

CBER CMC BLA Review Memorandum

BLA STN 125743/0

**Immune Globulin Intravenous (Human)-stwk, 10% Liquid
ALYGLO**

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1. **BLA#:** STN 125743/0

2. **APPLICANT NAME AND LICENSE NUMBER**

Green Cross Biopharma Corporation (GCBP)
US License # 2033

3. **PRODUCT NAME/PRODUCT TYPE**

Immune Globulin Intravenous (Human)-stwk, 10% Liquid
ALYGLO

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

ALYGLO (Immune Globulin Intravenous, Human-stwk) is a 10% (100 mg/mL) immune globulin liquid solution for intravenous injection, indicated for the treatment of primary humoral immunodeficiency (PI) in adults.

ALYGLO contains 100 mg/mL protein, of which not less than $\geq 96\%$ is human IgG obtained from human Source Plasma. It is formulated with glycine as a stabilizer targeted at 18.8 mg/mL (15.0 – 22.6 mg/mL) and water for injection as a solvent, with a final pH of 4.8 (pH 4.5 – 5.5). ALYGLO contains ≤ 100 µg/mL of IgA.

ALYGLO is supplied as 5 g in 50 mL, 10 g in 100 mL, and 20 g in 200 mL fill sizes.

5. **MAJOR MILESTONES**

Milestones	Dates
BLA submitted/received	February 25, 2021
Complete Response (CR) Letter issued	February 25, 2022
Pre-License Inspection (PLI)	April 17-28, 2023
PLI 483 Response	May 19, 2023
CR Resubmission received	July 14, 2023
Resubmission Kickoff	July 27, 2023
Mid-cycle Meeting	October 12, 2023
Labeling Meeting #1	October 30, 2023
Labeling Meeting #2	November 16, 2023
Labeling Meeting #3	November 30, 2023
Target Due Date	December 15, 2023
PDUFA Action Date	January 12, 2024

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Lu Deng OTP/OPPT/DPD/PDB2	Adventitious Agents safety evaluation and validation of viral clearance (Sections S.2.3, S.3.2., P.4.5, P.5.5 and A.2)
Nancy Eller OTP/OPPT/DPD/PDB1	3.2.S.2 Drug Substance Manufacture (Sections S.2.2 through S.2.6)
Malgorzata Norton OTP/OPPT/DPD/PDB1	Please see attached "Documents Reviewed"
Olga Simakova OTP/OPPT/DPD/PDB1	3.2.P.5 Control of Drug Product (Sections P.5.1., P.5.2, P.5.4, P.5.5 and P.5.6), Lot Release Protocol
Maria Luisa Virata OTP/OPPT/DPD/PDB2	Parvovirus B19 Nucleic Acid Test change evaluation (Sections 3.2.S.2.3 Control of Materials, 3.2.S.2.4 Controls of Critical Steps and Intermediates, 3.2.R Regional Information)

7. INTER-CENTER CONSULTS REQUESTED

N/A

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
July 14, 2023	STN 125743/0/68 (CR Letter Response)	Reviewed and found acceptable
September 18, 2023	Seq. 0075 STN 125743/0/71 (response to CMC IR #1)	Reviewed and found acceptable
September 18, 2023	Seq. 0076 STN 125743/0/72 (response to CMC IR #2)	Reviewed and found acceptable with some follow up questions in Seq. 0078 STN 125743/0/0/74 (response to CMC IR #4)
September 21, 2023	Seq. 0077 STN 125743/0/73 (response to CMC IR #3)	Reviewed and found acceptable
October 13, 2023	Seq. 0078 STN 125743/0/74 (response to CMC IR #4)	Reviewed and found acceptable

Date Received	Submission	Comments/ Status
November 17, 2023	Seq. 0084 STN 125743/0/80 (response to CMC IR #5)	Following clarifications with GCBP about the correct wording for storage temperatures, the responses were found acceptable.
November 29, 2023	Seq. 0086 STN 125743/0/82 (response to CMC IR #5)	Reviewed and found acceptable
December 4, 2023	Seq. 0087 STN 125743/0/83 (response to Labeling/CMC IR #6)	Reviewed and found acceptable after additional IRs
December 5, 2023	Seq. 0088 STN 125743/0/84 (response to Labeling/CMC IR #7)	Reviewed and found acceptable after additional IRs
December 5, 2023	Seq. 0089 STN 125743/0/85 (response to Labeling/CMC IR #8)	Reviewed and found acceptable after additional IRs
December 6, 2023	Seq. 0090 STN 125743/0/86 (updated stability data)	Reviewed and found acceptable
December 6, 2023	Seq. 0091 STN 125743/0/87 (response to CMC IR #9)	Reviewed and found acceptable

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

Submission Type & No.	Holder	Referenced Item	Comments/Status
IND 016897	GC Biopharma Corp.	IND	No IND review is required. All information is included in the BLA.

Submission Type & No.	Holder	Referenced Item	Comments/Status
BLA 125743/0	GC Biopharma Corp.	BLA	BLA was received on February 25, 2021, and resulted in a CR Letter on February 25, 2022. As the review here focuses on the CR Letter response, no additional review of the original submission is required. Please see the CMC review memo for the original BLA review: "BLA 125743-0_02-18-2022_Memo_Committee Memo_Review.pdf"
DMF (b) (4) (Type III)	(b) (4)	Pharmaceutical Closure (Stopper)-Elastomer Formulations, Coatings and Films	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4) (Type III)	(b) (4)	Glass vials for Parenteral Preparation	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4) (Type III)	(b) (4)	(b) (4)	No DMF review required, information is provided in the BLA

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

ALYGLO is a 10% intravenous immune globulin (IGIV) product which is indicated for the treatment of primary humoral immune deficiency (PI) in adults. It is manufactured from Source Plasma donated by healthy qualified donors using a modified Cohn-Onclay ethanol fractionation method, followed by (b) (4) (b) (4) processes. The manufacturing process has three virus inactivation/removal steps: Fractionation I+III, Solvent/Detergent (S/D) treatment, and Nanofiltration (NF). The formulated Drug Substance (DS) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4). The final Drug Product (DP) contains 100 mg/mL IgG and is stabilized with glycine at a targeted concentration of 18.8 mg/mL at pH 4.8. ALYGLO is manufactured, filled, packaged

and labeled at the Green Cross BioPharma (GCBP) (formerly Green Cross Corporation) facility in Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea. The proposed storage conditions for all three fill sizes (50 mL, 100 mL, and 200 mL) of ALYGLO are 36 months at 2-8°C and 24 months at 8-25°C from the date of manufacture.

Dating periods

Material	Storage/Hold time/Expiration
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Drug Substance	(b) (4)
Drug Product	8 – 25°C for 24 months, or at 2 – 8°C for 36 months

Due to travel restrictions brought about by the COVID-19 pandemic, a Remote Interactive Evaluation (RIE) of the Ochang facility was conducted on October 27-30, November 1-5, November 7-10, and November 16, 2021. The RIE resulted in eleven Observations and eleven Discussion Items. The RIE team identified a significant number of deficiencies indicative of underlying GMP compliance issues with the quality systems, production and process controls, laboratory controls and other CGMP systems. Based on these findings, a pre-license inspection (PLI) was recommended.

A CR Letter was issued on February 25, 2022, due to the necessity of a PLI of the Ochang site. The CR Letter included four (4) additional CMC concerns regarding TSE risk assessment, (b) (4) content measurement, process validation report omissions and the need for a (b) (4) study under worst-case conditions.

The PLI was conducted on April 17-28, 2023, and resulted in a 483 issued with 3 Observations regarding cleaning validations and quality oversight concerns. GCBP submitted written responses via docuBridge to CBER on May 19, 2023 (STN 125743/0.67), which outlined the proposed corrective actions to address the inspectional observations. The responses were found satisfactory with the corrective actions (b) (5), (b) (7)(E) (please see the GCBP 483 Response Rev Memo-STN 125743-0).

GCBP responded to the CR Letter on July 14, 2023. The responses were deemed satisfactory. GCBP also submitted changes to documents since the RIE, such as amended assay validations, amended assay SOPs, updated interim AEX and CEX column (b) (4) lifetime validation reports, and an updated leachables study report. Approval with seven (7) CMC Post Marketing Commitments (PMCs) is recommended.

The PDUFA Action Due Date is January 13, 2024

B. RECOMMENDATION

I. APPROVAL

- a. List of Drug Substance and Drug Product manufacturing facilities to include in the Letter-ready comments for approval or CR letter:

GC Biopharma Corp. Ochang plant:
586, Gwahaksaneop 2-ro, Ochang-eup,
Cheongwon-gu, Cheongju-si,
Chungcheongbuk-do, Republic of Korea
FEI: 3009561235

- b. List of approvable Comparability Protocols: N/A

- c. List of CMC Post-Marketing Commitments (PMCs):

PMC 1

Green Cross BioPharm (GCBP) commits to characterize (b) (4) consecutive lots of ALYGLO at release and at 6, 9, 12, and 24 months at both storage temperatures (2°C to 8°C and 25°C) using a method such as (b) (4) to measure (b) (4). GCBP also commits to include visual inspection and (b) (4) testing at each timepoint. GCBP commits to submitting an interim study report by December 31, 2025, and a Post-Marketing Final Study Report by December 31, 2026.

PMC 2

GCBP commits to submitting the final report of the lifetime validation studies to support the proposed maximum (b) (4) of the (b) (4) as outlined in Protocol GC-PROT-00708, and (b) (4) as outlined in Protocol GC-PROT-00711, as Changes Being Effectuated (CBE) by December 31, 2025.

PMC 3

GCBP commits to submitting the final report of the lifetime validation studies to support the proposed maximum (b) (4) of the (b) (4) as outlined in Protocol GC-PROT-03857 as Changes Being Effectuated (CBE) by December 31, 2025.

PMC 4

GCBP commits to submitting the final report of the lifetime validation studies to support the proposed maximum (b) (4) of the (b) (4) as outlined in Protocol GC-PROT-00714 as Changes Being Effectuated (CBE) by December 31, 2025.

PMC 5

GCBP commits to analyzing the (b) (4) content starting from the (b) (4) manufactured during Pre-License Inspection (PLI) batches until obtaining of at least (b) (4) lots of (b) (4). The final report will be submitted as PMC Submission/Final Study Report by December 31, 2024.

PMC 6

GCBP commits to submit the levels of Parvovirus B19 DNA from the (b) (4) ALYGLO manufacturing pools tested by the (b) (4) test on the (b) (4). Please also include the corresponding pool volumes and turnaround times of B19 NAT results of the (b) (4) manufacturing pools tested. The testing data will be submitted as a PMC Submission/Final Study Report by December 31, 2024.

PMC7

GCBP commits to submit data from leachables study/ies for the (b) (4) used for the storage of (b) (4) and a toxicological risk assessment demonstrating the ability of the process to remove potential impurities to safe levels. GCBP also commits to submitting an interim study report by July 31, 2024, and a Post-Marketing Final Study Report by December 31, 2026.

- d. Consideration for Inspectional Follow-up (e.g., flagging inspectional issues for future surveillance inspections)
 - (b) (5), (b) (7)(E)
- e. Lot release requirements:
Yes, Lot Release Protocol is provided in the DBSQC Review Memo.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Lu Deng Nancy Eller Malgorzata Norton Olga Simakova Maria Luisa Virata	Concur	
Secondary Level Review (e.g., Branch/Lab Chief)	Concur	
Tertiary Level Review (e.g., Division Director)	Concur	

Complete Response (CR) Letter Response Review

1. Based on the manufacturing activities observed, the documents reviewed, and the GCC personnel interviewed during the Remote Interactive Evaluation (RIE), CBER has determined that a PLI of the Ochang site is required to support approval of this BLA.

Reviewer's Response: *The PLI occurred on April 17-28, 2023, and resulted in a 483 issued with 3 Observations. The first two Observations were issued by OCBQ/DMPQ and involved deficiencies with equipment cleaning and maintenance and cleaning validation. The third Observation was issued by the Product Office (OTP/OPPT/DPD).*

GCBP submitted written responses via docuBridge to CBER on May 19, 2023 (STN 125743/0/67), which outlined the proposed corrective actions to address the inspectional observations. The responses were found satisfactory with the (b) (4) (b) (5), (b) (7)(E) (please see the GCBP 483 Response Rev Memo-STN 125743-0).

Other deficiencies (non-CR)

1. Your current risk assessment on Transmissible Spongiform Encephalopathies (TSE) is insufficient. Please do a risk assessment to estimate TSE removal by your manufacturing process. This should include citing of literature and identifying steps in your process which have the potential to remove the TSE agent.

GCBP Response: GCBP conducted a risk assessment to estimate TSE agent removal by ALYGLO's manufacturing process and identified steps in the process which have the potential to remove the TSE agent. The steps are (b) (4)

Reviewer's Response: *The process-related clearance estimates are reasonable, and the steps discussed have been shown capable of removing TSE agents.*

2. (b) (4) are important product intermediates. The (b) (4) content affects the properties of the plasma proteins, including immune globulin G, in the (b) (4) during the (b) (4) process. The (b) (4) content of the abovementioned (b) (4) should be monitored for at least (b) (4) lots to ensure consistent manufacture of product intermediates.

GCBP Response: GCBP submitted the (b) (4) content for (b) (4) and (b) (4) in 3.2.S.2.5.4.4 "Additional Testing Data for (b) (4) (b) (4) Content". GCBP also replied that they will analyze the (b) (4) content starting from the (b) (4) manufactured during Pre-License Inspection (PLI) batches until manufacturing at least (b) (4) lots of (b) (4)

(b) (4)

Additional documents for the (b) (4) assay SOP and validation were requested in an IR sent on September 8, 2023; requested documents were submitted in Seq. 0076 STN 125743/0/72, received September 18, 2023.

- GC-SOP-03602 (b) (4) Content Test (Alyglo)[OCP]
- OB-AV-0118-22 Analytical Method Validation – (b) (4) Content Test

Reviewer's Response: The (b) (4) content results for the lots submitted to date appear satisfactory. A PMC (PMC #5) for a final report after testing (b) (4) lots of (b) (4) will be requested from GCBP.

3. The final process validation report is incomplete. It does not contain an evaluation of the lots manufactured under worst-case conditions, i.e., the engineering lots and lot (b) (4). The report should contain the following lots (b) (4)

as well as the evaluation of critical process parameters, in-process controls, in-process specifications, and impurities. Please update your impurity profile analysis to include lots (b) (4). Following this analysis, please re-evaluate your Drug Product specifications.

GCBP Response: GCBP submitted updated process validation reports for Drug Substance (DS) 3.2.S.2.5.4 and Drug Product (DP) 3.2.P.3.5.4 sections.

Drug Substance

In Section 3.2.S.2.5.4 Continued Process Verification (CPV), GCBP also stated that at the completion of the first phase of the CPV program (summation of (b) (4) lots of DS including three PPQ lots), a statistical evaluation of data will be performed to demonstrate the process is in a state of control. As a result of the statistical

evaluation, the CPPs, IPCs, IPSs, and release specifications that are subject to ongoing evaluation and/or trending shall be selected based on their potential to impact CQAs. Subsequently, the selected parameters and release specification will be monitored for the lifecycle of the product. The data from the CPV lots are presented in Table 3.2.S.2.5-119 to Table 3.2.S.2.5-134.

Drug Product

3.2.P.3.5.4 Continued Process Verification, at the completion of the first phase of the CPV program (summation of (b) (4) lots including (b) (4) PPQ lots), a statistical evaluation of data will be performed to demonstrate the process is in a state of control. As a result of the statistical evaluation, the CPPs, IPCs, IPSs, and release specification results that are subject to ongoing evaluation and/or trending shall be selected based on their potential to impact CQAs. Subsequently, the selected parameters and release specifications will be monitored for the lifecycle of the product. The data from the CPV lots are presented in Table 3.2.P.3.5-92.

Reviewer's Response: *The updated process validation reports are acceptable. The supplemental CPV lot data were within the set specifications.*

4. Your (b) (4) study under the condition of (b) (4) is incomplete. It does not contain the data and evaluation of samples taken at (b) (4) at (b) (4) points during the (b) (4) process of lot (b) (4).

GCBP Response: GCBP explained that a study using the RIE batch (lot (b) (4)) evaluated process robustness and potential impact to product quality under the worst-case conditions of (b) (4). However, samples were not taken at (b) (4) (b) (4) (b) (4) during the (b) (4) process of lot (b) (4).

As discussed in the Type A meeting, GCBP performed an additional (b) (4) study to evaluate the conditions of (b) (4). To fully evaluate the kinetics and robustness of the (b) (4) processes at the critical (b) (4) steps, samples were not only taken at the (b) (4).

- TS^{(b) (4)}-22-001-R (b) (4) Study under the Conditions of (b) (4)

Reviewer's Response: *The (b) (4) study report was acceptable and confirmed the (b) (4).*

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

(b) (4)

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(b) (4)

(b) (4)

(b) (4)

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

The information in this section is deemed acceptable.

3.2.P DRUG PRODUCT²

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

ALYGLO DP is a 10% (100 mg/ml) Immune globulin intravenous (IGIV) formulated to the physiological (b) (4) with 18.8 mg/mL glycine as a stabilizer and Water for Injection (WFI) at pH 4.8. ALYGLO is supplied in a liquid dosage and administered intravenously. ALYGLO DP is filled into a 50 mL, 100 mL, and 200 mL Type (b) (4) glass

vials. Each filled vial is stoppered with a rubber stopper and capped using a flip-off aluminum cap.

3.2.P.1.1 Overfill

An overfill is applied to each vial of ALYGLO DP for adequate withdrawal and administration of the labeled.

The fill volume is measured as a part of the release testing (volume in a container) for ALYGLO DP with the following acceptance criteria:

50 mL fill size: 50 (b) (4) mL

100 mL fill size: 100 (b) (4) mL

200 mL fill size: 200 (b) (4) mL

3.2.P.2 Pharmaceutical Development

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

ALYGLO DS contains glycine as an excipient/ (b) (4) at a concentration of 250 mM or 18.8 mg/mL. (b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

ALYGLO formulation was studied for glycine, pH and (b) (4) ranges using (b) (4) as test markers. The pH was found to be optimal at 4.8 with a proven acceptable range (PAR) of pH (b) (4) – 5.5 and normal operating range (NOR) of (b) (4). The glycine concentration as found optimal at 18.8 g/L with a PAR of (b) (4) and NOR of (b) (4) (b) (4)

The clinical and PPQ lots have the same formulation.

3.2.P.2.2.3 Physicochemical and Biological Properties

ALYGLO DP has the (b) (4)

3.2.P.2.3 Manufacturing Process Development

The process development of ALYGLO was reviewed in the original submission. For more details, please see the original final CMC review memo “BLA 125743-0_02-18-2022_Memo_Committee Memo_Review.pdf”

Table 19. ALYGLO DP Process History (taken from the submission)

Process	Lot No.	Date of Manufacture	Use of Material
Process 1	(b) (4)		Non-clinical studies (pharmacokinetic, safety and toxicity)
	(b) (4)		
	(b) (4)		
	394C16004	(b) (4)	Clinical lots for Canadian clinical trial
	394C16005	(b) (4)	
Process 2	394C16006	(b) (4)	
	394C16007	(b) (4)	
	394C16008	(b) (4)	
	394C16009	(b) (4)	
	(b) (4)	(b) (4)	Development of additional fill volume, 50 mL and 100 mL
	(b) (4)	(b) (4)	
	(b) (4)	(b) (4)	
	(b) (4)	(b) (4)	
	(b) (4)	(b) (4)	
	(b) (4)	(b) (4)	
	394C17001	(b) (4)	Clinical lots for U.S. clinical trial
	394C17003	(b) (4)	
	394C17004	(b) (4)	
	394C17005	(b) (4)	
	394C18001	(b) (4)	
	394C18003	(b) (4)	
Process 3	(b) (4)		Engineering lots to assess the optimization of the manufacturing process before manufacturing of PPQ lots
	(b) (4)		
	(b) (4)		
	(b) (4)		Process Performance Qualification (PPQ) lots for validation of the process
	(b) (4)		
	(b) (4)		

Process	Lot No.	Date of Manufacture	Use of Material
	(b) (4)		

3.2.P.2.4 Container Closure System

The primary packaging components of ALYGLO DP consists of a Type ^(b)₍₄₎ borosilicate glass vial and Type ^(b)₍₄₎ chlorobutyl rubber (latex-free) stopper. Type ^(b)₍₄₎ glass vials which are selected in accordance with (b) (4) (b) (4) are suitable for parenteral uses and have a high hydrolytic and thermal resistance due to its chemical composition.

For elastomeric closure, Type ^(b)₍₄₎ rubber stoppers were selected in accordance with (b) (4) (b) (4) since they are suitable for use with aqueous preparations, have lower levels of extractables compared to other rubbers, and have excellent resistance to permeation by water and oxygen.

Extractables and leachables (E&L) studies were performed by a contract testing laboratory, (b) (4). Up to 6 months data were submitted in the original submission and reviewed in the Pre-Clinical Pharm Tox Review memo "BLA 125743-0_10-19-2021_Memo_Committee Memo_Pharm-.pdf" with a conclusion that the organic compounds detected at 6 months do not represent a toxicologic concern.

Updated leachables data up to 24 months was submitted in report Doc. No. 19-VR-818.

Table 20. Acceptable Limits of Extractable/Leachable Compounds (taken from the submission)

(b) (4)

(b) (4)

The levels of leachables detected at 24 months are below the maximum allowable concentrations (MAC) based on permitted daily exposure (PDE). These levels therefore do not represent a toxicological concern.

One notable deviation in the study was NCR-22049/IN-220040:

At the time of T24m (b) (4), the 25 °C / (b) (4) RH vial container closures were found (b) (4) oriented, going against instructions for vial (b) (4) stated in the protocol. The stoppers were, however, still in contact with the drug product while (b) (4) due to the large fill volume and shape of the vial. Confident that the stopper and drug product were in contact for the entire duration of storage, it was determined there is no impact to the integrity of the samples.

We had samples of the product in the laboratory and confirmed that when the vials are (b) (4), the product is still in full contact with the stopper.

3.2.P.2.5 Microbiological Attributes

Table 21. In-Process Microbiological Tests Performed during the Manufacturing Process for ALYGLO (taken from the submission)

(b) (4)

(b) (4)

3.2.P.2.6 Comparability

DP comparability was assessed in the original BLA review. Please see the CMC Final memo “BLA 125743-0_02-18-2022_Memo_Committee Memo_Review.pdf”

Overall, the clinical lots and the PPQ lots were comparable, including the increase in (b) (4) over time when stored at 25 (b) (4). It should be noted that the impurity profile of the PPQ lots improved following the manufacturing changes, and that the level of (b) (4) significantly decreased in the PPQ lots as well. During storage, the ER and PPQ lots were typically (b) (4) under both storage conditions, so the (b) (4) (b) (4) It should be noted that the anti-HBsAg titers (b) (4) more rapidly at 25 (b) (4) for the PPQ and CPV lots than the clinical lots. However, the anti-HBs levels remained within specification.

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

The information in this section is acceptable.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Please see section 3.2.S.1.

3.2.P.3.2 Batch Formula

The batch formula and the amounts per batch for manufacturing ALYGLO Drug Product (DP) are shown in the table below. The ALYGLO DP fill volumes are 50 mL, 100 mL,

and 200 mL. (b) (4) of ALYGLO IGIV DS (batch size of (b) (4)) is filled into either 50 mL, 100 mL, or 200 mL fill sizes.

No overage or overfill is applied in the calculation for any of the components.

Table 22. Batch Formula for ALYGLO DP (Batch Size: (b) (4)

Component	Function	Amount of Component (mg per mL)	Targeted Amount per Batch (b) (4)	Grade
Human Immunoglobulin G	Active Pharmaceutical Ingredient	100 mg	(b) (4)	Manufactured according to GMP
Glycine	Stabilizer	18.8 mg	(b) (4)	(b) (4) "Glycine"
Water for Injection	Solvent	q.s. ¹	q.s.	(b) (4) "Water for Injection", (b) (4) "Water for Injections"

¹ q.s.: quantum sufficit

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

The information in this section is acceptable.

3.2.P.3.3 Description of Manufacturing Process

The DP manufacturing process includes three steps: Filling, Visual Inspection, and Labeling & Packaging. The Filling step includes Receiving of DS, (b) (4) and four Aseptic Filling sub-steps which are Filtration, Filling and Stoppering, and Capping. Subsequently, Visual Inspection and Labeling & Packaging are performed following aseptic filling in sequential order. The finished DP is stored at 8 – 25°C for 24 months, or 2 – 8°C for 36 months. The ALYGLO DP process does not allow for any reprocessing.

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

The information in this section is acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Table 23. In-Process Manufacturing Control – Aseptic Filling (taken from the

(b) (4)

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

(b) (4)

Table 24. Analytical Test Methods for In-Process Testing of ALYGLO IGIV Drug Product (taken from the submission)

(b) (4)

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

The information in this section is acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

Table 25. Aseptic Filling Critical Process Parameters (taken from the submission)

(b) (4)

(b) (4)

The following information was updated in the CR Letter Response and is deemed acceptable:

- Continued Process Verification (CPV) for ALYGLO Drug Product (DP) was performed, and the results were provided. All CPV lots met the acceptance criteria.
- Proven acceptable range for adjusted (b) (4) was updated from (b) (4) based on pre-qualification report.
- (b) (4) was changed from (b) (4)
- 3.2.P.3.5 Doc. No. GC-REP-00417: Aseptic Process Simulation Validation - DMPQ
- 3.2.P.3.5 Doc. No. GC-REP-13568: Aseptic Process Simulation Validation Report – DMPQ

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

The information in this section is acceptable.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

The excipient Glycine (DMF No. (b) (4)) for ALYGLO is manufactured by (b) (4). The manufacturers' specifications comply with the (b) (4). The incoming test items and acceptance criteria are established based on the (b) (4) for glycine.

Table 26. Incoming Specification of Glycine (taken from the submission)

(b) (4)

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

The method is based on the (b) (4) for glycine.

3.2.P.4.4 Justification of Specifications

Specifications are established based on the (b) (4) for glycine.

3.2.P.4.5 Excipients of Human or Animal Origin

N/A

3.2.P.4.6 Novel Excipient

N/A

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

The information in this section is acceptable.

3.2.P.5 Control of Drug Product

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

Table 27. ALYGLO Drug Product Lot Release Specification (taken from the submission)

Category	Test	Method	Acceptance Criteria
Product Characteristics	Appearance	Visual	Colorless or pale yellow, clear or slightly opalescent liquid (b) (4)
	pH (b) (4)	(b) (4)	4.5 – 5.5
	(b) (4)	(b) (4)	(b) (4)
	Total Protein	(b) (4)	(b) (4)
	Heat Stability	Visual	No gelation
	Volume in Container	Measurement of the (b) (4)	50 mL: 50 (b) (4) 100 mL: 100 (b) (4) 200 mL: 200 (b) (4)
Identity	Identification: Immunoglobulin G	(b) (4)	Main preparation component corresponds to the IgG component of normal human serum
	Identification: Origin	(b) (4)	Only protein of human origin
Potency	Anti-Hepatitis (b) (4) (b) (4) Potency	(b) (4)	(b) (4)
	Diphtheria Potency	(b) (4)	(b) (4) units of diphtheria antitoxin/mL

Category	Test	Method	Acceptance Criteria
	Measles Potency	Neutralizing Antibody Assay	(b) (4) x CBER Ref 176
	Polio Potency ¹	Neutralizing Antibody Assay	(b) (4) x CBER Ref176
Excipient	Glycine	(b) (4)	15.0 – 22.6 mg/mL
Purity and Impurity	Protein Composition: IgG	(b) (4)	≥ 96% of total protein
			(b) (4)
Purity and Impurity			(b) (4)
		(b) (4)	
	Particulate Matter: (b) (4)		(b) (4)

Category	Test	Method	Acceptance Criteria
			(b) (4)
	Particulate Matter: Visible	Visual	No visible particles
	Bacterial Endotoxins	(b) (4)	(b) (4)
Safety	Sterility	(b) (4)	No growth

* (b) (4) lowered from (b) (4) according to the Agency's recommendation due to lot release results of PPQ and CPV lots.

(b) (4)
¹ For poliomyelitis Type (b) (4)

Table 28. Identity Test for ALYGLO Drug Product after Packaging and Labeling (taken from the submission)

Test	Method	Acceptance Criteria
Identification: Immunoglobulin G	(b) (4)	Main preparation component corresponds to the IgG component of normal human serum
Total Protein	(b) (4)	(b) (4)
Identification: Color of Flip-Off Cap	Visual	Yellow

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

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

Validation of analytical procedures was reviewed in the original BLA submission. Please see the CMC final memo "BLA 125743-0_02-18-2022_Memo_Committee Memo_Review.pdf" and DBSQC memo. GCBP submitted new English version SOPs in the CR response and the SOP numbers changed when migrating between documentation systems from GMP-EDMS to (b) (4) system. GCBP stated that the methods did not change.

Additionally, the referencing SOP for the identification test (Color of Flip-Off Cap) changed to GC-SOP-03629 after creating the SOP as part of RIE CAPA.

Table 29. List of Analytical Procedures for ALYGLO DP (taken from the submission)

Category	Test	SOP	Reference of Test Method, Method Principle
Product Characteristics	Appearance	GC-SOP-03628	(b) (4) Visual
	pH (b) (4)	GC-SOP-02968	(b) (4) (b) (4) (b) (4)
	(b) (4)	GC-SOP-03114	(b) (4)
	Total Protein	GC-SOP-03299	In-house, (b) (4)
	Heat Stability	GC-SOP-03115	21 CFR 640.101 (a) "Heat Stability Test", Visual
	Volume in Container	GC-SOP-02921	(b) (4) (b) (4) Measurement of the (b) (4)
Identity	Identification: Immunoglobulin G	GC-SOP-03120	(b) (4) (b) (4) (b) (4)
	Identification: Origin	GC-SOP-02978	In-house, (b) (4)
Potency	Anti-Hepatitis (b) (4) Potency	GC-SOP-03597	In-house, (b) (4)
	Diphtheria Potency	GC-SOP-03067	In-house, (b) (4)
	Measles Potency	GC-SOP-03604	(b) (4) Neutralizing Antibody Assay
	Polio Potency	GC-SOP-03003	In-house, Neutralizing Antibody Assay
Excipient	Glycine	GC-SOP-03121	In-house, (b) (4)
Purity and Impurity	Protein Composition: IgG	GC-SOP-03606	In-house, (b) (4)
	(b) (4)	GC-SOP-03595	(b) (4)
	(b) (4)	GC-SOP-03605	(b) (4)

Category	Test	SOP	Reference of Test Method, Method Principle
	(b) (4)	GC-SOP-03010	(b) (4)
	(b) (4)	GC-SOP-03075	(b) (4)
Purity and Impurity	(b) (4)	GC-SOP-03176	(b) (4)
	(b) (4)	GC-SOP-03250	(b) (4)
	(b) (4)	GC-SOP-03070	(b) (4)
	(b) (4)	GC-SOP-03313	(b) (4)
	(b) (4)	GC-SOP-03011	(b) (4)
	(b) (4)	GC-SOP-02931	(b) (4)
	(b) (4)	GC-SOP-02965	(b) (4)
	(b) (4)	GC-SOP-03272	(b) (4)
	Particulate Matter: Visible	GC-SOP-03598	(b) (4)
Safety	Bacterial Endotoxins	GC-SOP-02934	(b) (4) (b) (4)
	Sterility	GC-SOP-03352	(b) (4) (b) (4) (b) (4)
	CCIT	GC-SOP-02975	(b) (4)

Table 30. List of Analytical Procedures for ALYGLO DP after Packaging and Labeling Process (taken from the submission)

Test	SOP	Reference of Test Method, Principle
Identification: Immunoglobulin G	GC-SOP-03120	(b) (4) (b) (4)
Total Protein	GC-SOP-03299	In-house, (b) (4)
Identification: Color of Flip-Off Cap	GC-SOP-03629	In-house, Visual

The following supplemental reports were submitted in the CR Letter response:

- GC-REP-13500: Analytical Method Validation Report – (b) (4) Anti-Hbs test due to change in reagent catalog number.
 - The method validation was acceptable.
- GC-REP-13591: Analytical Method Validation Report - (b) (4)
(b) (4)
 - DBSQC reviewed this document.
- GC-REP-13796: Analytical Method Validation Report – Identification: Immunoglobulin (b) (4)
 - DBSQC reviewed this document.
- OBV-AV-0042-20: AMV Report (Sterility Test) [OCP]
 - DBSQC reviewed this document.

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

The information in this section is acceptable.

3.2.P.5.4 Batch Analyses

The original clinical, engineering and PPQ batch analysis data were reviewed in the original submission. Please see the CMC final memo “BLA 125743-0_02-18-2022_Memo_Committee Memo_Review.pdf”

GCBP amended the report with the CPV lot results. All results met the specifications.

3.2.P.5.5 Characterization of Impurities

The impurities in DP were reviewed in the original submission. Please see the CMC final memo “BLA 125743-0_02-18-2022_Memo_Committee Memo_Review.pdf”.

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

The information in this section is acceptable.

3.2.P.6 Reference Standards or Materials

Table 31. Summary of Reference Standards for ALYGLO Drug Product (taken from the submission)

Test	Reference Standard	
	Standard Name	Supplier
Release Testing		
Appearance	(b) (4)	

Test	Reference Standard	
	Standard Name	Supplier
Release Testing		
	(b) (4)	In-house
(b) (4) (Anti-HBs) Potency	(b) (4)	(b) (4)
Diphtheria Potency	CBER Standard Diphtheria Antitoxin	U.S. Food and Drug Administration (FDA)
Measles Potency	Immune Serum Globulin for Polio and Measles, CBER Reference Lot 176	FDA
	Immune Serum Globulin for Polio and Measles, CBER Reference Lot 177 ¹	FDA
Polio Potency	Immune Serum Globulin for Polio and Measles, CBER Reference Lot 176	FDA
	Immune Serum Globulin for Polio and Measles, CBER Reference Lot 177 ¹	FDA
Glycine	(b) (4)	(b) (4)
Protein Composition: IgG	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Test	Reference Standard	
	Standard Name	Supplier
Release Testing		
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Bacterial Endotoxins	(b) (4)	(b) (4)

¹ Immune Serum Globulin for polio and measles, CBER Reference Lot 177: Through the side-by-side comparison tests between CBER Reference standard Lot 176 and 177, GCBP established the correlation between them. GCBP can use both reference standards in these test methods.

3.2.P.7 Container Closure System

Table 32. Description and Quality Information of Primary Packaging Components (taken from the submission)

Primary Packaging Component	Manufacturer	Product Description/ Classification	DMF Reference	Quality Standard	Representative CoA
Glass Vial 50 mL 100 mL 200 mL	(b) (4)	Colorless borosilicate glass vial with 32 mm neck finish/ Type (b) (4)	DMF (b) (4)	(b) (4)	50 mL vial CoA 100 mL vial CoA 200 mL vial CoA
Rubber Stopper	(b) (4)	FEP film-coated rubber stopper (Chlorobutyl (b) (4)) 32 mm/ Type (b) (4)	DMF (b) (4)	(b) (4)	Rubber Stopper CoA
Flip-Off aluminum cap	(b) (4)	Tamper evident plastic cap sustained with aluminum	Not applicable	Not compendial	Aluminum seal CoA

Primary Packaging Component	Manufacturer	Product Description/ Classification	DMF Reference	Quality Standard	Representative CoA
	(b) (4)				
(b) (4)					

Please see the review of the 24-month leachables data in Section 3.2.P.2.4 Container Closure System.

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

The information in this section was acceptable.

3.2.P.8 Stability

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

Table 33. Summary of Stability Studies for ALYGLO DP up to the PPQ lots (taken from the submission)

Lot Information	Lot Number	Manufacture Date	Fill Volume	Stability Study Status	
				Storage Condition	Status
Clinical Lots	(b) (4)	(b) (4)	200 mL	25 ± (b) (4) RH for 24 months	Completed
	(b) (4)	(b) (4)		5 ± 3°C for 24 months, 25 (b) (4) RH for 24 months	Completed
	(b) (4)	(b) (4)			
	(b) (4)	(b) (4)			
Engineering Lots	(b) (4)		50 mL	5 ± 3°C for 36 months 25 (b) (4) (b) (4) months	Completed
	(b) (4)		200 mL	(b) (4) (b) (4) months	
	(b) (4)		100 mL	(b) (4)	Completed
PPQ Lots	(b) (4)		50 mL	5 ± 3°C for 36 months 25 (b) (4) (b) (4) months (b) (4) (b) (4) months	Completed

Lot Information	Lot Number	Manufacture Date	Fill Volume	Stability Study Status	
				Storage Condition	Status
	(b) (4)		200 mL	25 5 ± 3°C for 36 months (b) (4) (b) (4) months (b) (4) (b) (4) months	Completed

The following changes were submitted in the CR Letter response:

- Proposed shelf-life of ALYGLO DP was changed to 24 months at 2 - 25°C and 36 months at 5 ± 3°C based on the long-term stability results and temperature-shift results.
- Results from long-term stability for ER lots (5 ± 3°C, 25 (b) (4) RH) (b) (4) (b) (4)
- Thirty-six-months results from long-term stability (25 (b) (4) RH and 5 ± 3°C) for PPQ lots were updated.
- A process robustness study was performed under the worst-case conditions of the (b) (4) for each (b) (4) step of the ALYGLO (b) (4) manufacturing process for a commercial lot (b) (4) and its 12-months results from long-term stability were updated.
- Six-months results from long-term stability (25 (b) (4) RH and 5 ± 3°C) for a commercial scale lot was updated. The DP was manufactured using (b) (4) (b) (4) (b) (4).
- Results from long-term stability (25 (b) (4) RH and 5 ± 3°C) for PLI lots were updated. This was requested by the Agency at the meeting.

In addition to the PPQ lots included with the initial submission, GGBP has manufactured additional lots which included lots they refer to as Continued Process Validation or CPV lots and the (b) (4) PLI lots which are outlined in the Stability Tables below.

Stability Table 1 – CPV lot for Process Robustness

(b) (4)

Stability Table 2 – CPV Lot for Intermediate Storage Time

(b) (4)

Stability Table 3 – PLI Lots

(b) (4)

The stability study for the initial PPQ lots have been completed. Storage at $5 \pm 3^\circ\text{C}$ supports a shelf-life of 3 years, but a 2-year expiration date is supported for storage at 25°C . An (b) (4) is seen when the product is stored at 25°C . The (b) (4) can be seen as soon as 3 months. This same pattern is seen with the 3-month stability timepoint for the PLI lots. It should be noted that an (b) (4) is associated with a (b) (4) in the results for the anti-Hepatitis (b) (4) assay which stays well within the specification.

The stability data also supported lowering the specification for (b) (4) in the final product to (b) (4). All other release specifications were acceptable, including endotoxin (b) (4). The following calculations were done to determine the acceptable specification for endotoxin (from the (b) (4) (b) (4))

- (b) (4)

Samples of the RIE, CPV, and PLI lots were submitted for visual inspection and (b) (4). The submitted CPV and PLI lots arrived with excessive levels of (b) (4) than what is seen in other IGIVs received for testing. The RIE lots were manufactured 2 years ago and visually were more (b) (4) than the other lots, but they had significantly (b) (4) than the other lots. The (b) (4) data was inconsistent with typical results, possibly due to the (b) (4).

The same lots were also submitted for HPLC testing (by Ms. Hailing Yan of OTP/OPPT/DPD for research purposes). The tested lots have met the specifications set by us for IGIV products (i.e., $\geq 90\%$ Monomer + Dimers), except for lot 393C21001 with the code JM8CR (89.7%). However, a Fab/Fc or F(ab')₂ size peak has been detected in both lots 394C21001 (JM7CR) and 393C21001 (JM8CR) (6.1% and 6.6% respectively), with increased Polymers + Aggregates, Dimers, Fab and decreased Monomer in these two lots (JM7CR and JM8CR), comparing with the other 4 lots submitted for testing. These lots were compared with the in-house human IG standards (b) (4). The two lots showing the elevated fragmentation were the lots manufactured in 2021 during the RIE.

Reviewer's Comments: It is speculated that the (b) (4) is due in part to the shipping of the vials (b) (4) which increases the (b) (4). Shipping may increase the (b) (4) to the point where the presence of the (b) (4) is now visible. Since the RIE lots did not appear to have the same levels of (b) (4), it is possible that the (b) (4) are long-lasting but eventually dissipate. To understand the presence of the (b) (4) and the potential effects, such as an (b) (4) (b) (4), on the final product, a post-marketing commitment was requested. This PMC has requested GCBP to use a method, such as (b) (4) below the (b) (4).

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

An annual stability study at the long-term conditions will be conducted using a routine production lot to monitor the quality of the ALYGLO DP and confirm the product stability at the labeled storage conditions.

As per internal procedure "Stability Test Management", the stability samples for ALYGLO DP will be stored in the (b) (4) position at $5 \pm 3^\circ\text{C}$ for 36 months from the date of manufacture, and at 25 (b) (4) RH for 24 months from the date of manufacture.

GC Biopharma Corp. (GCBP) commits to providing all available annual stability data for ALYGLO DP in the annual reports.

The section was updated according to the changes listed in 3.2.P.8.1.

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

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Please see DMPQ Review memo.

Overall Reviewer's Assessment of Section 3.2.A.1:

Please see DMPQ Review memo.


3.2.A.2 Adventitious Agents Safety Evaluation

- Doc. No. GC5107B-QMR-023: GC5107 TSE Risk Assessment for Alyglo Manufacturing Process
- No. K14-g10-21: Evaluation of the removal of Bovine Viral Diarrhea Virus and Porcine Parvovirus by Virus Filtration (b) (4)

Viral Clearance Studies

U.S. Source Plasma that meets all applicable screening and testing requirements per 21 CFR 640 Subpart G will be used as the starting material for ALYGLO. Three manufacturing steps of ALYGLO contribute to remove or inactivate viruses; they are Fractionation I+III, Solvent/Detergent (S/D) treatment, and Nanofiltration. Fractionation I+III and Nanofiltration are orthogonal steps to remove viruses. The S/D treatment step is to inactivate viruses.

In this resubmission, GCBP provided a new viral clearance study K4/G10/21. The purpose of this study was to evaluate the effectiveness of the Nanofiltration step for Bovine Viral Diarrhea Virus (BVDV) and Porcine Parvovirus (PPV) removal due to a change in (b) (4) at the Nanofiltration step. Upon IR, GCBP stated that the changes made to the Nanofiltration process includes the (b) (4)



(b) (4)

. The proposed virus reduction claim is shown in Table 1.

Table 34. Overall virus clearance log reduction factors

Manufacturing Step	Virus Reduction (log ₁₀)				
	Enveloped Viruses			Non-enveloped Viruses	
	HIV-1	PRV	BVDV	EMCV	PPV
Fractionation I+III	4.27	3.53	3.00	2.95	4.28
S/D treatment	≥ 5.51	≥ 4.43	≥ 4.63	N/T	N/T
Nanofiltration	≥ 4.77	≥ 4.45	≥ 5.67	≥ 5.20	3.65
Total Virus Reduction Factor (log ₁₀)	≥ 14.55	≥ 12.41	≥ 13.30	≥ 8.15	7.93

The specification for the total (b) (4) (b) (4) at Step (b) (4) Nanofiltration is set as (b) (4) (b) (4). However, the actual (b) (4) (b) (4) used in PPQ lots, engineering lots and the lots manufactured during the Remote Interactive Evaluation (RIE) are significantly (b) (4) than (b) (4) (b) (4). Upon IR, GCBP proposed a new specification of (b) (4) (b) (4) for the total (b) (4) (b) (4) by taking the actual manufacturing data into consideration: total (b) (4) (b) (4) data were collected from (b) (4) lots of (b) (4) (b) (4); the new specification was established based on the mean and the (b) (4) standard deviation (SD).

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

The information in this section is acceptable.

3.2.R Regional Information (USA)

□ Executed Batch Records

GCBP provided master and executed batch records in the original BLA submission. Several batch records were also reviewed during the PLI.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

GCBP states that ALYGLO is composed of naturally occurring substance and therefore the manufacture of this product will not significantly alter the concentration or distribution of the substance, its metabolites or degradation product in the environment.

GCBP is not aware of any extraordinary circumstances that exist per 21 CFR 25 .21 that would require the preparation of an environmental assessment or environmental impact statement.

The claim of categorical exclusion is deemed acceptable.

B. Labeling Review

Full Prescribing Information (PI):

The following comments were sent to GCBP regarding the PI.

- 1) To improve clarity, please add the final statement below the room temperature storage. For example,
Refrigeration: 2°C to 8°C [36° to 46°F] for up to 36 months.
Room Temperature: 8°C to 25°C [46°F to 77°F] for up to 24 months.
Once moved to room temperature storage, do not return to refrigerator.
- 2) Please revise the date format to the US version of MM/DD/YYYY.

Carton and Container Label:

The following comments and clarification were sent to GCBP.

1. Please revise the vial label and carton to include the updated room temperature range of 8°C to 25°C.
2. The wording $\leq 25^{\circ}\text{C}$ implies that the material can be stored at any temperature below this which includes refrigeration, a separate storage condition with a different shelf-life. To improve clarity, please add the final statement below the room temperature storage. For example,
Refrigeration: 2°C to 8°C [36° to 46°F] for up to 36 months.
Room Temperature: 8°C to 25°C [46°F to 77°F] for up to 24 months.
Once moved to room temperature storage, do not return to refrigerator.
3. Please revise the date format to the US version of MM/DD/YYYY on the vial label and carton.
4. To minimize storage and expiration date confusion, please include expiration dates for both storage conditions Refrigeration (2°C to 8°C [36°F to 46°F] for up to 36 months) and Room Temperature (8°C to 25°C [46°F to 77°F] for up to 24 months) on the vial label and carton.

GCBP modified the vial/container labels and PI with our comments.

Modules 4 and 5

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

The assays used for assessment of clinical and animal study endpoints were reviewed during the IND process.

Information Requests

Seq. 0075 125743/0/71 Sent August 18, 2023, Received September 18, 2023 - CMC

- Questions on the availability of next stability data timepoint, difference in (b) (4) of CPV lots, deviations, and sample request.

Seq. 0076 125743/0/72 Sent September 8, 2023, Received September 18, 2023 - CMC

- Questions regarding viral clearance study, (b) (4) content SOP and assay validation, and impurity calculations.

- Documents

GC-SOP-03602 (b) (4) Content Test (Alyglo)[OCP]

OB-AV-0118-22 Analytical Method Validation – (b) (4) Content Test

GC-REP-13500 – Analytical Method Validation (OCP,21, 0153, 02) Anti HBs Test – change in reagent catalog number.

OB-AV-0021-21 Analytical Method Validation (OCP,21,0021,02) In-process material/ (b) (4)

GC-REP-20073 Analytical Method Validation – Anti-HCV test in (b) (4) – change in reagent catalog number.

Seq. 0077 125743/0/73 Sent September 1, 2023, Received September 21, 2023 - CMC

- Questions about Appearance test validation
- GC-REP-20094 Analytical Method Validation Report (OCP,23,01625) – Appearance test

Seq. 0078 125743/0/74 Sent October 4, 2023, Received October 13, 2023 - CMC

- Viral clearance comments

Seq. 0084 125743/0/80 Sent November 17, 2023, Received November 17, 2023 - CMC

- Storage temperature label wording, (b) (4) specification lowering, amended lot release protocol.

Seq. 0086 125743/0/82 Sent September 12, 2023, Received November 29, 2023 – CMC

- Updated stability data

Seq. 0087 125743/0/83 Sent November 28-29, 2023, Received December 4, 2023

- Labeling

Seq. 0088 125743/0/84 Sent November 30, 2023, Received December 4, 2023

- Labeling

Seq. 0089 125743/0/85 Sent November 30, 2023, Received December 4, 2023

- Labeling

Seq. 0088 125743/0/84 Sent November 30, 2023, Received December 4, 2023

- Labeling

Seq. 0089 125743/0/85 Sent November 30, 2023, Received December 4, 2023

- Labeling

Seq. 0090 STN 125743/0/86 Received December 6, 2023

- updated stability data.

Seq. 0091 STN 125743/0/87 Received December 6, 2023

- To update documents with correct specifications and to trend impurities
- GCBP made the amendments and agreed to trend impurities.