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CBER CMC BLA Review Memorandum

BLA STN 125832

**zopapogene imadenovec-drba
PAPZIMEOS**

Reviewers

**Sukyoung Sohn, PhD, OTP/OGT/DGT1/GTB1
Joydeep Ghosh, PhD, OTP/OGT/DGT1/GTB3
Jianyang Wang, PhD, OTP/OGT/DGT1/GTB2**

1. BLA#: STN 125832

2. APPLICANT NAME AND LICENSE NUMBER

Precigen, Inc., License No. 2364

3. PRODUCT NAME/PRODUCT TYPE

- a. Non-Proprietary/Proper/USAN: zopapogene imadenovec-drba
- b. Proprietary Name: PAPZIMEOS
- c. Company Code Name: PRGN-2012
- d. UNII Code: C525BYS7TP
- e. NDC (vial): 84768-511-99
NDC (outer carton): 84768-511-01
NDC (pouch): 84768-511-00
- f. Chemical Abstract Service (CAS) Registry Number: 1801342-60-8

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological category: Non-replicating adenoviral vector-based immunotherapy
- b. Dosage form: Suspension for injection
- c. Strength/Potency: 5×10^{11} particle units (PU) per mL
- d. Route of administration: Subcutaneous injection
- e. Indication(s): Treatment of adults with recurrent respiratory papillomatosis

5. MAJOR MILESTONES

- a. Pre-BLA meeting (IND 26884/43): August 29, 2024
- b. BLA rolling submission completed: December 27, 2024
- c. Filed: February 24, 2025
- d. Mid-cycle communication: May 6, 2025
- e. Late-cycle meeting: June 12, 2025
- f. PDUFA action due date: August 27, 2025 (priority review)

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Sukyoung Sohn, PhD, OTP/OGT/DGT1/GTB1	Control of materials, comparability, manufacturing process development, product characterization, reference standards, container closure system, clinical assays, excipients, labeling, and environmental assessment
Jianyang Wang, PhD, OTP/OGT/DGT1/GTB2	Manufacturing process, controls of critical steps and intermediates, manufacturing process validation, labeling and packaging validation, shipping validation, stability and device compatibility, adventitious agent safety evaluation, labels, and labeling
Joydeep Ghosh, PhD, OTP/OGT/DGT1/GTB3	Analytical methods, validation of analytical methods, in-process tests, specifications, justification of specifications, batch analysis, and characterization of impurities

Andrey Sarafanov, PhD, OTP/OPPT/DH/HB2	Extractables and leachables (separate memo)
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7. INTER-CENTER CONSULTS REQUESTED: N/A

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
10/25/2025	125832/0.00	Module 4 submission
12/16/2025	125832/0.01	Module 5 submission
12/27/2025	125832/0.02	Module 3 submission (completion of rolling BLA submission)
1/30/2025	125832/0.05	Response to DBSQC IR #1 dated 1/23/2025
1/31/2025	125832/0.06	Response to CMC IR #1 dated 1/25/2025
2/7/2025	125832/0.08	Response to DMPQ IR #1 dated 1/27/2025
2/6/2025	125832/0.07	Response to CMC IR #2 dated 1/29/2025
3/3/2025	125832/0.10	Response to DBSQC IR #2 dated 2/24/2025
3/6/2025	125832/0.12	Response to CMC IR #3 dated 2/27/2025
3/7/2025	125832/0.11	Response to CMC IR #3 dated 2/27/2025
3/10/2025	125832/0.13	Response to DBSQC IR #3 dated 2/26/2025
3/20/2025	125832/0.14	Response to CMC IR #4 dated 3/6/2025
3/24/2025	125832/0.15	Response to CMC IR #5 dated 3/10/2025
3/31/2025	125832/0.16	Response to CMC IR #1 dated 1/25/2025
4/2/2025	125832/0.19	Response to DBSQC IR #4 dated 3/24/2025
4/7/2025	125832/0.20	Response to CMC IR #3 dated 2/27/2025
4/8/2025	125832/0.21	Responses to CMC IR #7 dated 3/27/2025 and CMC IR #8 dated 4/2/2025
4/9/2025	125832/0.22	Response to CMC IR #6 dated 3/26/2025
4/17/2025	125832/0.24	Response to CMC IR #9 dated 4/11/2025
4/18/2025	125832/0.25	Response to DMPQ IR #2 dated 4/4/2025
4/18/2025	125832/0.26	Response to DBSQC IR #5 dated 4/4/2025
4/25/2025	125832/0.28	Additional response to CMC IR#5 and DBSQC IRs #1 and #2
4/30/2025	125832/0.30	Response to DBSQC IR#6 dated 4/11/2025 and additional response to CMC IRs #4 and #5
5/5/2025	125832/0.31	Response to DBSQC IR#7 dated 4/29/2025
5/15/2025	125832/0.33	Response to DBSQC IR#8 dated 5/12/2025
5/19/2025	125832/0.34	Response to CMC IR#10 dated 5/12/2025
5/23/2025	125832/0.35	Additional responses to CMC IR#5 and DBSQC IR#5
5/27/2025	125832/0.36	Response to CMC IR#11, Comment #1 dated 5/20/2025
5/30/2025	125832/0.37	Responses to CMC IR#11 dated 5/20/2025 and CMC IR#12 dated 5/21/2025
6/3/2025	125832/0.38	Response to CMC IR #13 dated 5/29/2025

6/6/2025	125832/0.40	Response to CMC IR #14 dated 6/2/2025
6/10/2025	125832/0.41	Response to DBSQC IR#9 dated 5/28/2025
6/17/2025	125832/0.42	Responses to CMC IR#15 (DS and DP specifications) dated 6/6/2025 and CMC IR#16 dated 6/13/2025
6/23/2025	125832/0.43	Additional responses to CMC IR #13 dated 5/29/2025, DBSQC IR #5 dated 4/4/2025, DBSQC IR #8 dated 5/12/2025, and DBSQC IR #9 dated 5/28/2025
6/24/2025	125832/0.44	Response to CMC IR #17 dated 6/18/2025 and additional responses to CMC IR #15 dated 6/6/2025, CMC IR #16 dated 6/13/2025, and DBSQC IR #9 dated 5/28/2025 (Final DS/DP release specifications)
6/25/2025	125832/0.45	Late component submission (additional stability data) and study reports for in-use stability and device compatibility
7/1/2025	125832/0.47	Response to CMC IR #18 dated 6/30/2025
7/7/2025	125832/0.49	Response to CMC IR #19 dated 7/1/2025
7/9/2025	125832/0.50	Response to Form FDA 483 for (b) (4)
7/9/2025	125832/0.51	Additional response to CMC IR #19 dated 7/1/2025 and response to CMC IR #20 dated 7/2/2025
7/10/2025	125832/0.52	Response to CMC IR #21 dated 7/8/2025
7/14/2025	125832/0.53	Responses to CMC IR #22 dated 7/8/2025 and CMC IR #23 dated 7/9/2025
7/15/2025	125832/0.54	Additional response to CMC IR #23 dated 7/9/2025 (Final DS/DP stability specifications)
7/16/2025	125832/0.55	Response to DBSQC IR #10 dated 7/2/2025
7/17/2025	125832/0.57	Response to CMC IR #24 dated 7/16/2025
7/21/2025	125832/0.58	Additional response to CMC IR #19 dated 7/1/2025
7/23/2025	125832/0.59	Response to DBSQC IR #11 dated 7/2/2025 (LRP template final version)
7/25/2025	125832/0.60	Additional response to CMC IR #24 dated 7/16/2025 (additional leachables data)
7/28/2025	125832/0.61	Response to CMC IR #25 dated 7/22/2025
7/31/2025	125832/0.62	Response to CMC IR #26 dated 7/29/2025, PMR/PMC agreement, USPI revision #1
8/5/2025	125832/0.64	Response to CMC IR #27 dated 7/31/2025 (Final labels)

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

Submission Type & #	Holder	Referenced Item	LOA	Comments/Status
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BB-MF (b) (4)	(b) (4)	Facilities & Equipment of DP Manufacturer	Yes	Insufficient information for the facility and equipment was provided in the original submission. Upon request, additional information was submitted under Amendment #8 and reviewed by DMPQ. No outstanding issues identified.
BB-MF (b) (4)	(b) (4)	Component of Primary Packaging of DP (Vial)	Yes	No MF review required, information pertinent to container closure is provided in the BLA.
BB-MF (b) (4)	(b) (4)	Component of Primary Packaging of DP (Stopper: (b) (4))	Yes	No MF review required, information pertinent to container closure is provided in the BLA.
BB-MF (b) (4)	(b) (4)	Component of Primary Packaging of DP (Stopper: (b) (4))	Yes	No MF review required, information pertinent to container closure is provided in the BLA.
DMF (b) (4)	(b) (4)	Component of Primary Packaging of DP (Vial)	Yes	No MF review required, information pertinent to container closure is provided in the BLA.
DMF (b) (4)	(b) (4)	(b) (4)	Yes	No outstanding issues identified. Reviewed and assessed by Sukyoung Sohn in Section 3.2.S.2.3.
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	Reviewed and assessed by Joydeep Ghosh in Sections 3.2.S.4.2 and 3.2.S.4.3 (for (b) (4)) and 3.2.P.5.2 and 3.2.P.5.3 (for (b) (4))

10. REVIEWER SUMMARY AND RECOMMENDATION

EXECUTIVE SUMMARY

Based on the review of the information provided in the initial submission and subsequent information received throughout the review period, the CMC review team concludes that the manufacturing and controls for zopapogene imadenovec-drba (also referred to as PAPZIMEOS; PRGN-2012) can yield drug product with consistent quality attributes and, therefore, are deemed acceptable for commercial manufacturing under this BLA.

Description of the product: Zopapogene imadenovec-drba is a non-replicating adenoviral vector-based immunotherapy delivered via subcutaneous injection four times

on Days 1, 15, 43, and 85. The vector is a genetically modified recombinant gorilla adenovirus GC46 with deletions in the E1 (b) (4) regions and an insertion of the transgene expression cassette into the E1 region. The transgene encodes a fusion antigen comprising selected regions (b) (4) from human papillomavirus (HPV) 6 and HPV 11 under the control of the human cytomegalovirus (CMV) immediate early promoter and enhancer. Zopapogene imadenovec-drba is intended to generate T cell-mediated immune responses against papilloma cells that have been infected with HPV 6 or HPV 11 in patients with recurrent respiratory papillomatosis. The drug product (DP) is supplied as a sterile, frozen suspension in a single-dose vial that contains 5×10^{11} particle units (PU) per milliliter in a final formulation buffer with 10 mM Tris base, 75 mM sodium chloride, 1 mM magnesium chloride hexahydrate, 0.0025% (w/v) polysorbate 80, and 5.5% (w/v) trehalose dihydrate. The DP is stored frozen at $\leq -60^{\circ}\text{C}$, and each vial contains an extractable volume of 1.0 mL.

Manufacturing and process validation: The zopapogene imadenovec-drba drug substance (DS) is manufactured at the Precigen facility (Germantown, MD) using (b) (4)

(b) (4) the DP undergoes aseptic filling into 2 mL vials composed of cyclic olefin polymer. The filled vials are 100% visually inspected and stored at $\leq -60^{\circ}\text{C}$. Each vial of DP contains an extractable volume of 1.0 mL with a labeled nominal concentration of 5×10^{11} PU/mL in 10 mM Tris base, 75 mM sodium chloride, 1 mM magnesium chloride hexahydrate, 0.0025% (w/v) polysorbate 80, and 5.5% (w/v) trehalose dihydrate.

The frozen filled vials are shipped at $\leq -60^{\circ}\text{C}$ to the labeling site, (b) (4) where they undergo labeling at (b) (4). Subsequently, each labeled vial is individually packaged into a pouch made of (b) (4). Each pouched vial is then packaged into a separate carton with each carton containing one single-dose vial. The cartons are stored at $\leq -60^{\circ}\text{C}$ at the labeling and storage sites. For distribution, the DP cartons are shipped at $\leq -60^{\circ}\text{C}$ and maintained at this temperature until the time of administration at the clinical site.

The control strategy for zopapogene imadenovec-drba manufacturing includes (1) qualification of raw materials, reagents, starting materials, and manufacturing

consumables, (2) in-process monitoring and in-process control testing, (3) validation of the manufacturing process (DP process performance qualification will be completed post-approval), and (4) validated lot release tests. The manufacturer accepts raw materials based on verification of raw material specifications and routine incoming acceptance tests. 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. Additionally, the manufacturing process is controlled through testing of in-process materials, DS, and DP for microbial and viral contaminants, identity, purity, strength, and potency. The analytical methods used for lot release are appropriately validated or verified. Potency of the product is assessed using two quantitative assays and one qualitative assay: (b) (4)

The DS manufacturing process has been validated through (b) (4) consecutive successful (b) (4) process performance qualification (PPQ) runs and their subsequent (b) (4) PPQ runs. All DS PPQ runs met the pre-defined validation acceptance criteria (AC) and lot release AC.

To complete validation of the DP manufacturing process, concurrent release of PPQ lots is being implemented. The BLA contains the interim PPQ report including data from (b) (4) PPQ run, the protocol for concurrent release that includes (b) (4) additional DP PPQ runs, and additional evidence supporting control of the DP manufacturing process. Overall, the submitted information supports that the DP manufacturing process is under sufficient control for commercial distribution. The plan for concurrent release of DP PPQ lots is acceptable.

Stability: The DS is stable for up to (b) (4) when stored at the long-term storage condition of (b) (4). The DP is stable for up to 24 months when stored at the long-term storage condition of $\leq 60^{\circ}\text{C}$. The DP must be rapidly thawed at 37°C before use and preparation for immediate administration. Once thawed, the DP in a vial and/or syringe is stable for up to 60 minutes at ambient temperature.

Comparability: The current commercial manufacturing process has been optimized from the process used for the manufacture of clinical lots. (b) (4) clinical lot was used throughout the clinical trials. The comparability between the pre-change (clinical) and post-change (commercial) lots was demonstrated by analytical studies. The current manufacturing process is deemed to produce the DP with critical quality attributes that are comparable to the clinical lot used in clinical studies.

Manufacturing risks: The risk of extractables and leachables that could originate from the product manufacturing process and the container closure system was analyzed, and the analytical studies and toxicological assessments were sufficient to mitigate this risk. The risk of product contamination with microbial and viral adventitious agents is minimized by (i) ensuring adequate control of raw materials, especially those of biological origin that are used in the (b) (4), and product manufacturing; (ii) testing of (b) (4) for

microbials and adventitious viral agents; and (iii) lot release testing of (b) (4) DP for microbials. The overall risks of AVA contamination were determined to be low. However, the validation of the adventitious viral agent (AVA) testing by (b) (4) method was found to be inadequate. The Applicant will revalidate the AVA testing by (b) (4) method as a post-marketing requirement (PMR).

RECOMMENDATION:

APPROVAL

This Biological License Application (BLA) provides an adequate description of the manufacturing process and characterization of the drug product zopapogene imadenovec-drba. 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 a Post-Marketing Requirement (PMR) and Post-Marketing Commitments (PMCs) from Precigen, Inc., satisfies the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products.

Post-Marketing Requirement (PMR)

1. Precigen, Inc. will conduct an (b) (4) laboratory safety study to address the virus-detection-related safety concerns for the analytical method used to detect adventitious viral contamination in the (b) (4) during the zopapogene imadenovec-drba (b) (4) manufacturing process. This study will include: (1) validation of assay specificity and detection limits for control viruses by (b) (4); and (2) verification of method suitability by (b) (4)

Final Validation Protocol Submission Date for FDA's Review: September 30, 2025

Study Completion Date: January 31, 2025

Final Report Submission Date: February 28, 2025

Post-Marketing Commitments (PMCs)

PMC #5

Precigen, Inc. commits to completing the manufacturing process validation for the zopapogene imadenovec-drba drug product, including (b) (4) additional process performance qualification runs. A final study report for the drug product manufacturing process validation will be submitted as a "Post-marketing Study Commitment – Final Study Report".

Final study report submission: December 31, 2025

PMC #6

Precigen, Inc. commits to assessing (b) (4) from the zopapogene imadenovec-drba drug product stored at $\leq -60^{\circ}\text{C}$ for 24 months, at the end of the proposed shelf-life. A final (b) (4) assessment report will be submitted as a “Post-marketing Study Commitment – Final Study Report”.

Final study report submission: June 30, 2026

PMC #7

Precigen, Inc. commits to reassessing the (b) (4) of the zopapogene imadenovec-drba drug product. A final study report will be submitted as a “Postmarketing Study Commitment – Final Study Report”.

Final study report submission: December 31, 2025

PMC #8

Precigen, Inc. commits to reassessing the acceptance criteria for release testing of the zopapogene imadenovec-drba drug substance based on manufacturing experience and revising the acceptance criteria, as appropriate. A final acceptance criteria reassessment report will be submitted as a “Postmarketing Study Commitment – Final Study Report” within 60 days after release of the (b) (4) commercial drug substance batch.

Final study report submission: December 31, 2027

PMC #9

Precigen, Inc. commits to reassessing the acceptance criteria for release testing of the zopapogene imadenovec-drba drug product based on manufacturing experience and revising the acceptance criteria, as appropriate. A final acceptance criteria reassessment report will be submitted as a “Postmarketing Study Commitment – Final Study Report” within 60 days after release of the (b) (4) commercial drug product lot.

Final study report submission: December 31, 2031

SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Sukyoung Sohn Biologist, OTP/OGT/DGT1/GTB1	Concur	
Jianyang Wang Biologist, OTP/OGT/DGT1/GTB2	Concur	

Joydeep Ghosh Microbiologist, OTP/OGT/DGT1/GTB3	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


3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

Reviewed by Sukyoung Sohn (SS)



(b) (4)




(b) (4)



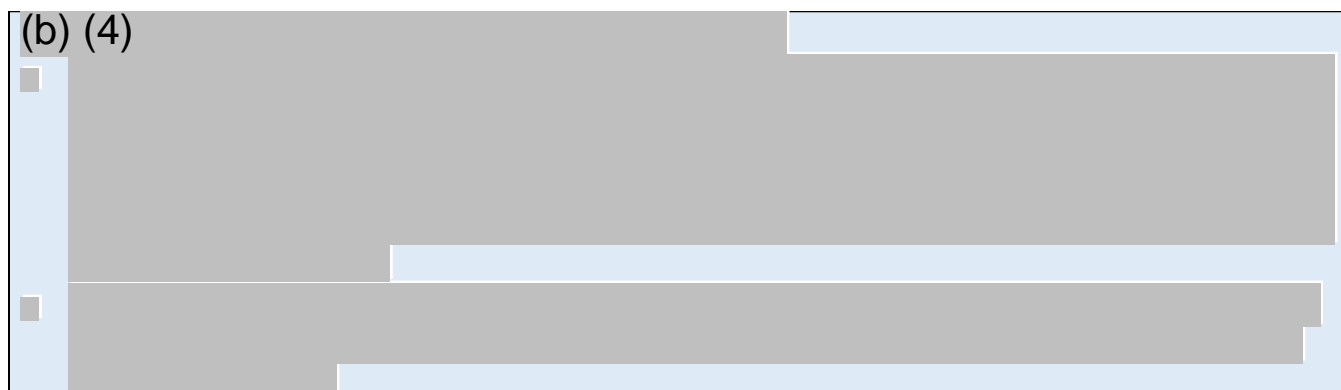
(b) (4)



(b) (4)



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



3.2.P DRUG PRODUCT

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

(Reviewed by SS)

The Drug Product (DP) of zopapogene imadenovec-drba is a sterile, frozen suspension for subcutaneous injection, packaged in a single dose 2 mL (b) (4) vial. The DP vial closure is a chlorobutyl rubber stopper with (b) (4) sealed with an aluminum seal with a flip-off plastic cap.

The DP is the purified adenoviral vector formulated in 10 mM Tris, 75 mM NaCl, 1 mM MgCl₂, 5.5% trehalose dihydrate, and 0.0025% polysorbate 80, pH (b) (4) and stored at ≤ -60°C. Each vial of DP is formulated to contain a dose of 5.0×10¹¹ particle units (PU) in a 1.0 mL suspension. Each vial is filled to a target volume of (b) (4) mL to deliver an extractable volume of 1.0 mL.

Table 63. Nominal Composition of PRGN-2012 DP

Component	Function	Reference to Quality Standard	Target Concentration	Quantity per 1 mL
PRGN-2012 Adenoviral Vector	DS	In-house	5.0×10 ¹¹ PU/mL	5.0×10 ¹¹ PU
Tris (Tromethamine)	Buffer	(b) (4)	10 mM	1.21 mg
Sodium Chloride	(b) (4)	(b) (4)	75 mM	4.38 mg
Magnesium Chloride Hexahydrate	Stabilizer	(b) (4)	1 mM	0.203 mg
Polysorbate 80	Stabilizer	(b) (4)	0.0025%	0.025 mg
α, α-Trehalose Dihydrate ¹	Stabilizer	(b) (4)	5.5%	55.25 mg
(b) (4) Sterile Water for Injection Specifications)	Solvent	(b) (4)	QS	QS
QS – <i>Quantum Satis</i> , USP – (b) (4)				
¹ Addition of 5.5% trehalose dihydrate results in a solution with 5% trehalose.				

3.2.P.2 Pharmaceutical Development

(Reviewed by SS)

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

(b) (4)

3.2.P.2.1.2 Excipients

Excipients used in DP formulation, their respective (b) (4), and functions are described in Table 63. No excipients of human or animal origin are used. None of the excipients in DP formulation are novel. Compatibility of DS with excipients is demonstrated by DS and DP stability data.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The PRGN-2012 DP is formulated in a Tris-based buffer as described in Table 63. The FFB formulation development took place from (b) (4)

This FFB formulation was selected for PRGN-2012, based on the following rationale:

- Similarity (b) (4)
- Historical data (b) (4)
- Experience with this FFB during the clinical development of PRGN-2012, during which stability was demonstrated for (b) (4) when stored in this formulation at $\leq -60^{\circ}\text{C}$.

(b) (4)

(b) (4)

Based on the stability study, the adenoviral vector is stable in trehalose buffer, with (b) (4) polysorbate 80, for more than (b) (4), with less than (b) (4) loss of activity and for over (b) (4) with a loss of less than (b) (4) activity, while the (b) (4)-containing formulations lost more than (b) (4) activity in (b) (4).

The preparation of FFB was transferred from (b) (4) to Precigen for the PRGN-2012 commercial (b) (4) manufacturing process. As part of the transfer, the reported trehalose concentration was adjusted from 5% trehalose to 5.5% trehalose dihydrate (with no actual change in trehalose concentration in the FFB) to account for the dihydrate water molecules. Multiple lots were made at Precigen and analytically compared to the (b) (4) material to ensure full comparability between the buffers.

3.2.P.2.2.2 Allowable (b) (4)

PRGN-2012 is intended to be a single-dose injectable product, with the vial contents removed as part of the dose preparation and administration procedure. Each DP vial is filled to a target volume of (b) (4) mL to deliver a (b) (4) extractable volume of 1.0 mL. The (b) (4) volume of (b) (4) mL is based on recommendations contained within (b) (4) and on process capability. Testing has demonstrated that this (b) (4) volume consistently results in an extractable volume of 1.0 mL. The PRGN-2012 DP has no overages.

3.2.P.2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties of the DP are (b) (4) as those described for the DS.

3.2.P.2.3 Manufacturing Process Development

The PRGN-2012 DP manufacturing process consists of (b) (4) steps: (b) (4) visual inspection of DP, and freezing of the filled DP vials. (b) (4)

The commercial DP manufacturing process was based on the Precigen's existing clinical manufacturing process, with modifications listed in Table 64. The clinical DP lot was filled at (b) (4). The Commercial DP is manufactured at (b) (4).

Table 64. Comparison of the Clinical and Commercial DP Manufacturing Processes

Manufacturing Operation	Clinical Manufacturing Process at (b) (4)	Commercial Manufacturing Process at (b) (4)	Rationale for Change

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

(b) (4)

Comparability

A comparability study was conducted to ensure that the DP lots manufactured using the pre-change and post-change DP processes are comparable. The DP lots used in the study are listed in Table 69 below.

Table 69. Pre-and Post-Changes DP Lots used in the Comparability Study

Manufacturing Site	DP Process	Lot Number	Date of Manufacture
--------------------	------------	------------	---------------------

(b) (4)

Similar to the DS comparability study, the DP process comparability study was performed using a (b) (4)-tiered approach. (b) (4)

The statistical methods used for comparability analysis vary depending on the tier, the presence of specification limits, and any intended process change evaluation. Additionally, comparability is assessed for special cases, such as qualitative data or data below the limit of quantitation (LOQ) and/or the limit of detection (LOD). For special cases, no statistical analysis is performed, and the processes are considered comparable by definition when the data are consistent and/or all data are below LOQ/LOD. The DP comparability study results are summarized in Table 70 below.

Table 70. DP Comparability Results

Attribute	Release AC	Change Impact	Comparability Acceptance Criteria	Comparability Result
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(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

In Study PRGN-2012-201, (b) (4) DP lot (Lot 13430820), (b) (4) (b) (4), was used. The PU concentration of this lot is (b) (4), and the Applicant confirmed that the participants in their clinical trial were dosed based on nominal titer, i.e., 15% higher than its intended dose of 5.0E+11 PU per injection.

The Phase 1 portion of the study includes three subjects who received 1.15E+11 PU/injection, which is approximately 23% of the intended commercial dose. None of them achieved the desired endpoint of a complete response. The number of surgical interventions from the three subjects was 8, 7, and 4 for 12 months before treatment and 3, 4, and 3 for 12 months after treatment. Therefore, we do not have data to support any dose level other than (b) (4) per injection.

To address this concern, we communicated with the Applicant through IRs (sent on 5/12/2025 and 6/6/2025) and discussed this at the Late-Cycle meeting held on June 12, 2025. The Applicant agreed to revise the PU concentration lower limit for DP release from (b) (4) PU/mL to (b) (4) PU/mL, and the revised DP specification was submitted under Amendment #44 dated 6/24/2025. The Applicant also proposed to use the (b) (4) in the confirmatory study.

Although this BLA was converted from accelerated approval to traditional approval and a confirmatory study is no longer required, those (b) (4) lots will be used in additional postmarketing studies for virus shedding (Clinical PMC #3) and for pediatric patients (Clinical PMC #4). This is expected to help address this issue. Additionally, given the mode of action of this product is to generate T cell-mediated immune responses (immunotherapy), the therapeutic dose range may be broader compared to other conventional gene replacement viral products. Collectively, the revised PU concentration AC for DP release is considered adequate to ensure that patients will receive a dose within the therapeutic range.

3.2.P.2.4 Container Closure System

(Reviewed by SS)

Primary Packaging

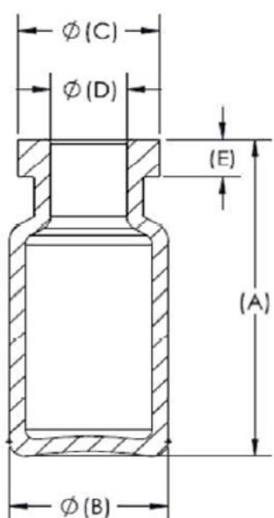
The primary container closure system for PRGN-2012 DP consists of three components: a (b) (4) vial, a rubber stopper, and an aluminum seal. Table 73 provides details of the container closure components.

- The vials are sterilized (b) (4) and ready to use. A dimensional drawing of the vial is shown in Figure 28.
- The stoppers are (b) (4) sterilized and delivered sterile and ready to use.
- The flip-off seals are sterilized by (b) (4) and delivered sterile and ready to use.

Table 73. PRGN-2012 DP Container Closure Components

Component	Description	Supplier	Part Number	DMF number
Vial	2 mL, cyclic olefin polymer (b) (4) vial	(b) (4)	(b) (4)	BB-MF (b) (4)
Stopper	13 mm, (b) (4) Chlorobutyl elastomer (b) (4)	(b) (4)	(b) (4)	STN (b) (4) BB-MF (b) (4)
Seal	Aluminum seals with a flip-off plastic top	(b) (4)	(b) (4)	N/A (no product contact)

Figure 28. Schematics of 2 mL (b) (4) Vial



(b) (4)

Reviewer's comment: (b) (4) incoming material specifications for vials, stoppers, and seals are included in the BLA, reviewed, and found to be acceptable.

The BLA does not include a sufficient assessment of cumulative leachables in the DP. Following a teleconference held on March 4, 2025, and follow-up IR communications (Amendment #14, #23, and #30), the Applicant agreed to measure the leachables from the DP stability samples at (b) (4)-month and (b) (4)-month timepoints. The (b) (4)-month timepoint data was provided under Amendment #60 dated 7/25/2025. The Applicant commits to assessing leachables from the DP stored at $\leq -60^{\circ}\text{C}$ for (b) (4) the shelf-life) and submitting a final leachables assessment report as PMC #6 (Amendment #62). Please refer to Dr. Andrey Sarafanov's review memo for further details on the extractables and leachables assessment.

Secondary Packaging

A single frozen DP vial is placed in a 3"x 4.5" (b) (4) pouch, which is then sealed and packaged in a 4.75" x 3.25" x 0.875" carton (secondary packaging). A tamper evident (TE) seal is applied to the carton. The cartons are packaged in a case and stored at $\leq -60^{\circ}\text{C}$ prior to shipping to a distributor. All secondary packaging components were evaluated and selected based on their suitability for required cold chain storage and shipment.

***Reviewer's comment:** The information provided regarding the DP CCS is acceptable to support its suitability for storage and stability studies.*

3.2.P.2.5 Microbiological Attributes

(Reviewed by SS)

The PRGN-2012 DP is a sterile suspension manufactured by aseptic processing for subcutaneous injection to avoid microbial contamination. The DP is supplied for single use and contains no antimicrobial preservative. As part of processing, DP is (b) (4). The DP is aseptically filled using a process that has been validated. Components that have direct contact with the DP are either received sterile or sterilized during the process. DP is subject to sterility and endotoxin testing as part of the release process. For assurance of CCS integrity, the DP vial is tested for CCS integrity during stability testing by (b) (4) method per (b) (4). See DBSQC and DMPQ memos for further details on the microbial containment strategy.

3.2.P.2.6 Compatibility

(Reviewed by JW)

Reviewer's note and comments:

- o In the original BLA submission, the design of "in-use stability and device compatibility study" was inappropriate. Instead of conducting an integrated "in-use stability and device compatibility study", two studies, i.e., "Vial Thaw and Ambient Temperature Hold" and "Device Compatibility Study", were performed independently. Therefore, neither study was conducted by mimicking the clinical administration process and conditions (from the vial thaw, syringe loading, to the patient administration)*
- o Meanwhile, results from "Vial Thaw and Ambient Temperature Hold" study (which cannot be considered as an in-use stability study) showed an approximately (b) (4) decrease in (b) (4) and (b) (4) increase in (b) (4) and there was a significant ((b) (4)) decrease in (b) (4) and a significant ((b) (4)) increase in (b) (4) in Arm 2 (at room temperature) compared to T=0, while product stability between T=0 and (b) (4)-hour timepoints was not evaluated.*

- *These issues and concerns were communicated to Precigen through CMC IR#11 (sent on 20-May-2025), an informal T-con on 28-May-2025 (internal T-con memo uploaded to CBER Connect on 30-May-2025), and then a follow-up CMC IR#13 dated 29-May-2025. In response, Precigen initiated 4 in-use stability and device compatibility studies that mimicked clinical administration conditions and submitted data in SN0039 on 25-June-2025 [prior to 60 days of ADD date (22-Aug-2025)] with final conclusions being summarized below.*

Four In-use stability and device compatibility studies evaluated the quality, strength, and potency of PRGN-2012 DP using conditions that mimic the intended use of the DP throughout the clinical preparation and administration process. Information on the DP and delivery devices used in in-use stability and compatibility studies is shown in Table 74. (b) (4) DP lots were manufactured at full-scale using the commercial DP manufacturing process and were packaged in the current container/closure system. These 4 studies were designed to confirm the product preparation and handling instructions on the USPI, including:

- Vials should be thawed at 37°C [98.6°F] for ≤ 5 minutes
- Withdraw from vial using a 3 mL syringe with an 18-gauge to 22-gauge needle
- Perform Subcutaneous administration of product using a 23-gauge to 25-gauge needle
- Maximum hold time in vial and syringe is 60 minutes
- Preparation and handling can be performed under ambient lighting conditions

Table 74. Product Information and Delivery Devices

Product Description	PRGN-2012 DP (b) (4)
Manufacturer	(b) (4)
Target Concentration	5 x 10 ¹¹ PU/mL
Dose Volume	1.0 mL
Container/Closure	2 mL (b) (4) Vial, 13MM Stoppers and Seals
Syringe / Needle	3 mL (b) (4) Syringe (Catalog number (b) (4)) (b) (4) needle (Catalog number (b) (4)) 25-gauge x (b) (4) needle (Catalog number (b) (4))

Study Procedures (Table 75): All DP vials were thawed in a 37°C water bath for no more than five (5) minutes until there were no visible ice crystals in the vial. Post-thaw DP was evaluated under one of two conditions:

- PRGN-2012 DP was held at ambient temperature in the original DP vial
- PRGN-2012 DP once thawed was immediately transferred to a 3 mL syringe via a 21-gauge needle, and held at ambient temperature in the syringe

Samples were collected at regular intervals up to (b) (4) minutes of hold at ambient temperature from the vials (first withdrawing from the vial using a (b) (4)-gauge needle) or syringe by dispensing using a (b) (4)-gauge or (b) (4)-gauge needle. Samples were then evaluated for CQAs shown in Table 76 and Table 77.

Table 75. In-Use Stability and Compatibility Studies for PRGN-2012

(b) (4)

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

Reviewer's comments:

- All results met the stability specifications which are the same as release specifications. Based on the study procedures and conditions tested during these “in-use stability and compatibility” studies, there results can support USPI Section 2.2. Preparation and Handling, including
 - Exposure of the thawed vial to the 37°C [98.6°F] water bath or dry bead bath should be less than or equal to 5 minutes.
 - DO NOT hold PAPZIMEOS at room temperature for more than 60 minutes after thawing.
- Meanwhile, to mitigate PRGN-2012 aggregation during the preparation and handling (as indicated in “Vial Thaw and Ambient Temperature Hold” study), in the CMC IR#27 dated 31-July-2025, FDA recommended Precigen to add “DO NOT shake” to the vial label, pouch label, and carton label. In SN0066, Precigen agreed and added “DO NOT shake” to all labels (in USPI, “DO NOT Shake the vial”).
- And one of (b) (4) lots used in these studies, PPQ1 Lot (b) (4), also underwent simulated labeling conditions, i.e., the DP vials were (b) (4) (maximum process time for labeling and packaging) before being returned to ≤ -60°C storage, prior to being used for these studies. Overall, results demonstrated that PRGN-2012 DP quality, strength, and potency are maintained throughout preparation, handling, and clinical administration process and the preparation and handling procedures outline in the USPI are justified.

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

- Information provided to describe pharmaceutical development together with the additional IR responses are acceptable.
- To address the concern related to the 15% lower dose used during the clinical trial, the lower limit of PU concentration for DP release has been revised. Given the immunotherapeutic action of this product, revision of the PU concentration AC is considered adequate to ensure that patients will receive a therapeutically effective dose.
- The Applicant provided cumulative process leachables data using the DP stored at ≤ -60°C for 12 months (Amendment #60), and it found to be acceptable. To support the DP shelf life of 24 months, the Applicant committed to assessing (b) (4) in the DP stored at ≤ -60°C for 24 months (at the end of shelf life) as PMC #6 (See Dr. Andrey Sarafanov's review memo).

3.2.P.3 Manufacture**3.2.P.3.1 Manufacturer(s)***(Reviewed by SS)*

The names and addresses of the facilities used in manufacturing and testing of DP are summarized in Table 78.

Table 78. List of Manufacturing, Testing, Packaging and Storage Facilities

Site Name	Site Address	FEI and DUNS	Specific Manufacturing Responsibilities or Testing
Precigen, Inc.	20358 Seneca Meadows Pkwy Germantown, MD 20876	FEI: 3014429654 DUNS: 054652865	<ul style="list-style-type: none"> • DP testing: Appearance, pH, Volume in Container, (b) (4)

			(b) (4) Purity, (b) (4) Endotoxin
(b) (4)			<ul style="list-style-type: none"> DP manufacturing (b) (4) and filling into vials) and primary packaging
(b) (4)			<ul style="list-style-type: none"> DP testing: Volume in Container, (b) (4), Particulates DP in-process testing: (b) (4)
(b) (4)			<ul style="list-style-type: none"> DP testing: Sterility (managed by (b) (4))
(b) (4)			<ul style="list-style-type: none"> DP testing: Container closure integrity (CCIT)
(b) (4)			<ul style="list-style-type: none"> DP storage
(b) (4)			<ul style="list-style-type: none"> DP labeling and secondary packaging site
(b) (4)			<ul style="list-style-type: none"> DP storage and distribution

Reviewer's comment: Upon request (IR #11 sent on 5/20/2025), an updated list of manufacturers was provided under Amendment #37 dated 5/30/2025. See the DMPQ Inspection Waiver memo regarding inspection waivers for the DP labeling and DP release testing sites.

3.2.P.3.2 Batch Formula

(Reviewed by SS)

The target batch size for the commercial PRGN-2012 DP is (b) (4) vials. No additional materials are added to the (b) (4) to create the DP. The DS is (b) (4). Table 79 lists the components that are included in the final dosage form with the target concentration of each component. The quantity of each component per batch is based on the (b) (4) target volume used to support the target batch size of (b) (4) vials. Vials of DP are filled to a target volume of (b) (4) mL/vial to ensure a recoverable volume of (b) (4) 1 mL/vial containing the target concentration of 5.0×10^{11} particle units (PU)/mL.

Table 79. PRGN-2012 DP Batch Formula

Component	Function/Purpose	Quality Standard	Target Concentration	Quantity per Batch
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(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:
Descriptions of DP manufacturers and the DP batch formular are acceptable.

3.2.P.3.3 Description of Manufacturing Process

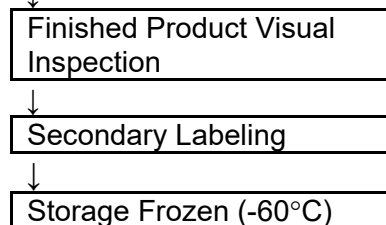
(Reviewed by JW)

For PRGN-2012 DP manufacture, Applicant's Contract Manufacturing Organization (CMO) (b) (4) is responsible for the manufacturing with (b) (4) for DP vial labeling and Secondary Packaging.

PRGN-2012 DP manufacturing process starts with (b) (4) , 100% visual inspection, and storage at $\leq -60^{\circ}\text{C}$ (Figure 29 and Figure 30).

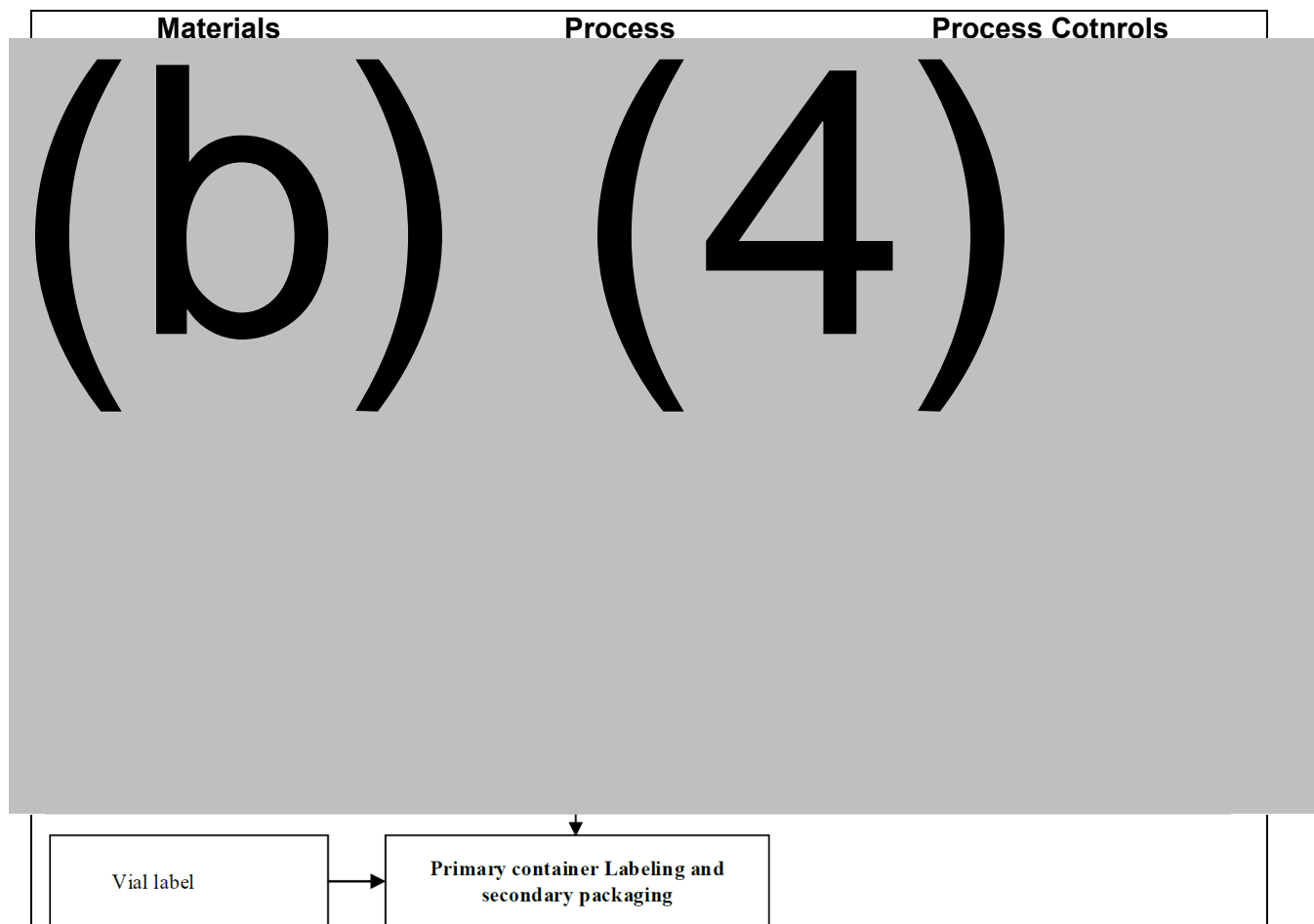
Figure 29. High-Level Overview of PRGN-2012 DP Manufacturing Process at CMO

(b) (4)



Reviewer's notes: For PRGN-2012 DP manufacturing:

- No reprocessing procedures were employed;*
- (b) (4) 21 CFR 820 compliant, pre-sterilized, single-use, disposable supplies (e.g., (b) (4) cryovials, and stoppers) are used;*
- All product contact parts are disposable and are not reused;*
- (b) (4) are received non-sterile and integrity tested prior to use. Following a passing integrity test, the (b) (4) are incorporated into a (b) (4)*
- The compatibility of the (b) (4) with DP is provided in Module 3.2.P.2.3 Manufacturing Process Development.*


Figure 30. PRGN-2012 DP Manufacturing Process Flow Diagram

Reviewer's comments:

- In the Process Validation Master Plan (PVMP) for PRGN-2012 (b) (4), it stated that "Approximately (b) (4) lots are (b) (4)". Meanwhile, due to the concurrent process validation approach, only limited consistency and reproducibility of the intended commercial manufacturing process have been demonstrated with execution of a successful engineering run, a (b) (4)-PPQ lot, and (b) (4) PPQ lot (PPQ#1), all of which pooled (b) (4).
- Therefore, the CMC IR #11 was sent on 20-May-2025 to request Precigen to either provide additional available process validation data from (b) (4) lots (b) (4) lots to demonstrate the effectiveness and consistency of the commercial manufacturing process, or to provide a risk assessment to evaluate the adequacy of process control and process validation for the manufacturing of (b) (4) lots (b) (4).
- In response (SN0038), Precigen confirmed that:
 - All DP lots manufactured with commercial process to date utilized (b) (4) lots of (b) (4) and that they plan to utilize (b) (4) lots of (b) (4) in future commercial production for each lot of DP.
 - Using (b) (4) lots for each DP lot will minimize variability and ensure consistency across process validation batches and future commercial batches.
 - In the future, if a business need arises to use more or less than (b) (4) lots in (b) (4) lot, a comprehensive risk assessment will be performed prior to implementing such a change and submitted as a PAS (as stated in SN0066)
- This is acceptable.
- During the pre-license inspection (PLI) for the (b) (4) facility conducted from (b) (4), it was discovered that identity testing was not performed on the incoming (b) (4), and this led to Observation #1 on the 483. (b) (4) submitted their responses to Form FDA 483 directly to the FDA on 5/19/2025 and 6/24/2025 to address this concern and revised the material specification for PRGN-2012 (b) (4) to include a requirement for identity testing on each batch of (b) (4) received at their facility. The updated corresponding sections were submitted in Amendment #50. The testing will be performed by Precigen using the (b) (4), and identity assay results will be provided to (b) (4) release prior to use in DP manufacturing. See the establishment inspection report (EIR) for the (b) (4) facility for additional information.

□ Preparation

(b) (4)



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

Table 82. PRGN-2012 DP, Lot#(b) (4) , Test Results

(b) (4)

Table 83. PRGN-2012 DP Lot#(b) (4) (b) (4) Vials Inspection Results

(b) (4)

As shown in Table 82 and Table 83, all tested CQAs were within specifications for up to (b) (4) hours, Precigen stated that the labeling and packaging process study demonstrated that the labeling and packaging condition does not adversely impact the DP quality. Precigen set an (b) (4) maximum processing time for commercial labeling and packaging process.

Shipping and Shipping Validation

Reviewer's note and comments:

- *Shipping lane performance qualification study for PRGN-2012 DP transportation seems acceptable from DMPQ's perspective (Please refer to the final DMPQ review memo).*
- *However, from a CMC perspective, the shipping lane performance qualification study is incomplete since it did not investigate any potential adverse effects of shipping conditions on DP quality and potency. This issue was communicated to Precigen in an informal T-con on 28-May-2025 (Memo of T-con has been uploaded to CBER Connect on 30-May-2025 as "Telecon") and the CMC IR#13 (dated 29-May-2025).*

- *In response, Precigen initiated an additional shipping performance qualification study and submitted data in SN0039 on 25-June-2025 with final conclusions summarized below.*

The complete shipping flow from the sites of the DS and DP manufacture is shown in Figure 32.

Figure 32. PRGN-2012 Shipping Flow from the Sites of DS and DP Manufacture

(b) (4)

To validate the shipping process, The FDP Cartons were packaged according to the (b) (4) (b) (4) configuration listed in QV- SOP-00079, *Storage, Shipping and Handling Requirements for GMP Materials*. The (b) (4) Package Systems used in this PQ were (b) (4) FDP Cartons. Each (b) (4) Carton contains (b) (4) FDP 2.0 mL vial containing 1.0 mL of extractable FDP (Table 84).

Table 84. Shipping Validation: Shipment Itinerary, (b) (4) Packages, and DP Lots

(b) (4)

(b) (4)

After the shipments were received at the Precigen, Inc. Germantown, MD Facility, the (b) (4) packaging systems and their contents were inspected for damage. The temperature data was analyzed to ensure the (b) (4) packaging systems maintained temperature at $\leq -60^{\circ}\text{C}$ for at least (b) (4) hours. The FDP vials tested in this Shipping Lane Performance Qualification have gone through commercial manufacturing and packaging operation and represent worst-case supply chain nodes. All testing results of shipped and control vials met all AC with Table 85 shown results from PPQ1 lot.

Table 85. Shipped PPQ1 Lot # (b) (4) QC Testing Summary

(b) (4)

Conclusions: Shipping validation results confirmed that DP quality and potency are not adversely affected and the (b) (4) Packaging Systems are suitable for the DP shipping. Precigen stated that any changes to the approved validated commercial supply chain shipping container systems and lanes shall be managed via change control. *Acceptable.*

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

The information provided in the DP manufacturing process description and flowcharts in the BLA is acceptable. Process validation design and results for PRGN-2012 DP labeling & packaging process and DP shipping process are acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

(Reviewed by JW)

Reviewer's note and comments:

- *In response the IR#11 dated 10-March-2025, Applicant submitted the Process Control Strategy Reports (PCSR) QV-RPT-00306 for DP manufacturing in Module 3.2.P.3.3.*
- *Please refer to [Section 3.2.S.2.4](#) Control Strategy Related Terms: Process Parameters and Attributes, including CPP, KPP, NKPP, NOR, PAR, CQA, IPC, IPM, KPI, in this memo.*

The proposed integrated commercial control strategy is comprised of multiple elements, including **parameter criticality designation** and **defined operating ranges**, **in-process controls**, **in-process testing**, and **release specifications**.

Per ICH Q9, *Quality Risk Management*, a high-level risk assessment was conducted (document# PRGN2012-2024-012) for the DP manufacturing process to identify the unit operations that require characterization in order to mitigate the risk. Further a low-level risk assessment was used to rationalize the selection of factors, the responses, operational ranges, and model terms to be used in process characterization studies to assess the quality and performance attributes that would impact the final DP production process efficiency.

The PRGN-2012 DP production process is controlled throughout the manufacturing process with the help of established NORs and PARs to ensure that the process remains consistent between batches and is able to produce a consistently high-quality drug product. Applicant stated that running the process within the established ranges ensures that the process is well controlled, which enables maintenance of process performance and product quality. For purposes of process qualification, the process parameters are recorded and verified in the master batch record and/or process validation protocols and will be continuously monitored, as appropriate. The process control strategy input and outputs are shown in Table 86 with the in-process testing in Table 87. There is no manufacturing intermediate during PRGN-2021 DP manufacture.

Table 86. PRGN-2012 DP Process Control Strategy Inputs and Outputs

(b) (4)

(b) (4)

Table 87. PRGN-2012 DP Process In-Process Control Testing

(b) (4)

In-process Testing for PRGN-2012 Drug Product (DP)

(Reviewed by JG)

Based on the information and clarifications provided in: (1) eCTD 3.2.P.3.3 of Amendment #2 (received 12.27.2024); and (2) Table 1 of Precigen Response #1 submitted under Amendment #12 (received 03.06.2025), Precigen uses the following in-process tests for the PRGN-2012 DP:

Table 88. In-Process Testing for the PRGN-2012 (b) (4) DP

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.4:

- The proposed in-process test specifications for the PRGN-2012 DP are acceptable.
- The information detailing control of critical steps and intermediates in the manufacturing of PRGN-2012 DP is acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

(Reviewed by JW)

Reviewer's notes and comments:

- *A concurrent PPQ approach is being implemented for PRGN-2012 DP manufacturing process validation: results from (b) (4) PPQ lot (Lot #1) and supporting information from the full-scale Engineering run and Pre-PPQ run are provided in the BLA original submission while those from (b) (4) will be submitted and reviewed post-approval, which were agreed upon during the Pre-BLA meeting on 29-August-2024.*
- *Applicant provided the following justifications for the concurrent DP approach:*
 - *The limited use of PRGN-2012. It fills an urgent medical need: due to the current dosing regimen for PRGN-2012 (4 administrations over a 12-week interval), and the rareness of the indication. RRP is a rare disease and as such PRGN-2012 has received Orphan Drug Designation (ODD). There are no approved medical treatment for RRP, and the only treatment available to patients is repeated surgical procedures to remove the Surgeries are not curative in RRP, and repeat surgeries are associated with significant morbidity related to anesthetic and surgical risks.*
 - *Applicant stated that evidence that DP manufacturing process is under a state of control is sufficient, which includes all testing done on all lots manufactured to date, including release testing, in-process testing, and additional product or process characterization studies.*
 - *Processes to mitigate risk (to patients): Applicant stated that a robust Quality Assurance (QA) system is put in place to ensure appropriate release of product, track materials, and respond to any product complaints or quality concerns. In addition, multiple systems are in place to continuously collect product information and to provide to Precigen QA to respond rapidly and appropriately, including:*
 1. **Medical Information Point of Contact:** *The Sponsor is contracting a third party vendor to serve as the medical information point of contact to manage information including product complaints and medical information requests. The medical information team is also responsible for communication of risks to physicians and patients.*
 2. **Pharmacovigilance:** *A third party vendor will quickly detect and address adverse events and customer feedback (via toll free/call center) to minimize patient risks.*
 3. **Regulatory Compliance:** *Precigen will adhere to post-marketing reporting requirements and support transparent communication with regulators and stakeholders.*
- *Concurrent release of DP PPQ lots approach is justified and acceptable. Meanwhile, PMC #5 has been put in place to ensure the completion, submission, and review of (b) (4) The due date for the PMC #5 is 31-Dec-2025 (Amendment #62).*

Process Validation Studies

Process validation was executed under PPQ protocol 55-307-PPQ-0001 Rev 00 and in accordance with FDA Guidance for Industry (2011) *Process Validation: General Principles and Practices incorporating Process Design, Process Qualification, and Continued Process Verification*. The PPQ activities included completion of (b) (4) PPQ DP lot ((b) (4)) supported by data from a full-scale Engineering Run (Lot#: (b) (4)) and from a full-scale Pre-PPQ GMP run (Lot#: (b) (4)), both of which fully represent the commercial DP manufacturing process. Precigen stated (b) (4) subsequent consecutive PPQ DP lots will be manufactured as a PMC.

The process validation program at the (b) (4) facility follows guidelines per SOP 12.0024 *Process Validation*. PPQ will be performed in (b) (4) and all (b) (4) PPQ runs must meet acceptance criteria as defined in the protocol. Sampling will follow sampling plan (b) (4) (b) (4) *Sampling Plan* and SOP 05.0246, *Additional Sample Request Procedure*. All release testing associated with this process phase must meet specification. Critical Process Parameters (CPPs), and In-Process Controls (IPCs) are expected to be maintained within the ranges specified in the protocol. The CPP validation criteria will be determined based upon process control strategy document PRGN2012-2024-013-V1 and (b) (4)

Any deviations/discrepancies must be evaluated through the deviation process per SOP 05.0240 *Deviation Management in (b) (4)* and discrepancy process SOP 12.0002 *Validation Discrepancy Management*.

An interim report for the (b) (4) PPQ run is provided, and the (b) (4) run met specifications for all CPPs, KPPs, IPCs and release test results. This report did not close the PPQ protocol and runs (b) (4) will be required prior to closure of the PPQ protocol.

❑ Pre-Requisite Process Validation Activities

Prior to executing the PPQ activities, the following items in Table 89 are to be addressed to ensure site readiness:

Table 89. Process Validation Pre-Requisites

Pre-Requisite	Description
Documentation	Master Production Records (MPRs), Standard Operating Procedures (SOPs), and Standard Manufacturing Procedures (SMPs) used in the manufacturing process must be approved and confirmed to be in an appropriate state prior to execution of process validation studies. Any changes to the documents shall be approved in the electronic document management system.
Training	Personnel involved in the manufacturing process must be properly trained per SOP 05.0057, <i>Training Program</i> . Additionally, personnel performing or assigned to perform validation studies must also be trained. All training must be documented.
Equipment Facilities, and Utilities	Qualification of process equipment will be confirmed to be in an appropriate state; qualification of the facility and any process-related utilities will be confirmed complete, prior to the start of PPQ.
Materials and Components	Significant process input materials, including buffers, solutions, and product contact single-use items, are required to have controls/specifications for

	incoming quality release. All materials utilized in support of the PPQ campaign will be released prior to use.
Component Qualification	Component qualification studies were conducted prior to commercial GMP manufacturing: 1. Container Closure Integrity Testing for (b) (4) 2. Engineering Test Plan for (b) (4)
Sampling Plans	The process-relevant sampling plan (b) (4) is incorporated into the Master Production Records. MPR revision being used for PPQ also includes non-routine samples that will not be routinely taken following the execution of the PPQ.
Analytical Assay Validation	All analytical methods, used to support commercial production of PRGN-2012 DP (e.g., IPCs and CQAs), as well as the associated PPQ, are required to be validated/verified/qualified prior to PPQ final report approval with the exception of compendial methods.
Change Control	Any changes to the process or equipment will be controlled through the site change control management system per SOP 05.0174, <i>Change Control Management in (b) (4)</i> . The change control program will ensure that proposed changes to the equipment, processes, or systems are evaluated for their potential impact on the validated state.
Cleaning Validation/Verification	Cleaning and verification of (b) (4) parts will be performed per SOP 05.1364 <i>Manual Cleaning of the (b) (4) Parts at (b) (4)</i> will be attached to MPR for confirmation of (b) (4) parts cleaning.
Continued Process Verification (CPV)	The overall approach to CPV is managed according to SOP 12.0025, <i>Continued Process Verification (CPV)</i> .

□ Process Validation Acceptance Criteria (55-307-PPQ-001)

The acceptance criteria encompass the numerical limits and ranges for critical and non-critical process parameters, and CQAs (3.2.P.5.1. *Specifications* in this memo). Normal operating ranges (NOR), which are within the proven acceptable ranges (PAR), will be used as the validation acceptance criteria for PPQ. Any excursion outside the acceptance criteria will be documented and assessed per SOP 12.0002 *Validation Discrepancy Management*.

A successful PPQ lot is defined as having the following:

1. Batch record documentation reviewed and approved.
2. Any lot specific deviations and/or PPQ Discrepancies and Corrective Action Reports (DCAR) have been resolved and do not adversely impact this qualification.
3. All PPQ batches manufactured meet the DP release testing specifications according to (b) (4) *Final Drug Product*,

□ PPQ DP Release Results

The (b) (4) PPQ DP lot (#(b) (4)) met all the pre-defined PPQ lot release AC for DP lot release tests (Table 90):

Table 90. PPQ1 Lot (b) (4) Release Testing and Specifications

Test	Acceptance Criteria (AC)	PPQ Run (b) (4) Product Lot # (b) (4)	PPQ Run Met AC (Yes / No)
------	--------------------------	--	------------------------------

(b) (4)

Reviewer's comments:

- *Acceptance criteria for the PPQ were determined per QV-MSPEC-00048, Commercial Specification for PRGN-2012 DP. Parameters (highlighted in blue) had the AC different from the finalized commercial lot release criteria (highlighted in red font) (Please refer to Module 3.2.P.5.1 Specifications in this memo). The AC for the remaining parameters are the same as the finalized commercial lot release criteria. PPQ1 release results met all finalized commercial lot release criteria.*
- *A PMC (PMC #5) has been put in place for Precigen to complete the process validation of the other (b) (4) PPQ runs. The PMC #5 is due 31-Dec-2025.*

□ **Supporting Information:** (b) (4)

Run Results

Information of (b) (4) Runs

Table 91 summarized the high-level comparison of PPQ runs with (b) (4) supporting runs: the full-scale (b) (4) all of which were manufactured using the commercial manufacturing process (post-change) at full-scale of target (b) (4) vials.

Table 91. High-level comparison of PPQ, (b) (4)

(b) (4)

(b) (4) Run DP Testing Results

Table 101 summarized PRGN-2012 DP lot release results from (b) (4) supporting runs (b) (4) all of which met all the lot release AC for DP lot release tests. For comparison, results from PPQ1 are included.

Table 92. Batch Analysis Results for (b) (4) Commercial Process DP Lots

(b) (4)

(b) (4)

Reviewer's comments: Parameters (highlighted in blue) had the AC different from the finalized commercial lot release criteria (highlighted in red font) (Please refer to Module 3.2.P.5.1 Specifications in this memo). The AC for the remaining parameters are the same as the finalized commercial lot release criteria. Lot release results of all these (b) (4) full-scale lots met all finalized commercial lot release criteria.

□ Comparison of (b) (4) Lots

Overall Differences Among (b) (4) Lots

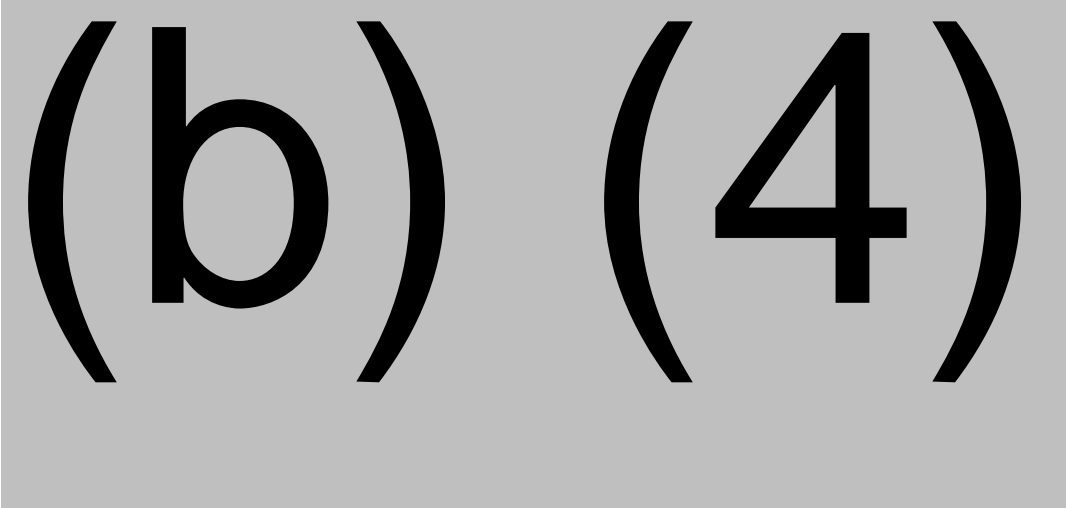
Table 93 summarized 7 major differences among (b) (4) run identified after the batch comparison of materials, equipment, operations, and process data (Document #55-307-TR-0002).

Table 93. Major Differences Among (b) (4) run

(b) (4)


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

(b) (4)



(b) (4)

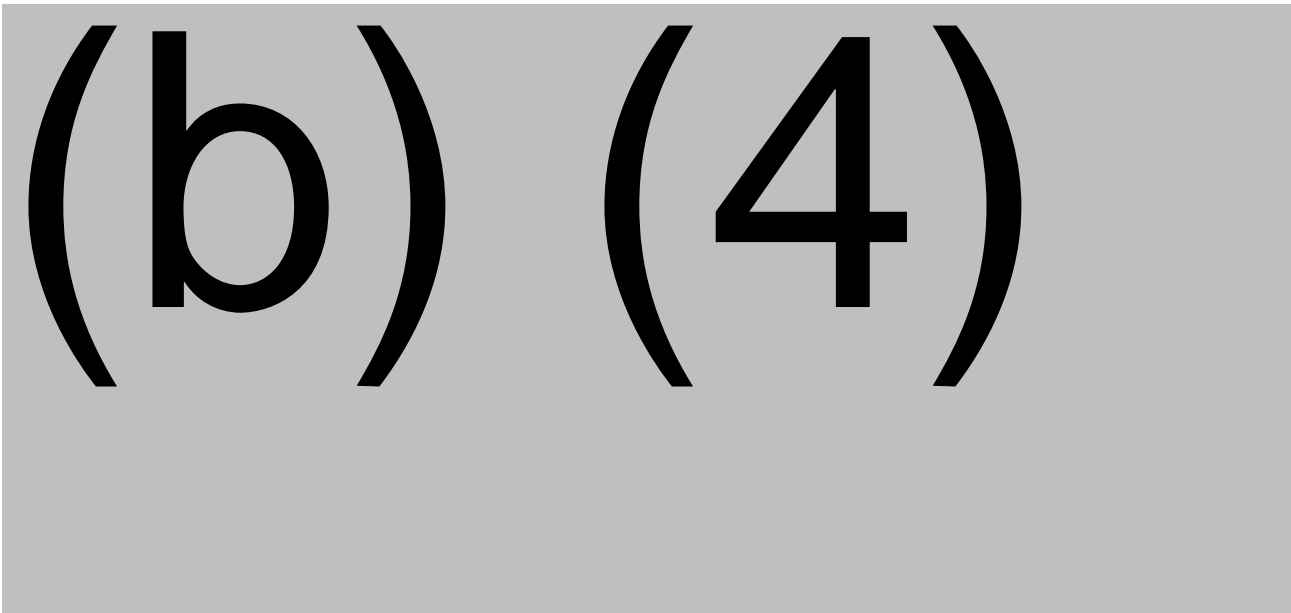

(b) (4)



3.2.P.3.5.2. Conformance of CPPs, KPPs, and IPCs During Process Validation

Table 96 compared results of process parameters, including CPPs and KPPs, during the manufacture of (b) (4) runs, all of which fell into the NOR, except the overall process time for PPQ1 (Please refer to Reviewer's comments).

(b) (4)

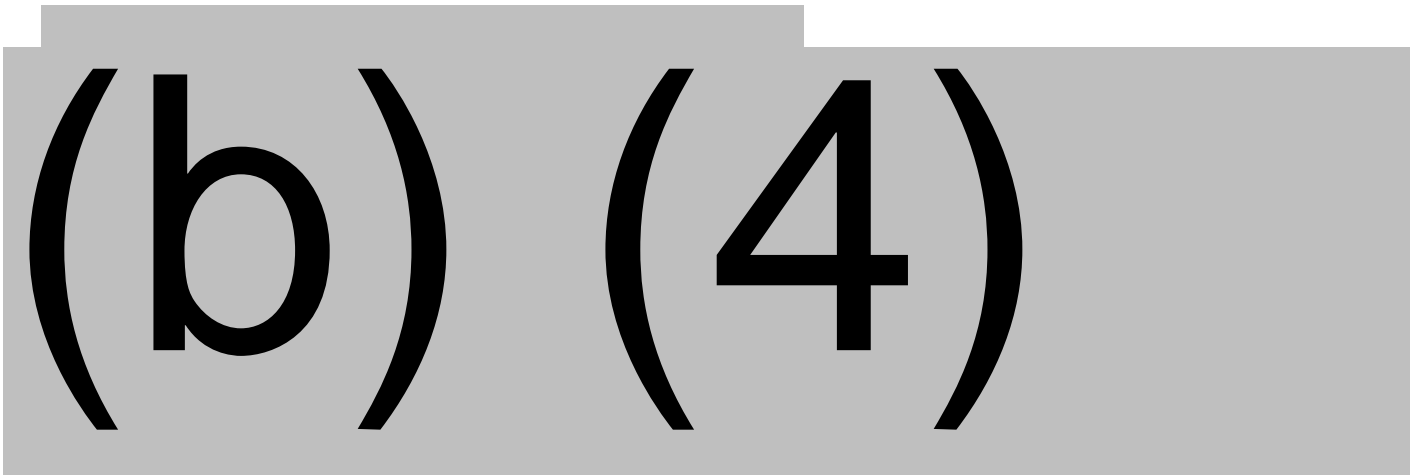
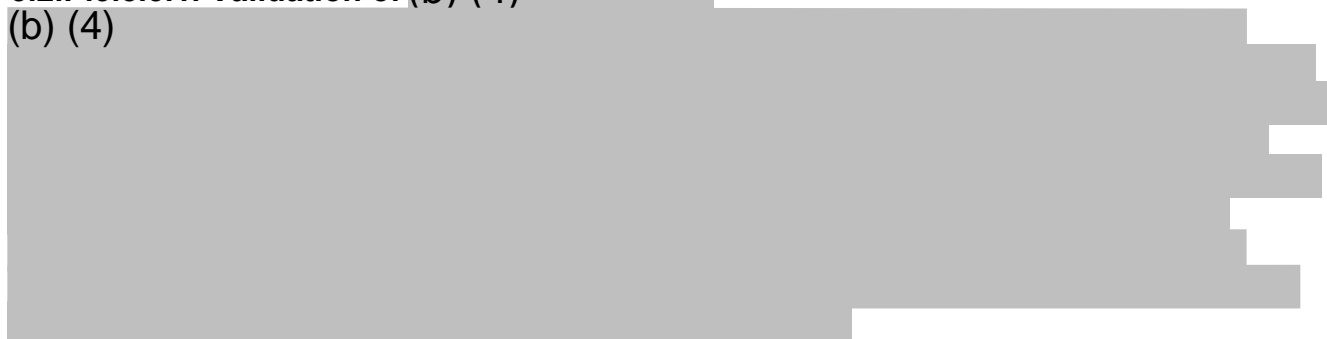


Reviewer's comment: Results from all parameters during all (b) (4) runs fell into the NOR, except the overall process time for PPQ1 and engineering run, in which the overall processing time, which has a PAR of (b) (4) hr ([Module 3.2.P.3.4](#) in this memo), therefore it is acceptable.

3.2.P.3.5.3. Validation of PRGN-2012 DP Filling Process

3.2.P.3.5.3.1. Validation of (b) (4)

(b) (4)



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

(b) (4)

(b) (4)

Reviewer's note: Please refer to the DMPQ review memo for other supportive validation studies, such as aseptic process simulation to demonstrate the contamination controls, and cleaning validation/verification of equipment.

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

The preliminary control, effectiveness, and consistency of DP fill and finish process has been demonstrated using a concurrent PPQ approach by meeting the AC for CPPs, KPPs, and selected quality attributes (QAs/CQAs) through an engineering run, a pre-PPQ run, and PPQ1 run. Two PMCs (PMC #5 and #7) have been put in place to provide additional assurance for the control, consistency, and effectiveness of process performance and DP (b) (4)

3.2.P.4 Control of Excipients

(Reviewed by SS)

3.2.P.4.1 Specifications

All the excipients in DP are (b) (4) grade. A list of the excipients and (b) (4) references are provided in Table 99.

Table 99. Specifications for (b) (4) Excipients

Component	Quality Standard
Tris (Tromethamine)	(b) (4)
Sodium Chloride	
Magnesium Chloride Hexahydrate	
Polysorbate 80	
α, α-Trehalose Dihydrate ¹	
(b) (4) Sterile Water for Injection Specifications)	

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

The excipients used in manufacture of DP are tested in accordance with current (b) (4) analytical procedures.

3.2.P.4.4 Justification of Specifications

All excipients are tested in accordance with (b) (4) standards and methods.

3.2.P.4.5 Excipients of Human or Animal Origin

No excipients of human or animal excipients are used in manufacture of DP.

3.2.P.4.6 Novel Excipient

No novel excipients are used in the manufacture of DP.

Overall Reviewer's Assessment of Section 3.2.P.4:

Information on excipients in the DP is acceptable.

3.2.P.5 Control of Drug Product

(Reviewed by JG)

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

3.2.P.5.1 Specifications(s)

The PRGN-2012 DP release and stability specifications (as applicable) are shown in the Table 100 below. This table is adapted from: (1) the revised/updated Table 1 of eCTD 3.2.P.5.1; and (2) Sections 5.1 and 6.0 of QV-MSPEC-00048, both submitted under Amendment #44 (received June 24, 2025). In this table:

- The DP test parameters, methods, and AC that were proposed in the original submission (i.e., Amendment #2) and remained unchanged during this review cycle are shown in black font.
- Any added or updated parameters, methods, and AC proposed in Amendment #44 and #54 are shown in blue font.

Table 100. Zopapogene imadenovec DP Specification

Quality Attribute	Parameter	Method	Method SOP(s)	Acceptance Criteria	
				Release	Stability
General Test	Appearance	Visual Inspection	QV-TM-00033	Slightly Opalescent to Opalescent Colorless Liquid and Free of Visible Particulates	Slightly Opalescent to Opalescent Colorless Liquid and Free of Visible Particulates
	pH	(b) (4)	QV-TM-00023	(b) (4)	N/A
	Volume in Container	(b) (4)	QV-TM-00051 / (b) (4)	Recoverable Volume (b) (4) 1 mL	N/A
	(b) (4)	(b) (4)	QV-TM-00053 / (b) (4)	(b) (4)	N/A
Identity	(b) (4)	(b) (4)	QV-TM-00020	(b) (4)	N/A
Quantity	(b) (4)	(b) (4)	QV-TM-00001	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	QV-TM-00008	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	QV-TM-00009	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	QV-TM-00003	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	QV-TM-00021	(b) (4)	N/A
Purity/ Impurity	Purity	(b) (4)	QV-TM-00012	(b) (4)	N/A
	(b) (4)	(b) (4)	QV-TM-00002	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)	N/A
Safety	Particulates	(b) (4)	(b) (4)	(b) (4)	N/A
	Endotoxin	(b) (4)	QV-TM-00032	(b) (4)	N/A

Quality Attribute	Parameter	Method	Method SOP(s)	Acceptance Criteria	
				Release	Stability
	Sterility	(b) (4)	(b) (4)	No Growth	N/A
	Container Closure Integrity Test (CCIT)	(b) (4)	(b) (4)	N/A	(b) (4)
Abbreviations: (b) (4); EU – Endotoxin Units, (b) (4) N/A = Not Applicable.					

Reviewer's Comments:

- The above PRGN-2012 DP release and stability (as applicable) specifications are acceptable for the BLA. For details on the evolution of and our rationale behind accepting each of the above AC, please see the respective Justifications of Specifications below.
- During the pre-license inspection (PLI) for the (b) (4) facility conducted from (b) (4), it was discovered that identity testing was not performed on the incoming (b) (4), and this led to Observation #1 on the 483. (b) (4) submitted their responses to Form FDA 483 directly to the FDA on 5/19/2025 and 6/24/2025 to address this concern and revised the material specification for PRGN-2012 (b) (4) to include a requirement for identity testing on each (b) (4) received at their facility. The updated corresponding sections were submitted in Amendment #50. The testing will be performed by Precigen using the (b) (4) assay per QV-TM-00020, and identity assay results will be provided to (b) (4) release prior to use in DP manufacturing. See the establishment inspection report (EIR) for the (b) (4) facility for additional information.
- In Amendment #15 (CMC IR #5, Question 10), Precigen has committed to establishing a procedure to test the final labeled DP vials (b) (4) packaging site by performing an identity test using the (b) (4) Assay. They have also revised the eCTD Module 3.2.P.3.3 Description of Manufacturing Process and Process Controls, Section 3.4.6 to specify that the DP identity testing will be performed on the final labeled DP vials (b) (4) packaging site to storage and distribution. This action complies with the requirements of 21 CFR §610.14, Identity.

3.2.P.5.6 Justification of Specification(s)

Precigen's DP lot release and stability AC are derived from two sources: (1) (b) (4) or FDA-recommended AC; and (2) statistical analysis of the actual DP lot release data. They provided information on the (b) (4) DP lots (comprised of Clinical, Engineering, Pre-PPQ, and PPQ lots) used for their justification in Table 1 of eCTD 3.2.P.5.6 (submitted under Amendment #44).

Reviewer's Comments: The original eCTD 3.2.P.5.6 (submitted under Amendment #2), Justification of DP Specifications, were updated three times during this review cycle: (1) under Amendment 28 (received April 25, 2025), as per the FDA information request (IR) given through CMC IR #5, Comment 1b (March 27, 2025); (2) under Amendment #44 (received June 24, 2025), as per the FDA advice given through CMC IR #15 (June 06, 2025); and (3) under Amendment #47, as per the FDA advice given through CMC IR #18 (June 30, 2025).

3.2.P.5.6.1.2.1. Appearance

In Amendment #28, Precigen stated that “Slightly Opalescent to Opalescent Colorless Liquid” confirms the expected DP appearance” and provided the following justifications to exclude the “free of visible particles” phrase that was used for the first three DP lots.

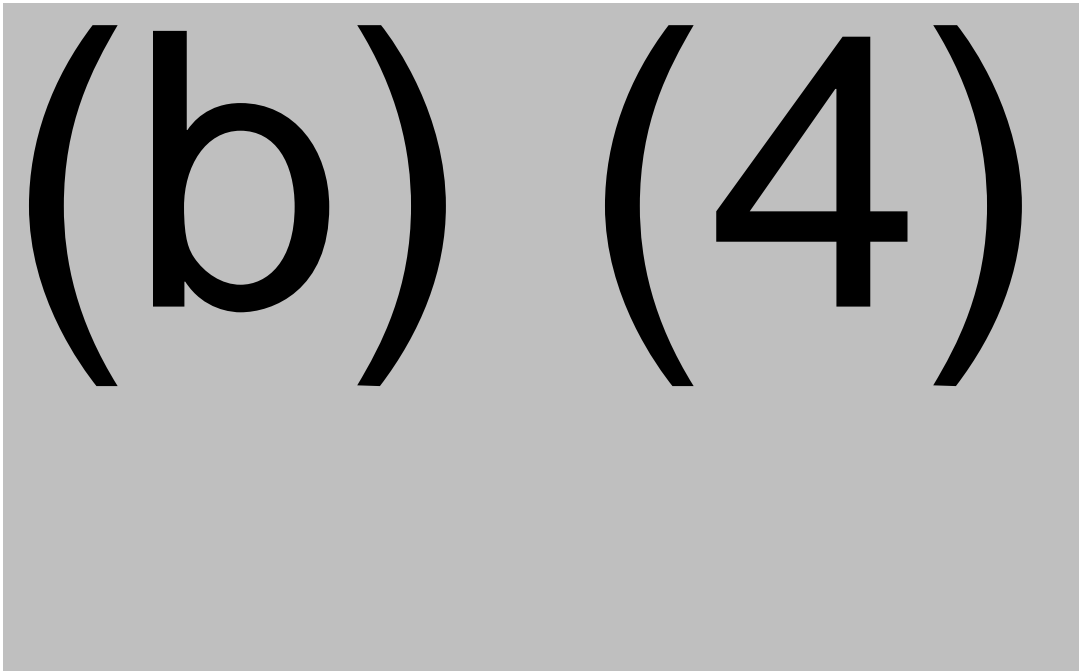
- For the commercial PRGN-2012, “Individual DP vials containing visible particulates are identified and rejected (i.e., not released) during the 100% visual inspection (VI) and statistical Acceptance Quality Limit (AQL) inspection.”
- Throughout the clinical development, the DP was found to be “free of visible particles” in all release and stability tests.
- The release and stability results of the (b) (4) method provided “no evidence of particulate formation through aggregation”.
- They have an AC for (b) (4) as per (b) (4) for the DP release.

Reviewer’s Comments: As injectable products should be free of visible particulates and there was a DP appearance-related observation during the pre-license inspection for (b) (4), (b) (4) (detailed in the FDA 483 form, Observation #5, issued on (b) (4) the FDA did not agree with the Appearance AC proposed and the justification provided in Amendment #28. FDA subsequently recommended that Precigen revise the Appearance AC by including the phrase “free from visible particulates.” Precigen agreed with the FDA’s recommendation and under Amendment #44 revised the DP Appearance AC to “Slightly Opalescent to Opalescent Colorless Liquid, and Free of Visible Particulates.”

3.2.P.5.6.1.2.2. pH

In Amendment #28, Precigen stated that the proposed AC for DP pH, (b) (4) is based on the mean, SD, and the (b) (4) values of the release data from the (b) (4) DP lots.

Reviewer’s Comments: As shown in Figure 34 below, the proposed pH AC is well within the (b) (4) calculated by the FDA, it is acceptable for the BLA.

Figure 34. FDA Analysis of Precigen's DP pH Data**3.2.P.5.6.1.2.3. Volume in Container**

In Amendment #28, Precigen stated that as the proposed AC for DP Volume in Container, "Recoverable volume (b) (4) 1 mL," is based on the intended dose, they did not statistically analyze the data to calculate the (b) (4). All (b) (4) DP lots (manufactured so far) had (b) (4) 1 mL extractable volume.

Reviewer's Comments: Each PRGN-2012 vial is filled to a target volume of (b) (4) mL (reference – eCTD 3.2.P.2.2.2) to deliver an extractable volume of 1.0 mL. Although the (b) (4) volume used, (b) (4) mL is (b) (4) volumes for the 1 mL labeled size (i.e., (b) (4) considering Precigen's limited DP manufacturing experience and the submitted DP lot data, the proposed AC is reasonable and acceptable for the BLA.

3.2.P.5.6.1.2.4. (b) (4)

In Amendment #28, Precigen stated that the proposed DP AC for (b) (4) (b) (4) " is based on the mean, SD, and the (b) (4) values of the release data from the (b) (4) DP lots.

Reviewer's Comments: We have summarized our statistical analyses of Precigen's DP (b) (4) data in Figure 35 below. The proposed (b) (4) AC is outside of the (b) (4) calculated by the FDA. However, as it is currently set at the calculated (b) (4) and Precigen has agreed to reevaluate this AC after manufacturing (b) (4) DP lots, it is reasonable and acceptable for the BLA.

(b) (4)

(b) (4)

3.2.P.5.6.1.2.5. (b) (4)

In Amendment #47, Precigen stated that the proposed DP AC is (b) (4) and their (b) (4) design is specific to the (b) (4) as well as confirmation of (b) (4). All (b) (4) DP lots met this qualitative AC.

Reviewer's Comments: The proposed AC is acceptable.

3.2.P.5.6.1.2.6. (b) (4)

In Amendment #28, Precigen stated that the proposed DP AC for (b) (4) is based on: (1) DP dose target of 5.0×10^{11} PU/mL; and (2) the mean, SD, and the (b) (4) values of the release data from the (b) (4) DP lots.

Reviewer's Comments: We have summarized our statistical analyses of Precigen's DP PU/mL data in Figure 36 below. We agree that the proposed (b) (4) (b) (4) AC is well within the (b) (4) calculated by the FDA. However, as Precigen's intended commercial dose would be 5.0×10^{11} PU/injection, we advised (Reference: CMC IR #15) them to raise the lower limit of the DP AC to (b) (4) PU/mL." Precigen agreed and proposed a new AC of (b) (4) PU/mL to (b) (4) PU/mL" under Amendment #44, and this revised AC is acceptable for the BLA.

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

(b) (4)

(b) (4)

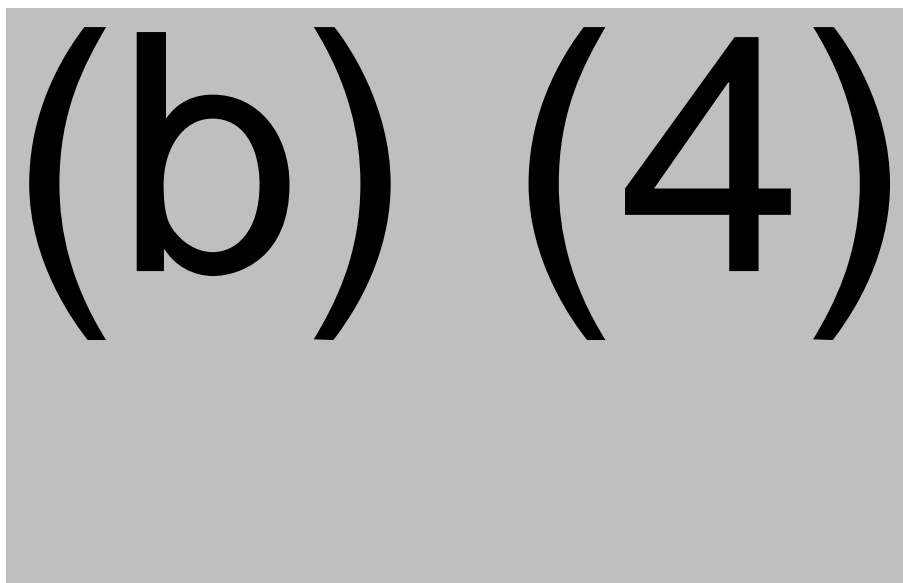
(b) (4)

Reviewer's Comments: The proposed AC is acceptable.


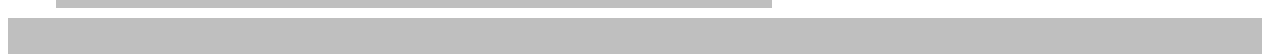




3.2.P.5.6.1.2.10. Purity

In Amendment #28, Precigen stated that the DP Purity AC, (b) (4) is based on the release data from all (b) (4) DP lots. Due to the minimal variance in the data, Precigen calculated only the mean and SD.

Reviewer's Comments: We have summarized our statistical analyses of Precigen's DP Purity data in Figure 40 below. The proposed AC is well above the lower one-sided (b) (4) calculated by the FDA and acceptable for the BLA.

Figure 40. FDA Analysis of Precigen's DP Purity Data

(b) (4)



(b) (4)

(b) (4)

3.2.P.5.6.1.2.12. Particulates

In Amendment #28, Precigen stated that the DP AC for Particulates, (b) (4) are based on (b) (4) (b) (4) All (b) (4) DP lots met the above AC.

Reviewer's Comments: The proposed AC is acceptable.

3.2.P.5.6.1.2.13. Endotoxin

In Amendment #28, Precigen stated that the DP AC for Endotoxin, (b) (4) is based on (b) (4) They have provided data from (b) (4) DP lots showing that all of them were at (b) (4)

Reviewer's Comments: As the (b) (4) endotoxin threshold for a (b) (4) individual is (b) (4) and Precigen will administer 1 mL of PRGN-2012 DP, we agree that the proposed AC of (b) (4) is acceptable for the endotoxin level in the PRGN-2012 DP.

3.2.P.5.6.1.2.14. Sterility

In Amendment #28, Precigen stated that the DP AC for Sterility, "No growth," is based on the regulatory and safety requirements as stated in FDA Guidance for Industry - "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices." They have provided data from (b) (4) DP lots showing that all of them had "No Growth."

Reviewer's Comments: The proposed AC is acceptable. During the PLI for (b) (4) conducted from (b) (4), it was discovered that the SOP for sterility testing did not specify a required time limit from sample collection to performing the test. Sterility samples were stored at (b) (4) for up to (b) (4) before shipping to the testing site (b) (4) and stored at (b) (4) for an additional (b) (4) before testing. This led to Observation #2 on the 483. (b) (4) submitted their responses to Form FDA 483 directly to the FDA on 5/19/2025

and 6/24/2025 to address this concern and implemented a (b) (4) period from sample collection to testing in their SOP. The updated corresponding sections were submitted in Amendment #50. See the establishment inspection report (EIR) for the (b) (4) facility and DMPQ review memo for additional information.

3.2.P.5.6.1.2.15 Container Closure Integrity Test (CCIT)

Reviewer's Comments: This test is conducted for stability studies only. Although no formal justification was provided in the BLA for the proposed AC of (b) (4) using the (b) (4) type CCIT method, the proposed AC is self-explanatory and acceptable.

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

The current DP specification (i.e., test methods and their AC as amended in Amendment #44) for release is reasonably justified and acceptable. However, due to the limited number of post-change DP lots available at this time, the setting of commercial DP AC is not supported by sufficient statistical analysis. Therefore, we have sent a formal PMC communication to Precigen (Reference: PMC #9 of PMC Letter dated, July 28, 2025) and they have committed to reassessing commercial DP AC for release once (b) (4) lots DP are manufactured. Based on their current projections, Precigen anticipates a total of (b) (4) DP lots will be manufactured by 2031 (Reference: Amendments #44 and #62).

As Precigen has proposed the same DP AC for stability for the Appearance, PU/mL, (b) (4), relative potency by (b) (4), the proposed DP stability AC (including for the CCIT) are acceptable (for additional information, please see our assessment of the DP stability data).

Note: Specification for (b) (4) Testing

Although a specification for (b) (4) testing (including lot release data and method validation data) for PRGN-2012 was submitted under Amendment #2 (and Amendments #12 and #20) and reviewed by the FDA, the (b) (4) specification is no longer applicable for this BLA. The (b) (4) specification was removed from the commercial DP lot release specifications under Amendment #44 after the following actions:

Risk Assessment by FDA: After careful consideration of the (b) (4)

(b) (4) test data submitted under the BLA, the FDA determined that the risk of (b) (4) in the DP is low.

Agreement and Action: Based on this risk assessment: a) the FDA gave Precigen an option to remove the (b) (4) assay from their commercial DP lot release specifications; and b) Precigen subsequently removed the (b) (4) specification and related information from the BLA under Amendment #44.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures (Reviewed by JG)

Please refer to the DBSQC review memo for FDA's assessment of the following analytical procedures, used for testing the PRGN-2012 DP and the validation of these analytical procedures: **appearance, pH, volume in container, (b) (4), purity, (b) (4), particulates, endotoxin, and sterility**. DBSQC found the general descriptions (provided in eCTD 3.2.P.5.2) and the SOPs (provided in eCTD 3.2.R) for the above analytical procedures acceptable, and the respective validation reports adequate to ensure that the methods are appropriately validated for their intended use.

Please refer to the DMPQ review memo for FDA's assessment of the **container closure integrity test** and the validation of this analytical procedure. DMPQ found the general description (provided in eCTD 3.2.P.5.2) and the SOP (provided in eCTD 3.2.R) for the above analytical procedure acceptable, and its validation report adequate to ensure that the method is appropriately validated for its intended use.

We (OTP/OGT) reviewed the validation information related to the following analytical procedures used for testing the PRGN-2012 DP: (b) (4)

Precigen stated that "Some of the DP test methods are the (b) (4) test methods, including (b) (4), since there is (b) (4) DP with respect to Adenovector (b) (4) and cross-referenced the method validation information provided in eCTDs 3.2.S.4.2 and 3.2.S.4.3 for the following assays: (b) (4)

Reviewer's Comments: We agree: (1) with Precigen's justification for using (b) (4) method descriptions and SOPs for the above assays for PRGN-2012 (b) (4) DP; and (2) that cross-referencing the respective (b) (4)-specific analytical method validation is adequate for the above assays to ensure that the methods are appropriately validated for their intended use for analyzing the PRGN-2012 DP.

(b) (4)

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

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

- The standalone DP lot release testing methods and the methods used for testing (b) (4) DP, reviewed by OTP/OGT are acceptable. The DP lot release test methods are adequately validated for the BLA.
- The (b) (4) assay validation related information and data submitted under Amendment #2, #12, and #20 are no longer applicable and were reviewed for information only. As per FDA's recommendation, Precigen has removed the (b) (4) specification from the commercial DP lot release specifications. For detailed explanation on this issue, please see under "Overall Reviewer's Assessment of Sections [3.2.P.5.1](#) and [3.2.P.5.6](#)."

3.2.P.5.4 Batch Analyses

(Reviewed by JG)

DP lots produced during development (including investigational clinical studies), Pre-PPQ and PPQ are summarized in Table 104 below. Detailed lot release test results for these DP batches are submitted in the BLA.

Table 104. Summary of PRGN-2012 DP Lots

(b) (4)

Reviewer's comment: The Applicant intends to use the PPQ #1 DP lot as the commercial launch lot. The DS and DP lot release data meet the FDA-agreed commercial release specifications. On August 4, 2025, FDA notified Precigen that their lot release protocol (LRP) template submitted under Amendment #59 is acceptable for use. The LRP for the launch lot (PPQ #1) will be submitted to the FDA Gateway system for FDA review and approval prior to commercial release.

3.2.P.5.5 Characterization of Impurities

(Reviewed by JG)

The PRGN-2012 DP is tested to confirm the absence or acceptable limit (as applicable) of the following impurities:

Table 105. Possible Impurities in PRGN-2012

Type of Impurities	Test Method	Acceptable Limit
Product-related Impurities	(b) (4)	
Process-related Impurities		

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

- We have reviewed the submitted DP lot analysis data and used them as appropriate to evaluate the "Specifications" and "Justification of Specifications" proposed/submitted for the commercial PRGN-2012 DP. Overall, the DP lot analysis data provided in the submission are appropriate for the corresponding stages of PRGN-2012 product development and are acceptable for the BLA.
- The (b) (4) specification submitted under Amendment #2 is no longer applicable, as it has been removed from the commercial DP lot release specifications per FDA's recommendation. For a detailed explanation of this issue, please see "Overall Reviewer's Assessment of Sections [3.2.P.5.1](#) and [3.2.P.5.6](#)."
- Overall, we agree that the possible impurities in the DP are adequately controlled and monitored for their absence or acceptable limits, as applicable.

3.2.P.6 Reference Standards or Materials

(Reviewed by SS)

Refer to the information under [Section 3.2.S.5 Reference Standards or Materials](#).

3.2.P.7 Container Closure System

(Reviewed by SS)

Refer to the information under [Section 3.2.P.2.4 Container Closure System](#).

3.2.P.8 Stability

(Reviewed by JW)

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

Stability study design

Real-time stability study is being conducted using (b) (4) PRGN-2012 DP lots (Table 82) manufactured using full-scale commercial process and packaged in 2 mL (b) (4) vials at the intended storage condition -60°C (b) (4). For in-use stability studies, please refer to Module 3.2.P.2.6 Compatibility. Stability study designs are summarized Table 106 by the Reviewer with information on PRGN-2012 DP batches placed on stability shown in Table 107.

Table 106. Summary of PRGN-2012 Stability Study Designs

Item		Long-term stability (≤ -60°C)	(b) (4)	(b) (4)
Timepoint /Design		0, 3, 6, 9, 12, 18, 24, (b) (4)	(b) (4)	(b) (4)
DP Lot Used		(b) (4)	(b) (4)	(b) (4)
Specifications and Timepoints				
Appearance	Slightly Opalescent to Opalescent Colorless liquid and free of visible particulates	x	x	x

(b) (4)

Reviewer’s note: Stability specifications are the same as finalized commercial DP lot release specifications (Please refer to Section [3.2.P.4.1.Specifications](#) in this memo. Highlighted in red are finalized AC.

Table 107. Information on PRGN-2012 DP Batches placed on Stability

(b) (4)

(b) (4)

Stability Data


Please refer to Module [3.2.P.2.3](#) in the BLA submission for complete sets of stability data for all ^{(b) (4)} lots listed in Table 107 either at the intended long term storage condition at $\leq -60^{\circ}\text{C}$ ^{(b) (4)} . Table 108 and Table 109 below showed the updated stability data from the PPQ1 lot (up to 6 months) and pre-PPQ lot (up to 15 months) respectively.

Table 108. Stability Data of PRGN-2012 DP Lot (b) (4) (PPQ1) Stored at $\leq -60^{\circ}\text{C}$

(b) (4)

Table 109. Stability Data of PRGN-2012 DP – Lot (b) (4) (Pre-PPQ GMP) Stored at $\leq -60^{\circ}\text{C}$

(b) (4)

(b) (4)

Stability Data Analysis

Please refer to Module [3.2.S.7.1 Stability Data Analysis](#) in this memo for stability data poolability and stability models used for PRGN-2012 DP stability data analyses. The DP* Stability Data Poolability Assessment and Regression Analysis

Table 110. DP* Stability Data Poolability Assessment and Regression Analysis

(b) (4)

(b) (4)

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

(b) (4)	
Expiry estimation is based on the (b) (4)	supporting the 24-month shelf-life claim for PRGN-2012 DP stored at $\leq -60^{\circ}\text{C}$.
(b) (4)	

Stability Summary and Conclusion

Based on statistical analysis data for the primary batches and the available long-term data for the supporting batches, Precigen proposed an initial shelf-life of **24** month for PRGN 2012 DP stored at $\leq -60^{\circ}\text{C}$.

Reviewer's comments:

- Please note stability data from (b) (4) lots (instead of (b) (4) lots) were used for potency data poolability and regression analysis. This is due to the use a qualitative potency assay for the lot release of (b) (4) clinical lots.*
- The stability program did not include PRGN-2012 photostability testing, which was discussed in an informal T-con with Precigen on 28-May-2025. During the T-con, FDA recommended adding cautionary language such as "Protect from Light" in the USPI and labels. In response to CMC IR#11, Precigen stated that light exposure during clinical use is minimal (<2hrs) and additional in-use stability data (submitted in SN0046) indicated that there is no product quality impact during the handling at the clinics. In SN0051, Precigen agreed to add "Protect from Light" to all three labels (vial, pouch, and carton) and in SN0064, Precigen agreed to add "Protect PAPZIMEOS from Light" to the USPI. Overall, the mitigation strategy is acceptable.*
- Based on the (b) (4) and regression analyses of DP real-time stability data from (b) (4) clinical lots and (b) (4) lots manufactured using commercial manufacturing process, the proposed DP shelf-life of 24 months is acceptable.*

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

3.2.P.8.2.1. Stability Commitment

Applicant commits to continue the DP stability studies summarized in Table 82 in this memo. In addition, as agreed upon with the Agency (Meeting Summary-CRMTS 15245-BTD Type B CMC-Only Meeting-24Oct2023), (b) (4) PPQ lots will be manufactured and placed on the stability program provided in Module 3.2.P.8.1 Stability Summary and Conclusions.

3.2.P.8.2.2. Post-Approval Stability Program

(b) (4) that commercial manufacturing occurs, (b) (4) of unlabeled DP will be placed on stability for up to (b) (4) months (QV-PRTL-00139). Once (b) (4) is labeled, the labeled DP (b) (4) will also be placed on stability for up to (b) (4) months (QV-PRTL-00139). For clarification, (b) (4) unlabeled and labeled vials from the parent (b) (4) will continue to be tested for the duration of the stability protocol (Table 111). The shelf life will be established based on Date of Manufacture (T0). Stability samples will be stored at the recommended storage condition of $\leq -60^{\circ}\text{C}$.

Any batches found to fall outside the approved specifications may be withdrawn from the market and the situation will be discussed with the agency, as appropriate. In case of any post-approval changes that require new stability studies, Precigen commits to place the required number of production batches of the final labeled DP on a stability program and to investigate them in accordance with the same stability protocol.

Precigen will submit a Prior Approval Supplement with additional stability data to support (b) (4) of the DP.

Table 111. PRGN-2012 DP Post-Approval Stability Studies:

Assay Description	Long-term Storage Condition ($\leq -60^{\circ}\text{C}$)						
	Test Interval (months)						
	0 ¹	3M	6M	9M	12M	18M	24M
Appearance	X	X	X	X	X	X	X
(b) (4)	X	X	X	X	X	X	X
	X	X	X	X	X	X	X
	X	X	X	X	X	X	X
	X	X	X	X	X	X	X
	X	X	X	X	X	X	X
Container Closure Integrity	X	NT	NT	NT	X	NT	X

X = required test; NT = No Test (Test not performed at this sampling point)

¹ Tests listed for Time Point "0" were conducted as part of the initial PRGN-2012 DP release testing and are not repeated.

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

- Primary stability studies for DP included the following studies: (1) long term stability in conditions of $\leq -60^{\circ}$, (2) (b) (4) as well as (3) (b) (4). The DP shelf life is **24 months** from the date of manufacture when stored at the recommended temperature of $\leq -60^{\circ}$. The shelf-life claim is based on available data for (b) (4) months (b) (4) months from the (b) (4). Overall, the applicant demonstrated acceptable stability for up to 24 months with no major concerns. There are no remaining deficiencies.
- The applicant plans to enroll (b) (4) DP (b) (4) in the commercial stability program (b) (4). Any future post approval (b) (4) will be submitted as a prior approval supplement (PAS).

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Reviewed by DMPQ.

3.2.A.2 Adventitious Agents Safety Evaluation

(Reviewed by JW)

A risk assessment of the viral control strategy is presented in Module 3.2.S.2.6 Manufacturing Process Development and in the Virus Clearance Risk Assessment Report RGP2012-2024-015, a comprehensive risk assessment for virus control concluded that sufficient controls have been put in place to avoid/mitigate a potential virus contamination.

Overall, control of non-viral adventitious agents (b) (4)

and viral adventitious agents as well as viral adventitious agents in PRGN-2012 (b) (4) relies on the use of non-animal derived raw materials in the production of PRGN-2012 (b) (4) DP. Please refer to [Module 3.2.S.2.3. Control of Materials](#) in this memo for the evaluation of adventitious agents safety in raw materials, biological starting materials, (b) (4), and refer to [Module 3.2.S.2.4. Controls of Critical Steps and Intermediates](#) in this memo for the evaluation of adventitious agents safety (b) (4)

All batch analysis results from (b) (4) clinical lots and commercial lots met specifications and no adventitious agents have been detected.

Reviewer's comments: Despite no adventitious agents have been detected, it has been determined that the (b) (4), which is used to detect adventitious viral contamination in the (b) (4) manufacturing process, has not been adequately validated (Please refer to [Module 3.2.S.4.2 Analytical Procedures](#) in this memo). A post-marketing requirement (PMR) has been put in place for a proper validation of the (b) (4)

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

Overall, adventitious agent control relies on use of raw materials that do not contain adventitious agents that could be incorporated into the product PRGN-2012. Meanwhile, the deletion of E1 (b) (4) from PRGN-2012 vector genome can help prevent creation of RCA during vector production.

In addition, a risk assessment of the viral control strategy has been performed and concluded that sufficient controls have been put in place to avoid/mitigate a potential virus contamination. And no adventitious agents have been detected during the release testing for all batches manufactured so far.

The fulfillment of PMR#1 regarding revalidation of the (b) (4) will further provide adventitious agent control assurance.

3.2.A.3 Novel Excipients

No novel excipients are used in the manufacture of zopapogene imadenovec-drba.

3.2.R Regional Information (USA)

Executed Batch Records

(Reviewed by JW)

Executed master batch records (EBR) for (b) (4) zopapogene imadenovec-drba (b) (4) and (b) (4) lots, DP PPQ1, (b) (4) were submitted to the BLA and reviewed. During the PLI, executed batch records for (b) (4) were also reviewed. Please refer to Precigen Inc. FEI 3014429654 Establishment Inspection Report (EIR) for additional details on the review of executed batch records conducted during PLI.

Method Validation Package

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

Not applicable, as zopapogene imadenovec-drba is not a combination product.

Comparability Protocols

The Applicant did not propose any future comparability studies.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

(Reviewed by SS)

The Applicant submitted environmental (EA) assessment pursuant to 21 CFR part 25 requirement. The Applicant does not make a claim of categorical exclusion for EA. This application is not eligible for categorical exclusion. The EA provided an assessment of PRGN-2012 environmental exposure based on a comparison to existing information for related viral vector-based vaccine products.

Reviewer's comment: The information provided in the environmental assessment demonstrates that the PRGN-2012 poses no significant environmental risk from its approval. A finding of no significant impact (FONSI) has been prepared.

B. Reference Product Designation Request

(Reviewed by SS)

The Applicant has requested reference product designation under section 1.3.5.3 of the CTD.

C. Labeling Review

(Reviewed by JW)

C.1. Full Prescribing Information (PI):

PAPZIMEO - BLA 125832.0 USPI 03-31-25.docx (Sections 2, 11, 12, 16)

PAPZIMEOS suspension is supplied in a single-dose vial containing an extractable dose of 5×10^{11} particle units (PU) in a 1 mL suspension (Note, each vial contains a target volume of (b) (4) mL/vial and the nominal titer is 5.0×10^{11} PU/mL). Each carton of PAPZIMEOS contains one single-dose vial of PAPZIMEOS sterile frozen suspension.

The recommended dose of PAPZIMEOS is 5×10^{11} particle units (PU) per injection administered by subcutaneous injection four (4) times over a 12-week interval. The recommended treatment schedule is listed in Table 112.

Table 112. Recommended Treatment Schedule for PAPZIMEOS

Administration	Administration Interval
Initial	--
Second	2 weeks after initial administration (The second administration should occur no less than 11 days after the initial administration)
Third	6 weeks after initial administration
Fourth	12 weeks after initial administration

Preparation and Administration of PAPZIMEOS for Injection starts with thawing the vial in a 37°C water/dry bath until no visible ice crystals (typically less than 5 minutes), followed by wiping the vial and the rubber stoppers by 70% isopropyl alcohol or equivalent, visual inspection for a clear to slightly opalescent, colorless liquid, withdrawing 1 mL PAPZIMEOS using 3 mL syringe with the 18G to 22G needle (not a filter needle). After replacing with a 23-27 G subcutaneous injection needle, inject PAPZIMEOS by inserting the needle at an angle to ensure delivery in the subcutaneous space and in the lateral regions of the upper arm and thigh. Areas of edema, potential infection, wounds, scars or site of a recent subcutaneous injection should be avoided.

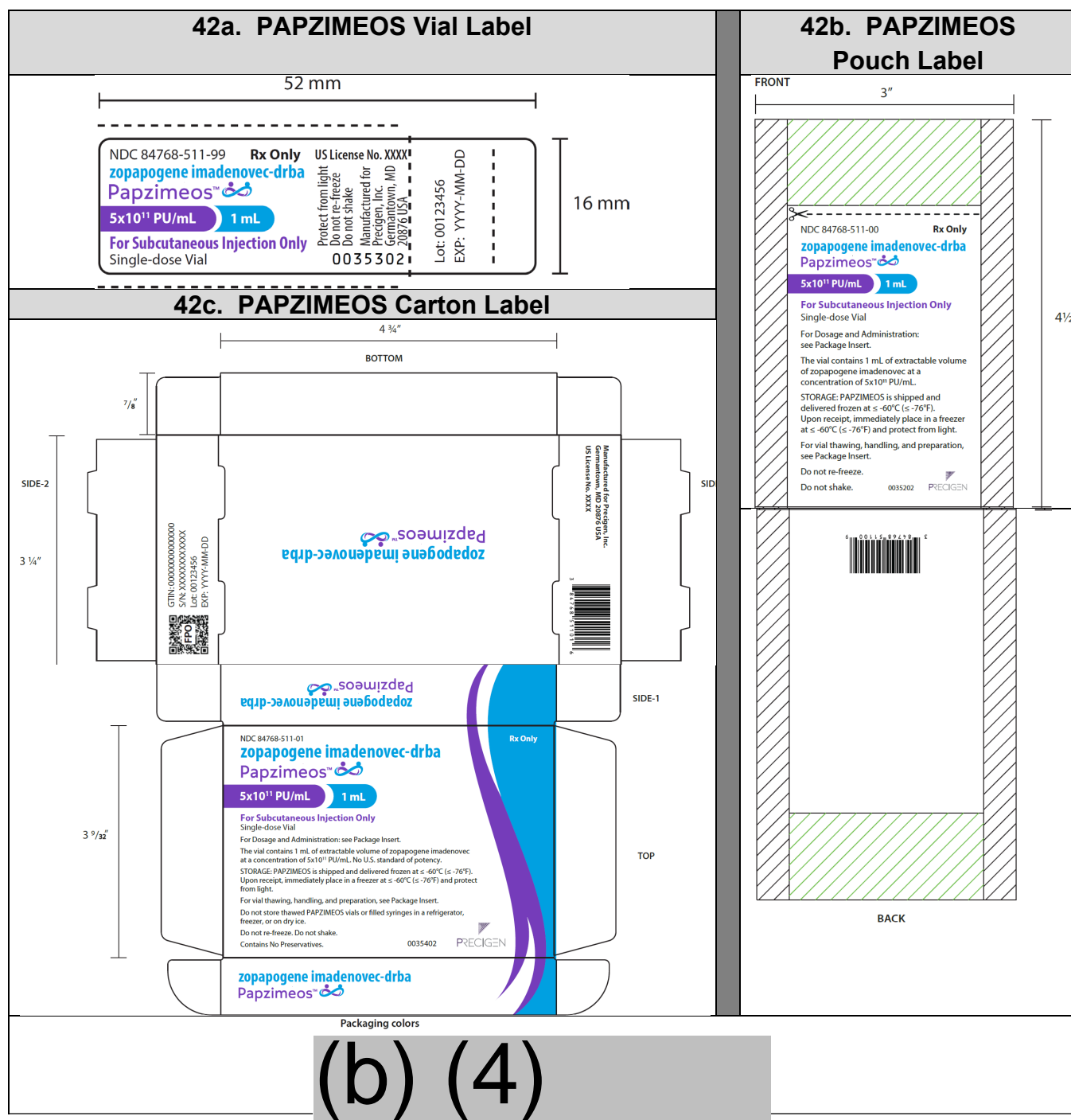
Storage and handling: PAPZIMEOS is shipped and stored frozen at $\leq -60^{\circ}\text{C}$ [$\leq -76^{\circ}\text{F}$] and should be stored in an appropriate freezer at $\leq -60^{\circ}\text{C}$ [$\leq -76^{\circ}\text{F}$] until ready to thaw and administer. Once removed from the pouch, the vial should not be placed in a refrigerator, freezer, or on dry ice at any time. For handling, universal biohazard precautions should be followed and dispose the used needle and empty vial in a biohazard container.

Reviewer's comment: In original submission, the overall instructions in the PI on PAPZIMEOS preparation lacked critical details and were not organized properly. Comments on the PI were sent to the applicant on 28-Jul-2025 and revised to provide the acceptable details.

C.2. Carton and Container Labels

The final revised vial, pouch, and carton labels for PAPZIMEOS (zopapogene imadenovec-drba) are shown below in Figure 42.

Figure 42. PAPZIMEOS Labels

**Reviewer's comments:**

- Per 21CFR 201.25, 21CFR 207.35, 21CFR 610.61, 21CFR 610.62, 21CFR610.63, 21CFR610.67, several IRs (Regulatory and CMC) were communicated to Precigen on 10-Feb-2025, 27-Mar-2025, 21-Apr-2025, 02-Jul-2025, 28-Jul-2025, and 31-July-2025 for the revision of USPI and the carton / pouch/ vial labels respectively, including rephrasing "single-use vial" to "single-dose vial", adding "Protect from light", "For subcutaneous

injection only (to the vial label), “Do not Re-freeze”, “Do not shake”, adding barcodes which should contain the corresponding NDC code, adding “No Preservative” or “Contains no preservative”, adding “No U.S. standard of potency”, replacing “Manufactured by” with “Manufactured for Precigen, Inc”, rephrasing the storage and thawing instructions on the pouch label and carton label, adding the proper name suffixes, and using unique NDC code for each label (the vial label, pouch label, and carton label).

- *In response, in SN0052, SN0064, and SN0066, Precigen accepted all suggestions listed above provide the revised labels as shown in Figure 89 and USPI respectively.*
- *Please refer to regulatory project manager (RPM)’s review memo for additional details.*

Modules 4 and 5

(Reviewed by SS)

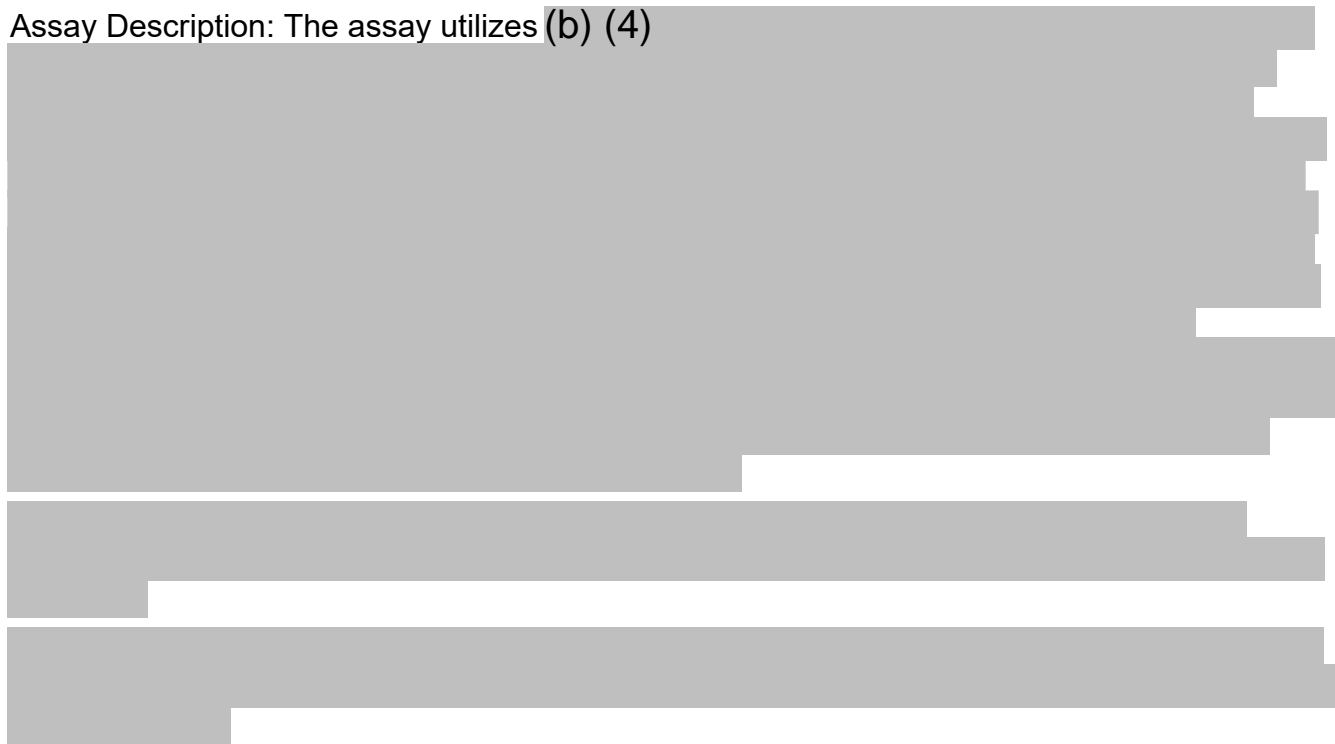
Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

The ELISpot and Neutralizing Antibody (NAb) assays were used to collect exploratory endpoint data and were performed under SOPs optimized for their intended purposes. *Although validation or qualification studies are not required for exploratory assays, none were conducted for these assays.*

HPV 6- and HPV 11-specific T Cell Response by Enzyme-linked Immunospot (ELISpot) Assay

The induction of HPV-specific T-cells in peripheral blood was measured at the end of treatment and 12 weeks following completion of treatment using an interferon (IFN)-gamma (γ) ELISpot assay. The assay was performed at Precigen (Germantown, MD) according to SOP #CLIN-TRI-057.

Assay Description: The assay utilizes (b) (4)



Assay Controls:

- Negative control: (b) (4)
- Positive control: (b) (4)

Reviewer's comment: *This assay was not validated or qualified. While validation or qualification studies are not required for exploratory assays, it should be demonstrated that the assay is reliable and fit for its purpose. In response to IR #5 sent on 3/10/2025 (Amendment #15 dated 3/24/2025), the Applicant explained that the SOPs were optimized and documented to ensure reliable data through several key improvements:*

The Applicant adjusted (b) (4) for (b) (4) and incorporated appropriate controls, including positive controls (b) (4) and negative controls (b) (4) at optimized concentrations for every assay and time point. To minimize potential variation, (b) (4) were integrated into the assay design. Additionally, instrument validation was completed through Installation Qualification (IQ) and Operational Qualification (OQ) procedures.

These optimization measures provide adequate assurance of assay reliability, and the Applicant's explanation is acceptable.

Luciferase-based Adenovirus Neutralization Assay

The development of neutralizing antibodies (Nab) to PRGN-2012 following treatment with PRGN-2012 was evaluated in serum samples from Baseline and up to 52 weeks following completion of treatment using a luciferase-based assay at the Precigen facility in Germantown, MD.

Assay Description: Serum samples diluted in DMEM at 1:16 to (b) (4), incubated with GC46 vectors expressing the firefly luciferase gene for 60 minutes at room temperature, and then transduce 5×10^4 A549 cells in triplicate at a multiplicity of infection of 2,000 PU/cell. Twenty-four hours after infection, the cells were lysed, and luciferase activity was measured using the ONE-Glo Luciferase Assay (Promega, Madison, WI).


Samples that resulted in >90% reduction in luciferase activity compared with that in the virus-only control were defined as positive for neutralizing antibodies. The endpoint titer was defined as the maximum dilution at which the serum sample displayed a 90% reduction in luciferase activity compared with that in the virus only control.

Assay Control and Acceptance Criteria:

(b) (4)

Reviewer's comment: *In response to IR #5 sent on 3/10/2025 (Amendment #15 dated 3/24/2025), the Applicant explained that the SOPs were optimized and documented to ensure reliable data through several key improvements:*

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. It covers approximately four lines of text.

These optimization measures provide adequate assurance of assay reliability, and the Applicant's explanation is acceptable.

Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5:

The assays used to collect exploratory endpoint data were performed under SOPs that were optimized for their intended purposes. While validation or qualification studies are not required for exploratory assays, none were performed for these assays. In Amendment #15 dated 3/24/2025, the Applicant explained SOP optimization measures that provide adequate assurance of assay reliability, and the Applicant's explanation is acceptable.