged (b) (4). Preventative maintenance of the equipment should prevent recurrence of this issue. To ensure the immediate action was successful the vendor ran the (b) (4) and determined the (b) (4) was (b) (4) properly after repair. Additionally, the (b) (4) of the (b) (4) ran the Temperature Controlled Unit for several hours to verify the repair met requirements. As a way to confirm this action remains effective, the shipping company has effectiveness checks as part of the corrective action program that is under the purview of Regeneron auditing oversight.

The second and third investigations looked at the (b) (4) shipment part of the validation. The following instances were noted: The root causes identified were that the standard operating procedure for shipping validations was not followed and that a contingency plan for (b) (4) was not a part of the procedure. Multiple corrective actions were implemented as a result of these instances:

A procedural update was made to the shipping validation procedure and sent out for additional training, with the following updates:

- (b) (4)
- 

In addition to the contingency plan to (b) (4) during (b) (4), an additional suggestion was to decrease the transit time as the (b) (4) transit schedule exceeds the operational parameters of the container for deep frozen shipments without (b) (4) replenishment activities. This consideration is being explored to support applications in other jurisdictions where the (b) (4) shipment duration cannot be implemented. A review of the QAAs and procedures that support commercial shipment of DB-OTO was completed in response to these investigations. The review concluded that the current procedures and quality oversight align with the corrective actions and would support that commercial shipments of DB-OTO would not experience deviations of the same root cause. In addition to the effectiveness checks required at the shipping company a review of historical investigations is required on the launch of any new investigation. This retroactive review would flag if similar deviations to the ones described above are

occurring allowing for further effectiveness assessments of the corrective actions implemented across all Regeneron programs.

Additional information was provided in amendment STN 125874/0.51 (eCTD 0053) received 02/05/2026, to provide details on worst-case conditions implemented in the shipping study. The environmental temperature ranges (outside of the (b) (4) ) challenged for the real-world transport qualification and addendum to the real-world qualification studies for (b) (4) DP are summarized below:

(b) (4)

Atmospheric pressure changes were not monitored as part of the real-world transport qualification for the DB-OTO (b) (4) DP because the (b) (4) are not able to withstand the cold temperatures required in the transport of this product. However, transport-simulation qualification of the (b) (4) DP included (b) (4) equivalent to (b) (4). The simulation of (b) (4) equivalent to (b) (4) is considered worst case because it is equivalent to (b) (4) transport (b) (4). This simulated (b) (4) transport (b) (4) exceeds (b) (4) transport conditions, as (b) (4) are required to be (b) (4).

Following transport simulation qualification, product quality and container closure integrity testing results were all within the acceptance criteria at the time of testing. Additionally, Regeneron has monitored (b) (4) for other product real-world transport qualification studies using the same shipping route as was used in the real-world transport qualification for DB-OTO (b) (4) DP. The (b) (4) experienced during this route ranged from a minimum of (b) (4) to a maximum of (b) (4) (b) (4) which are approximate to the aforementioned (b) (4) tested in the transport simulation qualification (e.g., (b) (4)).

Regarding the regulatory standard applied for the execution Real-World Transport Qualification of the (b) (4) DP and LDP shipping validation, the applicant indicated that a regulatory standard is not applicable to the real-world transport qualification because the study ships material based on the intended commercial shipping route. The intent of the (b) (4) DP and LDP studies are to demonstrate that the intended routine commercial shipping process can maintain the specified temperature and that the packaging configuration adequately protects the product, and that product quality is in accordance with the current effective specification (b) (4) DP only). The real-world transport qualification study is performed in a manner that is consistent with the intended routine shipment process for the product, including modes of transport, packaging, and packaging configurations. DB-OTO was qualified to (b) (4) using a transport simulation protocol. (b) (4) was determined to be appropriate based on the product packaging (e.g., individual packaged

products distributed by (b) (4) ). The transport simulation qualification was designed to challenge the upper and lower bounds of stressors that may be experienced during routine transport, including concurrent and continuous exposure to (b) (4)

### *Labeled Drug Product (LDP)*

The qualification was performed utilizing (b) (4) , which consisted of (b) (4) commercially representative vials rather than active product. This approach was deemed suitable as the primary container, packaging and packaging configuration are identical for both active and (b) (4) . As DP and LDP utilize the same transport system, quality testing will be conducted at the (b) (4) DP level as this is worst case in terms of the level of protection that the packaging provides to the product.

The challenges included (b) (4)

The approach for Real World LDP Transport Qualification included the following:

<b>Parameter</b>	<b>Approach</b>	<b>Testing Required</b>
Study variables	(b) (4)	Visual inspection of all packaging material and vials Temperature review
Shipment configuration	(b) (4)	Visual inspection of all packaging material and vials Temperature review
Container evaluated	Vial, (b) (4) barrier bag (b) (4)	Visual inspection of all packaging material and vials Temperature review

The real-world transport qualification routes for the LDP are delineated in the table below.

(b) (4)



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(b) (4)

(b) (4)

#### Administration Kit

The real-world transport qualification route consisted of round-trip (b) (4) (b) (4) transport in ambient temperature-controlled (b) (4) and/or (b) (4) between Regeneron in (b) (4). The

real-world transport qualification route was designed to exceed routine shipments in terms of distance and duration. This route contains a minimum of (b) (4) nodes where handling events occurred, which exceeds the number of nodes in the anticipated domestic or international shipping lanes.

#### Approach for Real-world Administration Kit Transport Qualification

Parameter	Approach	Testing Required
Study variables	(b) (4)	Visual inspection of all packaging material and components
Shipment configuration	(b) (4)	Visual inspection of all packaging material and components
Container evaluated	Shipper and carton	Visual inspection of all packaging material and components

#### Shipping load configuration for the administration kit

(b) (4)

The real-world transport qualification routes are delineated in the table below.

(b) (4)

(b) (4)

(b) (4)

Visual inspection of the packaging and individual components after simulated shipping passed with no failures, confirming that the components and secondary packaging were free from obvious physical damage.

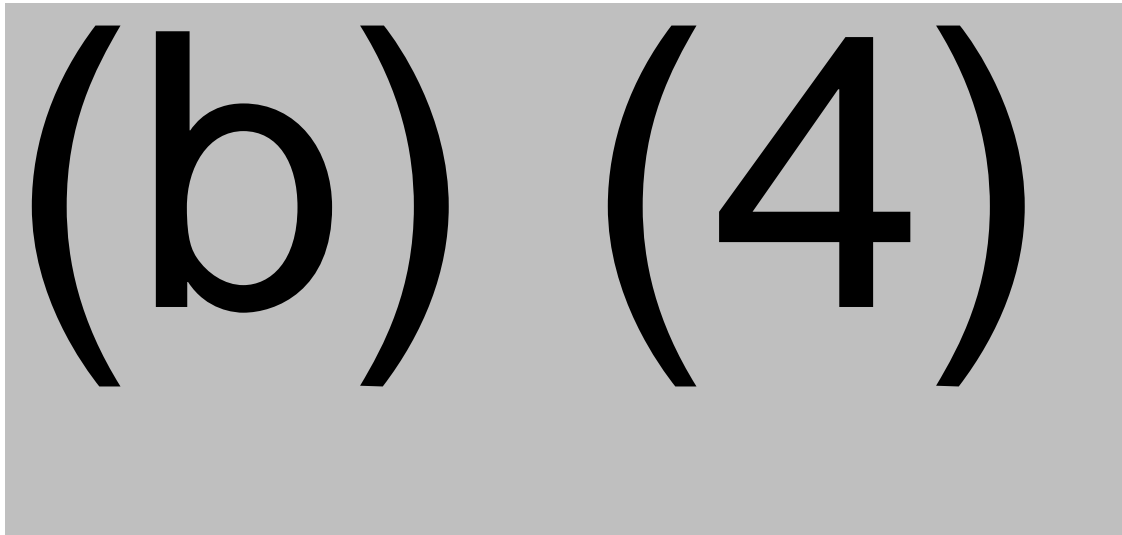
**Reviewer's Assessment:** The DP shipping validation (simulation and real-world transport) included visual inspection, (b) (4) CCIT (for DP simulation and (b) (4) DP) under the worst-case shipping condition.

Based on the information provided in the submission and the responses to the information requests, the shipping validations to support the (b) (4) DP, LDP and Administration Kit appear acceptable.

**3.2.S.6 Container Closure System for Drug Substance**

(b) (4)

Table 5: DS Container Closure System



**Reviewer Assessment:** The container closure used for the DS appears adequate and appropriately controlled. The assessment of the compatibility of the container for storage of the DS is deferred to the OTP reviewer.

**3.2.P.7 Container Closure System for Drug Product****Components of the Container Closure System (CCS)**

The components of the primary CCS for DB-OTO DP is detailed in the following table.

**DB-OTO DP Primary Container Closure Components**

	<b>Vial</b>	<b>Rubber stopper</b>	<b>Cap</b>
Description	(b) (4) serum vial, 2 mL	13-mm, (b) (4) grey chlorobutyl rubber stopper (b) (4)	Aluminum seals with a flip-off plastic top, Blue
Manufacturer	(b) (4)	(b) (4)	(b) (4)
Catalog	(b) (4)		
Sterilization	(b) (4)		

	Vial	Rubber stopper	Cap
Particulates	Unspecified	(b) (4)	Not applicable
Bacterial Endotoxin	(b) (4)	(b) (4)	Unspecified
(b) (4)			

RTU = ready to use (received pre-sterilized by supplier)

**Reviewer's Assessment:** The selected primary CCS for DB-OTO is commonly used for cell and gene therapy products due to its performance properties of break resistance and structural integrity under cryogenic storage conditions. The (b) (4) material is more durable than glass at low temperature, and DB-OTO DP is stored at -80 °C. Rubber stoppers and (b) (4) (b) (4) have more similar coefficients (than glass) of thermal expansion, reducing the risk of ingress. All components in the DP primary packaging components are received sterile and ready to use. The components of the CCS are released against vendor specifications based on the Certificate of Analysis (CoA) provided by the manufacturer.

### Container Closure Integrity Test (CCIT)

The firm provided the following regarding CCIT as a microbial contamination control (sterility) of the DP:

Manufacturing or Quality Activity	Summary	Reference
Equipment qualification	Equipment qualification is performed on the (b) (4) system to demonstrate appropriate (b) (4) at DP manufacturing process operating range	Process Validation-Aseptic processing
Manufacturing Process Validation	Manufacturing microbial control process consistency and container closure integrity are verified during DP manufacturing. CCS integrity is verified during DP PPQ. Sterility testing is performed on vials from (b) (4) of fill.	Process Validation-PPQ
Stability testing	CCIT is performed on DP stability samples (b) (4) to ensure integrity of the (b) (4) is maintained throughout the shelf life	Stability

To support the CCIT, the firm provided a CCIT Verification package that includes a CCIT Feasibility Study Report, a CCIT Qualification Protocol (AQ-PTCL-033238) and Qualification Summary Report (AQ-SR-047345). The firm uses the (b) (4) (b) (4) method for testing integrity of the final container. The testing is performed by (b) (4) in accordance with (b) (4) and FDA recognized standard (b) (4)

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(b) (4)

The firm indicated that CCIT will be performed as part of the post-approval stability protocol. A minimum of (b) (4) of DP will be placed on long-term stability at the recommended storage condition every (b) (4) that manufacturing of such lot(s) occurs. The lot(s) will be tested for integrity using the (b) (4) method at the following time intervals: 12, (b) (4) months for long-term storage at -80°C (long-term stability study for Lot (b) (4) ends at (b) (4) months).

Additional information was also provided in amendment STN 125874/0.81 (eCTD 0082) received 03/10/2026, to address an information sent to clarify if the firm had initially performed CCIT on vials filled on the (b) (4) filling system, as it was noted that CCIT will be performed on stability (b) (4) starting at 12 months and no data on CCIT was provided. Additionally, the CCIT method validation provided, did not clarify if the vials used for the study were prepared on the same filling line as DB-OTO DP, the (b) (4) filling system. The amendment including the following clarifications:

Regarding if CCIT had been initially performed for vials filled on (b) (4) filling system, the firm confirmed that the origin of the samples tested in the CCIT qualification protocol for the 2 mL vials were for an FDA-approved (b) (4) ) which was leveraged for method sensitivity. The sample vials were filled at a different (b) (4) site using a different filling line. The firm states that CCIT is not dependent on product, type of product, the amount of product in the vial or the filling site, indicating that the critical element is the vial configuration and the tooling and method configuration used for CCIT is the same for the vial configuration. The following table was included in the response that outlines the differences between DB-OTO and Reference lot for CCIT:

(b) (4)



(b) (4)

(b) (4)

#### Container Closure Integrity Results for Lot (b) (4)

(b) (4)

The firm indicated that there have been no CCIT timepoints tested for lots on long-term stability as the (b) (4) sample pull for the stability lots has not yet occurred. The PPQ lots put on stability are tested (b) (4) for CCIT and the first lot (PPQ lot (b) (4) Lot (b) (4) ) sample pull date is (b) (4) . The sample pull date for PPQ lot (b) (4) (Lot (b) (4) ) is (b) (4) and the pull date for PPQ Lot (b) (4) Lot (b) (4) ) is (b) (4) (b) (4) Data can be provided to the Agency for CCIT testing for the stability samples as early as August 14, 2026 or provided with the annual report.

**Reviewer's Assessment:** The qualification report for the CCIT method employing the (b) (4) method supports that the method has been adequately validated for the 2 mL vial configuration. The firm provided sufficient CCIT results of vials from a PPQ lot of DB-OTO DP with results meeting the acceptance criteria demonstrating that container closure system filled on the (b) (4) filling system is integral. Additionally, the firm plans to perform CCIT (b) (4) on stability and will provide the results in the annual report to support the CCS integrity over the shelf-life.

## Stability

The firm is performing the following stability studies and provided the protocols for the stability program:

- Long term stability conducted at -80°C to support expiry dating  
 (b) (4)  
 (b) (4)
- Accelerated stability studies conducted at (b) (4) (development (b) (4) only) to support DP manufacturing and handling at refrigerated conditions
- (b) (4) stability studies conducted at (b) (4) and (b) (4) (development (b) (4) only) to provide insight into possible DP degradation pathways

Testing performed on long-term stability under DMPQ purview includes CCIT using (b) (4). As previously noted, the firm plans to perform CCIT (b) (4) starting at 12 months, as part of the post-approval long-term stability study. There is no testing under DMPQ purview for the accelerated and (b) (4) stability studies.

**Reviewer Assessment:** CCIT testing is planned to be performed (b) (4) starting at 12 months, thus, data is not yet available but will be provided in the annual report as noted in amendment STN 125874/0.81.

## Combination Product: Quality Management System (QMS)

The administration kit components are delineated in the table below

<b>Component</b>	<b>Manufacturer</b>	<b>510K</b>
21-gauge, 1.5-inch Precision Glide needle	Becton Dickinson	K021475
1 mL Luer-Lok Syringe	Becton Dickinson	K941562
3 mL Luer-Lok Syringe	Becton Dickinson	K980987
Syringe Tip Cap	Becton Dickinson	510(k) exempt
Premicath Catheter	VYGON	K954302

All the components of the administration kit are 510k cleared devices except the syringed tip cap which is exempted.

The needle is supplied sterile by (b) (4) and is manufactured in compliance with International Organization for Standardization (ISO). The composition of the needle includes: needle hub and shield (polypropylene), Cannula (stainless steel), lubricant (Silicone) and bonding agent (medical device adhesive). The needle specifications include receiving acceptance and visual inspection.

The 1 mL syringe is supplied sterile by (b) (4) sterilization and is manufactured in compliance with applicable ISO standards. The composition of the 1 mL syringe

includes: syringe barrel (polycarbonate), stopper (elastomer), plunger rod (polypropylene) and lubricant (silicone). The specifications include receiving acceptance and visual inspection.

The 3mL is supplied sterile by (b) (4) sterilization and is manufactured in compliance with applicable ISO standards. The composition of the 1 mL syringe includes: syringe barrel (polypropylene), stopper (elastomer), plunger rod (polypropylene) and lubricant (silicone). The specifications include receiving acceptance and visual inspection.

The syringe tip cap is supplied sterile by (b) (4) and is manufactured in compliance with applicable ISO standards. The composition of the syringe tip cap includes tip cap (polypropylene). The specifications include receiving acceptance and visual inspection.

The catheter is supplied sterile by (b) (4) and is manufactured in compliance with applicable ISO standards. The composition of the catheter includes hub (polymer), extension line and catheter tubing (polyurethane), adhesives, stylet (metal) and rotating luer lock (polypropylene). The specifications include receiving acceptance and visual inspection.

**Reviewer's Assessment:** *All components in the administrative kit are received sterile and ready to use. The components of the CCS are released against vendor specifications based on the Certificate of Analysis (CoA) provided by the manufacturer.*

## Quality Management System

The QMS addresses device quality system requirements in 21 CFR Part 820, and this is applied across the manufacturing sites involved in the product lifecycle (manufacture, packaging/assembly and supply of device components). The Quality Management System for the DB-OTO Combination Product under DMPQ purview is delineated below.

### *Management responsibility (CFR 820.20(a))*

Regeneron has defined quality policies and objectives. The quality system includes management responsibility and authority, and resource management with an appropriately appointed management representative. Adequate resources have been allocated to achieve the objectives. Quality reviews are performed at defined intervals as per Regeneron's senior management team to assess and improve the overall health of the quality system. Regeneron's senior management team is also responsible for overseeing and owning the development, implementation, and maintenance of the quality system.

**Reviewer's Assessment:** *The firm confirmed accordance by 21 CFR 820 management responsibility and review is acceptable.*

*Purchasing controls (CFR 820.50)*

Regeneron has processes and procedures for the control of purchased materials and services which include evaluation of suppliers, contractors and consultants using a risk-based approach. Suppliers and service providers are subject to periodic audits and evaluations to maintain approved supplier status. The periodic frequencies are determined by the same risk-based approach used for categorization based on the goods and/or services. Regeneron also ensures the adequacy of specified purchasing requirements prior to their communication with any supplier.

***Reviewer's Assessment:*** *The firm confirmed accordance by 21 CFR 820 purchasing controls and review is acceptable.*

*Corrective and Preventive Action (CAPA) system (CFR 820.100)*

Regeneron has defined policies and procedures to implement CAPAs. A comprehensive review and analysis are performed that aims to determine the root cause of existing or potential problems. During this review, quality data from different sources within the quality system are examined to help identify existing and potential causes of nonconforming practices and product. A non-comprehensive list of quality data sources can be found below:

- Audit reports
- Trend analysis of quality data
- Investigations and deviations

Appropriate mechanisms are in place to identify and implement appropriate action(s) needed to correct, prevent, and mitigate recurrence of nonconforming product or other quality problems. Events are investigated to determine root cause, impact, and corrective actions. Relevant information on identified quality problems, in addition to corrective and preventive actions, are reviewed by management in accordance with internal procedures. Furthermore, verification of the corrective and preventive actions are required to confirm the action was effective and that the non-conformance has been adequately addressed. Where the verification has shown the actions taken are deemed ineffective, the need for further investigation/action is required. Records and results of any investigation and of action taken are maintained

***Reviewer's Assessment:*** *The firm confirmed accordance with 21 CFR 820 CAPAs and review is acceptable.*

### 3.2.A APPENDICES

## Facilities Table

[illegible]

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?*	RMS-BLA entry required?*	Comments
<p>(b) (4)</p> <p>DP release testing: appearance, pH, (b) (4) endotoxin, (b) (4) vector genome titer, (b) (4)</p> <p>and poloxamer 188.</p>				
<p><b>Facility:</b> (b) (4)</p> <p>DP release and stability testing</p> <p>(b) (4)</p>	Waiver	Yes	Yes	<p>OII Surveillance (b) (4) VAI</p>

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?*	RMS-BLA entry required?*	Comments
DP release testing: (b) (4)				
<b>Facility:</b> (b) (4) [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] [Redacted]	Not Required	No	Yes	Oil Surveillance (b) (4) [Redacted] NAI
<b>Facility:</b> (b) (4) [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] <b>Actions:</b> DP release testing	Waiver	Yes	Yes	Oil Surveillance (b) (4) VAI
<b>Facility:</b> (b) (4) [Redacted] [Redacted] [Redacted] [Redacted] [Redacted] <b>Actions:</b> DP release and stability testing	Waiver	Yes	Yes	Oil Surveillance (b) (4) [Redacted] NAI

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?*	RMS-BLA entry required?*	Comments
<b>Facility:</b> (b) (4) <div></div> <div></div> <div></div> <div></div> <div></div> <b>Actions:</b> DP release and stability testing  DP release testing: Potency by (b) (4) <div></div>	Waiver	Yes	Yes	ORA Surveillance (b) (4) VAI
<b>Facility:</b> (b) (4) <div></div> <div></div> <div></div> <div></div> <div></div> <b>Actions:</b> Secondary packaging and labeling of DP	Inspection	Yes	Yes	OII Surveillance (b) (4) VAI Limited to DP storage
<b>Facility:</b> (b) (4) <div></div> <div></div> <div></div> <div></div> <b>Actions:</b> Assembly, labeling, and packaging of the administration kit	Inspection	Yes	Yes	DMPQ PLI (b) (4) <div></div> VAI
<b>Facility:</b> (b) (4) <div></div> <div></div> <div></div>	Waiver	Yes	Yes	OII Surveillance





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