

Documents Reviewed CR Response ALYGLO BLA STN 125743/0/68

1.4 Letters of Authorization for Drug Master Files

Table 1. Letters of Authorization (taken from the submission)

Description of DMF or MF	DMF or MF Type	DMF Number	DMF or MF Holder	Date of Letter of Authorization
Pharmaceutical Closure (Stopper)- Elastomer Formulations, Coatings and Films	Type III	(b) (4)	(b) (4)	June 24, 2022
Glass Container for Parenteral Preparation	Type III	(b) (4)	(b) (4)	June 27, 2022
(b) (4)	Type III	(b) (4)	(b) (4)	July 5, 2022

1.11.4 CRL (Complete Response Letter) Response

1.11.4 Summary of Changes in eCTD

3.2.S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

3.2.P.2 Doc. No. GS-SOP-02975: Container Closure Integrity Test (CCIT) (Alyglo) [OCP] - DMPQ

3.2.P.2.4

Results for leachable study at (b) (4) were updated. Additional timepoint at (b) (4) was added for leachable study at (b) (4).

Doc No. 19-VR-818: Leachables Study for Immunoglobulin G Drug Product and (b) (4) Glass Vial and (b) (4) Rubber Stopper

3.2.P.3 CoA – Aseptic Connector (Female) – (b) (4)

3.2.P.3 CoA – Aseptic Connector (Male) – (b) (4)

3.2.P.3 CoA – (b) (4) (b) (4)

3.2.P.3.5 Process Validation and/or Evaluation

Continued Process Verification (CPV) for GCC 10% IGIV Drug Product (DP) was performed, and the results were provided.

Proven acceptable range for adjusted (b) (4) was updated from (b) (4) based on pre-qualification report.

(b) (4) was changed from (b) (4) to allow (b) (4) through the (b) (4) (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

3.2.P.5.2 Analytical Procedures

SOP number was updated after the documents were migrated from GMP-EDMS to (b) (4) system.

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

Table 3.2.P.5.2-1 List of Analytical Procedures for GCC 10% IGIV DP

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)	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)
	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)
	(b) (4)	GC-SOP-03010	(b) (4)

			(b) (4)
	(b) (4)	GC-SOP-03075	

Category	Test	SOP	Reference of Test Method, Method Principle
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) (b) (4)
Safety	Bacterial Endotoxins	GC-SOP-02934	(b) (4) (b) (4) (b) (4)
	Sterility	GC-SOP-03352	(b) (4) (b) (4) (b) (4)
	CCIT	GC-SOP-02975	(b) (4) (b) (4) (b) (4)

Table 3.2.P.5.2-2 List of Analytical Procedures for GCC 10% IGIV DP after Packaging and Labeling Process

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

3.2.P.5.3 Validation of Analytical Procedures

3.2.P.5.3 Doc. No. GC-REP-13500: Analytical Method Validation Report – (b) (4) Anti-Hbs test due to change in reagent catalog number

3.2.P.5.3 Doc. No. GC-REP-13591: Analytical Method Validation Report - (b) (4) (b) (4) - DBSQC

3.2.P.5.3 Doc. No. GC-REP-13796: Analytical Method Validation Report – Identification: Immunoglobulin (b) (4) - DBSQC

3.2.P.5.3 Doc. No. OBV-AV-0042-20: AMV Report (Sterility Test) [OCP] - DBSQC

3.2.P.5.4

Batch analysis results for the CPV lots were added.

3.2.P.6

Reference standard for glycine was changed from glycine (b) (4) to (b) (4) reference standard glycine (b) (4)

3.2.P.8.1 (Nancy Eller)

Proposed shelf-life of GCC 10% IGIV DP was changed to 24 months at (b) (4) 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) (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) step of the GCC 10% IGIV (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)

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.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment (reviewed by Nancy Eller)

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

3.2.P.8.3 Stability Data (reviewed by Nancy Eller)

The section was updated according to the changes listed in 3.2.P.8.1. Updated data submitted in IR response.

3.2.A.1 Facilities and Equipment (reviewed by DMPQ)

3.2.A.2 Adventitious Agents Safety Evaluation (reviewed by Dot Scott and Lu Deng)

3.2.A.2 Doc. No. GC5107B-QMR-023: GC5107 TSE Risk Assessment for Alyglo Manufacturing Process

3.2.A.2 Doc. No. K14-g10-21: Evaluation of the removal of Bovine Viral Diarrhea Virus and Porcine Parvovirus by Virus Filtration (b) (4)

Documents from Information Requests

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

Information Requests:

Seq. 0073 125743/0/0/69 Sent July 25, 2023, Received July 31, 2023 – Clinical

Seq. 0074 125743/0/0/70 Sent August 11, 2023, Received August 18, 2023 – Clinical

Seq. 0075 125743/0/0/71 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 125743/0/0/72 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 125743/0/0/73 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 125743/0/0/74 Sent October 4, 2023, Received October 13, 2023 - CMC

Viral clearance comments

Seq. 0079 125743/0/0/75 Sent October 11, 2023, Received October 18, 2023 - Clinical

Seq. 0080 125743/0/0/76 Sent October 26, 2023, Received November 1, 2023 - Clinical

Seq. 0081 125743/0/0/77 Sent October 30, 2023, Received November 3, 2023 - Clinical

Seq. 0082 125743/0/0/78 Sent November 9, 2023, Received November 17, 2023 – Clinical

Seq. 0083 125743/0/0/79 Sent November 15, 2023, Received November 20, 2023 – Clinical

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

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

Seq. 0085 125743/0/0/81 Sent November 20, 2023, Received November 24, 2023 – Clinical

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

Updated stability data

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

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

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