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Summary Basis for Regulatory Action

Date:	December 15, 2023
From:	Michael Kennedy, Review Committee Chair, Office of Plasma Protein Therapeutics
BLA STN:	125743/0
Applicant:	GC Biopharma Corp.
Submission Receipt Date:	July 14, 2023
PDUFA Action Due Date:	January 13, 2024
Proper Name:	immune globulin intravenous, human-stwk
Proprietary Name:	ALYGLO
Indication:	for the treatment of primary humoral immunodeficiency (PI) in adults

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Therapeutic Products

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Remote Interactive Evaluation (OCBQ/DMPQ and Product Office) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Michael Kennedy, Nancy Eller, Malgorzata Norton, Olga Simakova, Lu Deng, Maria Luisa Virata - CBER/OTP/OPPT/DPPT Lily Koo – CBER/OD Xiuju Lu, CBER/OCBQ/DMPQ 125743/0/.68- Hyesuk Kong, Jing Lin, Parmesh Dutt, George Kastanis, Emnet Yitbarek, Tao Pan, Jie He; 125743/0-Varsha Garnepudi
Clinical • Clinical (Product Office) • Post-marketing safety Pharmacovigilance review (OBPV/DPV) • BIMO	Elizabeth Sharpe, MD, CBER/OTP/OCE Alisha Thomas, MD, MPH, CBER/OBPV/DPV Adamma Mba-Jonas, MD, MPH, CBER/OBPV/DPV Triet Tran, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB)	BLA 125743/0: Boris Zaslavsky, PhD; BLA 125743/0.68: Hairong Shi, PhD, CBER/OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Evi Struble PhD, CBER/OPPT/DPD
Clinical Pharmacology	Million Tegenge, PhD, CBER/OTP/OCE
Labeling • Promotional (OCBQ/APLB)	Sonny Saini, PharmD, MBA, CBER/OCBQ/DCM/APLB
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	N/A
Advisory Committee Summary	N/A

Table of Contents

1. Introduction

The Original Biologics License Application (BLA) submission from GC Biopharma Corp.(formerly Green Cross Corporation (GCC) for its 10% solution of ALYGLO (immune globulin intravenous, human-stwk) product for treatment of patients with primary humoral immunodeficiency (PI) was submitted to STN125743/0 on 2/25/2021. Due to travel restrictions brought about by the COVID-19 pandemic, a Remote Interactive Evaluation (RIE) of the Ochang facility was conducted in October-November 2021. 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. Due to the necessity of a PLI and additional CMC concerns, FDA issued a complete response (CR) letter on February 25, 2022.

In the original submission, the Applicant submitted safety, efficacy and pharmacokinetic (PK) data from a 12-month prospective, open-label, single-arm, multi-center study to support the BLA. The primary efficacy analysis threshold was met as the annualized acute serious bacterial infection (SBI) rate was less than one acute SBI per subject per year. As part of the initial submission review, it was noted that PK data to support (b) (4) (b) (4) was inadequate. In response to the CR, the Applicant did not provide any new clinical data (b) (4) . The safety data is consistent with this class of products. The single adequate and well controlled study with supportive data supports approval of ALYGLO for adults with PI.

The Applicant resolved all CMC issues identified in the CR letter.

ALYGLO is manufactured by a modified Cohn-Oncley ethanol fractionation process from U.S. Source Plasma collected from FDA approved plasma collection centers. The applicant provided process validation studies, analytic method validations, comparability studies, and process control strategies.

2. Background

Primary Humoral Immunodeficiency (PI)

Primary immunodeficiencies are a large heterogenous group of disorders resulting from inborn errors of immunity that are broadly classified based on the component of the immune system that is primarily disrupted. Primary humoral immunodeficiency (PI) is a form of primary immunodeficiencies that is characterized by impaired B-cell immunity, and thus, impaired ability to produce specific antibodies in response to pathogenic microorganisms. PI diseases include, but are not limited to, X-linked agammaglobulinemia, Common Variable Immunodeficiency (CVID), Wiskott-Aldrich Syndrome (WAS), Severe Combined Immunodeficiency (SCID), and congenital agammaglobulinemia. Patients with PI experience recurrent and severe bacterial infections.

Treatment of PI usually includes lifelong maintenance immune globulin therapy. In accordance with FDA Guidance, several immune globulin products (both intravenously and subcutaneously administered) have been licensed based on demonstration of a SBI rate of less than 1.0 per person-year. The safety profile for immune globulins as a class is well-established; the class carries an obligate boxed warning for thrombosis, renal dysfunction, and acute renal failure. Other rare risks associated with the use of IGIV include transmission of infectious agents (e.g., viruses), hemolysis, aseptic meningitis, transfusion associated lung injury (TRALI), hyperproteinemia and increased viscosity.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	July 9, 2015
2. Original IND submission	January 31, 2017
3. IND placed on Clinical Hold	March 2, 2017
4. Clinical Hold lifted	April 11, 2017
5. Pre-BLA meeting	June 16, 2020
6. BLA 125743/0 submission	February 25, 2021
7. Complete Response Letter Issued	February 25, 2022
8. Type A Meeting	May 17, 2022
9. FDA granted an extension for the Applicant to resubmit the application by February 25, 2024	February 21, 2023
10. Re-submission after Complete Response	July 14, 2023
11. Action Due Date	January 13, 2024

3. Chemistry Manufacturing and Controls (CMC)

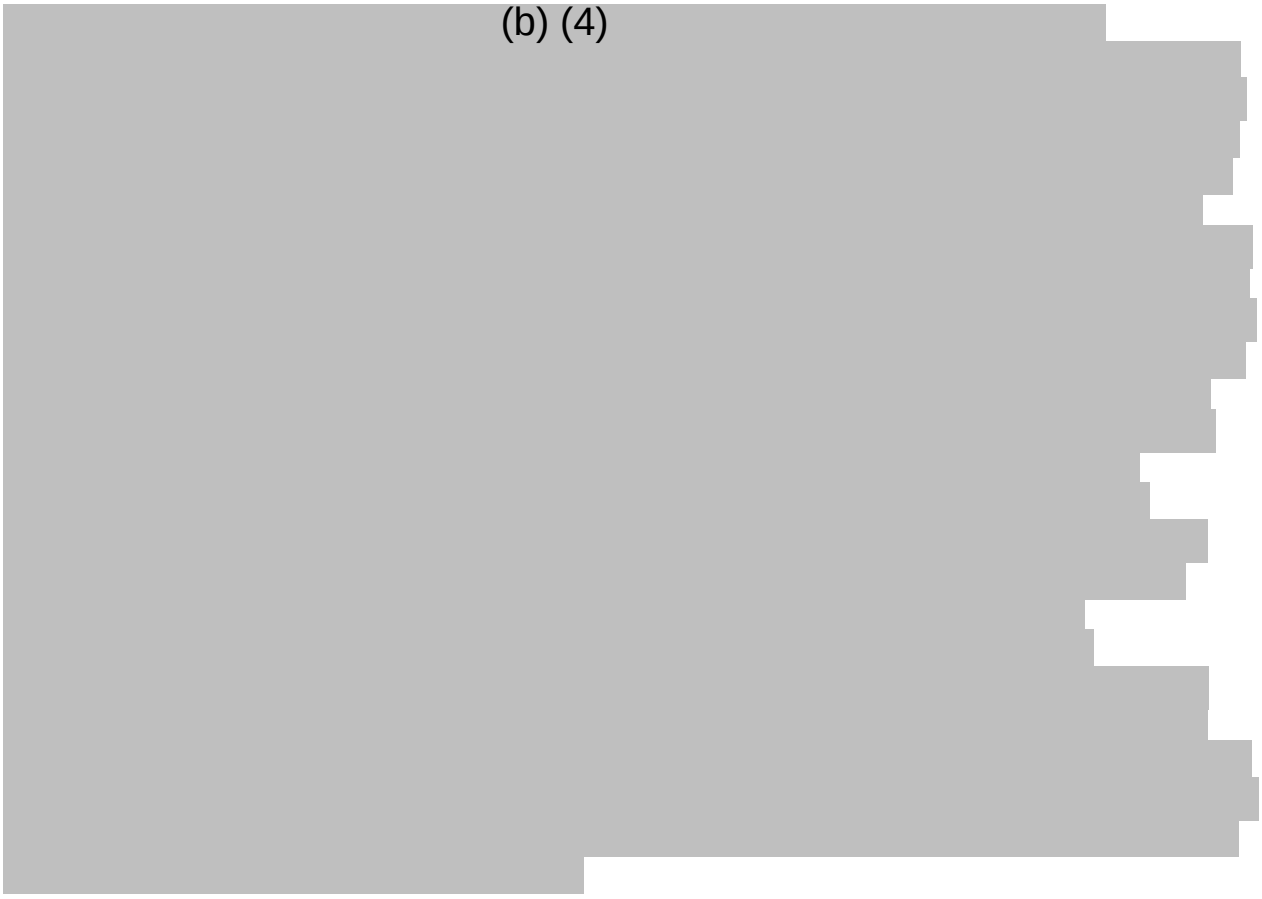
The ALYGLO process is an open bioburden-controlled process that relies on in-process testing and monitoring of critical process parameters to maintain product consistency and quality. There were many elements of the ALYGLO control strategy that the CMC review team felt needed additional strengthening before BLA approval.

The review committee determined that GCBP required additional process validation and determined Post-marketing Commitments were needed covering additional characterization of (b) (4) additional manufacturing lots, lifetime validation studies for (b) (4) (b) (4) content, manufacturing pool B19 parvovirus levels, and leachable studies for newly introduced (b) (4) (b) (4) (b) (4)

a. Product Quality

ALYGLO is a 10% immune globulin intravenous (IGIV) product which is indicated for the treatment of primary humoral immunodeficiency in adults. It is manufactured using a modified Cohn-Oncley ethanol fractionation method, followed by (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) is (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, and packaged/labeled at the GC BioPharma Corp. (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 volumes (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. The Fractionation process starts with the (b) (4)

(b) (4)



The Drug Product (DP) manufactured in three steps: Filling, Visual Inspection, and Labeling and Packaging. The Filling step includes Receiving of DS, Vial Washing & Depyrogenation, 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.

The ALYGLO process contains numerous methods to control product safety and purity. The starting source plasma is collected only from FDA licensed plasma centers and is tested for HBsAg, antibodies against HIV 1 and 2, HCV, Hepatitis B Surface antigen, as well as nucleic acid testing for HIV-1, HBV, HCV, and Parvovirus B-19. The manufacturing process for ALYGLO is an open bioburden-controlled process and as such it has multiple in-process tests for microbial bioburden (b) (4) In addition, it is tested for Endotoxin content and final product sterility. Controlled product characteristics include appearance, pH, (b) (4) , protein content, IgG (b) (4) total human IgG content. Impurities tested for include (b) (4) The manufacturing process also contains 3 viral clearance/viral inactivation steps (Table 2 below) which were validated to show the levels of viral clearance/inactivation achieved.

Table 2. Virus Reduction

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	NT	NT
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

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the ALYGLO drug substance and drug product were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of ALYGLO is listed in the table below. The activities performed and inspectional histories are noted in Table 3 below.

Table 3. Manufacturing Facilities Table for ALYGLO (immune globulin intravenous, human-stwk)

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
GC Biopharma Corp. (GCBP) 586 Gwahaksaneop 2-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea, 28119 Manufacturing: **Drug Substance (DS)-** Drug substance manufacturing. **Drug Product (DP)-** Drug product manufacturing, product visual inspection, packaging and labeling. Testing: **Quality Control Testing-** DP.	3009561235	689517000	Remote Interactive Evaluation (RIE), 2021 Pre-License Inspection (PLI), 2023	CBER DMPQ October 27-November 9, 2021, RIE Outcome of RIE: PLI recommended prior to BLA approval CBER DMPQ, PLI, April 17-28, 2023 VAI

Acronym key: BLA – Biologics License Application; CBER – Center for Biologics Evaluation and Research; DMPQ – Division of Manufacturing and Product Quality; DS – Drug Substance; DP – Drug Product; DUNS – Data Universal Numbering System (Dun & Bradstreet); FEI – FDA Establishment Identifier; GCBP - Green Cross Biopharma Corp.; PLI – Pre-License Inspection; RIE – Remote Interactive Evaluation; VAI – Voluntary Action Indicated.

CBER conducted a Remote Interactive Evaluation (RIE) for the GCBP – Ochang facility from October 27 – November 9, 2021. At the conclusion of the RIE, eleven RIE observations were issued, and CBER determined that a follow-up PLI was required to support the review of the Biologics License Application (BLA).

CBER conducted a Pre-License Inspection (PLI) of GCBP - Ochang facility in April 2023, and a Form FDA 483 was issued at the conclusion of the inspection. The firm's response to the observations and the corrective actions were reviewed and found to be adequate. The inspection was classified as voluntary action indicated (VAI).

e. Container/Closure System

The container closure system for the for the ALYGLO DP is in Table 4 below.

Table 4. ALYGLO DP Container Closure Components

Components	Manufacture	Description	Standards
Glass vial (b) (4) mL, 100 mL, 200 mL	(b) (4) .	Colorless borosilicate glass vial with 32 mm neck finish/ Type (b) (4)	(b) (4)
Rubber stopper	(b) (4)	Film-coated rubber stopper (chlorobutyl (b) (4) 32 mm/ Type (b) (4)	(b) (4)
Flip-off aluminum cap	(b) (4)	Tamper evident plastic cap sustained with aluminum	Non-product contact

(b) (4)

The glass vials are (b) (4) (b) (4) prior to use and the rubber stoppers are (b) (4) (b) (4) prior to use. The container closure integrity of the filled vials after stoppering was tested by a (b) (4) method during process validation. All acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

At the time of the original BLA submission, the applicant submitted several nonclinical studies performed with ALYGLO, including a single dose toxicity and toxicokinetic study in rats, a thrombogenicity study in rabbits, three safety pharmacology studies in rats (two studies) and mice (one study) and two pharmacology studies. Upon review of these studies, the discipline reviewer determined that there were no toxicities attributed to the administration of ALYGLO in these studies. Furthermore, the final formulation of ALYGLO did not raise toxicologic concerns with respect to human exposure. This determination remains for this resubmission, and the pharmacology/toxicology data support approval of ALYGLO.

5. Clinical Pharmacology

ALYGLO contains a broad spectrum of opsonic and neutralizing immunoglobulin G (IgG) antibodies against various infectious agents reflecting the IgG activity found in the donor population. ALYGLO has an IgG subclass distribution similar to that of native human

plasma as it is manufactured from pooled donors. Adequate doses of IGIV can restore abnormally low IgG level to the normal range. Standard pharmacodynamic studies were not performed.

The pharmacokinetics (PK) of ALYGLO was assessed in 22 adults (aged ≥ 17 to 70 years; 10 males and 12 females) with PI. The administered dose of ALYGLO during the PK assessment ranged from 313 to 821 mg/kg every 3 or 4 weeks. The mean half-life was 29.6 days, and the mean clearance (baseline uncorrected) was 1.7 mL/day/kg for 28-day day dosing regimen. The mean steady state trough total IgG concentrations was in the therapeutic range (above 500mg/dL); trough values ranged from 706 to 768 mg/dL for the 28-day dosing regimen.

Overall, the clinical pharmacology data support the approval of the proposed dosing regimen of 300-800 mg/kg every 21 or 28-day infusion as replacement therapy in adults with PI.

6. Clinical/Statistical

a. Clinical Program

The primary evidence of safety and effectiveness for this BLA comes from Study GC5107B_P3, a Phase 3, open-label, single-arm, historically controlled, prospective, multi-center study conducted in the U.S. and Canada. The study enrolled a total of 49 subjects aged 3 years through 70 years with PI of which 33 were adults. The PK sub-study included 27 subjects of which 22 were adults.

During the study, ALYGLO was infused at a dose of 300-900 mg/kg per infusion at 3- or 4- week intervals, depending on the subject's previous immunoglobulin replacement dose and schedule. Doses were adjusted based on weight at each infusion visit in order to maintain serum trough total IgG concentrations >500mg/dL.

The primary efficacy endpoint was annualized rate of acute SBIs, which included bacterial pneumonia, bacteremia/sepsis, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess over a 12-month treatment and observation period. There was a single acute SBI, a case of bacterial pneumonia. The acute SBI rate was 0.03 in adults (with an upper one-sided 99% confidence limit of 0.31), which is less than the pre-defined threshold of 1 SBI per subject-year. The study met its primary endpoint and conforms to FDA guidance and precedent for determining efficacy of immunoglobulin products for PI. Data for secondary infection-related endpoints further support the efficacy of ALYGLO.

No deaths occurred during the study. No adverse events of special interest (anaphylactic shock, aseptic meningitis, hemolytic anemia/hemolysis, and acute renal failure) were observed during the study. The most common (occurring in > 5% of subjects) adverse reactions (occurring within 72 hours of infusion) in adults were headache, nausea/vomiting, fatigue, nasal/sinus congestion, rash, arthralgia, diarrhea, muscle pain/aches, infusion site pain/swelling, abdominal pain/discomfort, cough, and dizziness. The safety profile is consistent with other approved IGIV products.

The clinical data support approval of ALYGLO in adults with PI.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

BIMO inspection assignments were issued for three domestic clinical study sites that participated in the conduct of Protocol GC5107B-P3. The inspections did not reveal substantive issues that impact the data submitted in this original BLA.

c. Pediatrics

The pediatric study requirement for ages 0 to <2 years was waived because the necessary studies are impossible or highly impracticable. It is rare for primary humoral immunodeficiency to be diagnosed in this age group.

The submission of a pediatric study for ages >2 to <17 years was deferred for this application because this product is ready for approval for use in adults, and there are insufficient pediatric study data. (b) (4) . The pediatric study has an agreed protocol and the study has initiated enrollment. For specific PREA PMR recommendations, please refer to Section 11c *Recommendation for Post Marketing Activities.*

d. Other Special Populations

No other special populations are under consideration for the use of this IGIV product.

7. Safety and Pharmacovigilance

Review of the clinical data found no safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety.

8. Labeling

The proposed proprietary name, ALYGLO, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on April 22, 2021, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on May 25, 2021.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed US Prescribing Information, and package and container labels, on January 22, 2022, and found them acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

10. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this BLA.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The review committee recommends approval of ALYGLO for the treatment of primary humoral immunodeficiency (PI) in adults with post-marketing commitments/requirements as detailed below.

b. Benefit/Risk Assessment

Data submitted in the BLA provide substantial evidence of effectiveness and safety in the target population of adults with PI. ALYGLO is effective in reducing the number of SBIs to <1 per patient per year in adults with PI. The most commonly reported adverse reactions (occurring within 72 hours of infusion) in adults were headache, nausea/vomiting, fatigue, nasal/sinus congestion, rash, arthralgia, diarrhea, muscle pain/aches, infusion site pain/swelling, abdominal pain/discomfort, cough, and dizziness. Adverse reactions were consistent with those anticipated with this class of products and were self-limited with ALYGLO. Overall, the benefits outweigh the risks of ALYGLO and the overall benefit-risk profile is favorable.

c. Recommendation for Post-marketing Activities

REQUIRED PEDIATRIC ASSESSMENTS

The applicant is required to complete the ongoing Phase 3 pediatric study, GC5017D, and submit a final report analyzing the pharmacokinetics (PK), safety and effectiveness of ALYGLO in children 2 to <17 years of age as a post-marketing requirement under PREA (Pediatric Research Equity Act).

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

The Applicant committed to complete the following studies as outlined below:

1. 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)

and to include visual inspection and (b) (4) testing at each timepoint.

2. To submit the final report from the lifetime validation studies to support the proposed maximum (b) (4) of the (b) (4)

3. To submit 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.

4. To submit 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.

5. To analyze the (b) (4) content starting from the (b) (4) manufactured during Pre-License Inspection (PLI) batches until obtaining at least (b) (4) lots of (b) (4)

6. 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.

7. 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.