

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125743/0.68

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Jing Lin, Ph.D.	Lead Reviewer	11/22/2023		Muhammad Shahabuddin, Ph.D.	
Hyesuk Kong, Ph.D.	Reviewer	8/29/2023		James L. Kenney, D.Sc.	
Parmesh Dutt, Ph.D.	Reviewer	11/22/2023		Kori Francis, Ph.D.	
Tao Pan, Ph.D.	Reviewer	11/22/2023		Kenneth S. Phillips, Ph.D.	
Emnet Yitbarek, Ph.D.	Reviewer	11/22/2023			

Through Maryna Eichelberger, Ph.D.
Division Director, DBSQC/OCBQ

Applicant: GC Biopharma Corp. (GCBP)

Subject: Review of Analytical Methods used for Lot Release of ALYGLO

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release of ALYGLO ((Immune Globulin Intravenous (Human), 10% Liquid) and the associated analytic method validations or qualifications were reviewed previously as described in a DBSQC memo submitted on February 1, 2022, and summarized in the following table. Any changes (assay, test location, and specification) listed in the table are reviewed in this memo.

Category	Assay Name	Assay change (Yes/No)	Test location change (Yes/No)	Specification change (Yes/No)	Reviewer
Safety	Microbial Bioburden Test	No	No	No	Hyesuk Kong
	(b) (4) Endotoxin	No	No	No	Hyesuk Kong
	Sterility Test for 10% IGIV DP	No/Additional sterility qualification report submitted	No	No	Hyesuk Kong
Product Characteristics	Appearance (b) (4) DP)	No	No	Yes	Tao Pan
	pH Measurement (b) (4) DP)	No	No	No	Tao Pan
	(b) (4)	No	No	No	Tao Pan
	Protein content by (b) (4) DP, and Packaged DP)	No	No	No	Tao Pan
	Volume of Injection (DP)	No	No	No	Tao Pan
Excipient	Glycine Content (b) (4) DP)	No	No	No	Tao Pan
Purity and Impurity	(b) (4)	No	No	No	Tao Pan
	(b) (4)	No	No	No	Emnet Yitbarek
	(b) (4)	No	No	No	Emnet Yitbarek
	(b) (4)	No	No	No	Parmesh Dutt
	(b) (4)	No	No	No	Jing Lin
Identification	Identification: Immunoglobulin G (DP)	No	No	No	Jing Lin
	Identification of product origin (DP)	No	No	No	Jing Lin

Conclusion:

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

Documents Reviewed:

Information in sections of the resubmission ((125743/0.68 (Amendment))) and the responses to the Complete Response Letter (CRL) submission that describe control of drug substance (DS) and drug product (DP) (3.2.S.4 and 3.2.P.5), including descriptions of specifications, analytical procedures, and validation of these analytical procedures were reviewed. Additional information in amendments specified by each reviewer were also reviewed.

Background:

On February 25, 2021, Green Cross Biopharma Corporation (GCBP) (previously called Green Cross Corporation (GCC)) submitted an original Biologics License Application (BLA), STN125743/0, for ALYGLO, Immune Globulin Intravenous (IGIV) 10% Liquid for treatment of primary immunodeficiency (PI) in adults (b) (4). ALYGLO is a highly purified IgG ($\geq 96\%$) derived from human normal source plasma collected from eligible donors at FDA-licensed plasma collection centers located in the United States (U.S.) and formulated to physiological (b) (4) with 18.8 mg/mL glycine as a (b) (4) at pH 4.8. The DP is manufactured at GCC's Ochang facility located in South Korea.

On February 25, 2022, a Complete Response Letter (CRL) was issued due to the conclusion from the manufacturing activities observed, the documents reviewed and the GCC personnel interviewed during the Remote Interactive Evaluation (RIE). On February 10, 2023, GCBP requested an extension of Complete Response (CR) resubmission based upon the discussion during the Type A meeting dated May 19, 2022, and the informal meeting dated January 19, 2023. On February 21, 2023, the CR Extension was granted.

On July 14, 2023, GCBP responded to the FDA's CRL and resubmitted the BLA 125743 ((125743/0.68 (Amendment))). Most assays and assay validations were not changed, except the following two changes: 1) Sponsor submitted additional sterility assay qualification study report; 2) The (b) (4) specifications were changed for (b) (4).

Review:**1. Sterility (DP) (Hyesuk Kong)**Introduction

In section 1.11.4, 'Multiple Module Information Amendment' included in the submission, an FDA recommendation (#3) was cited as follow: '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 lots (b) (4) as well as the evaluation of critical process parameters, in-process controls, in-process specification, and impurities. Please update your impurity profile analysis to include lots (b) (4). Following this analysis, please re-evaluate your Drug Product Specifications'. GCBP submitted a supplemental sterility qualification report and test details for sterility performed at GCBP site using three lots from the listed above. This review will focus on

the supplemental qualification of sterility test method for IGIV 10% DP, to indicate if the method is suitable under the actual conditions of use.

Sterility test is performed at GCBP's Ochang facility in South Korea. Acceptance criteria of 'No Growth Detected' must be met for the release of IGIV 10% DP.

Method

(b) (4)

The method is described in more detail below together with the tests performed to determine the suitability of the test method for its intended use.

Sterility Method Qualification

(b) (4)

(b) (4)

Conclusion

After review of sterility method qualification results, this reviewer concludes this method was qualified in accordance with (b) (4) and the test results indicate there is no product inhibition on microorganism growth, thus demonstrating the test method remain suitable under the actual conditions of use.

2. Appearance (DP) (Tao Pan)

Introduction

The appearance of Alyglo DP is examined by visual inspection; the release specifications for DP are: colorless or pale yellow (b) (4), clear or slightly opalescent (b) (4). The method was performed for the release of DP at GCBP's Ochang plant.

Method

The method for the appearance determination of Alyglo DP by visual inspection (GC-SOP-03628: APPEARANCE TEST (ALYGLO) [OCP]) is based on (b) (4).
(b) (4)

(b) (4)
The provided description of the analytical method is sufficient with details on the execution of the method, assay validity criteria, and the generation of reportable results.

Method Verification

In this submitted response to the Complete Response Letter, the specification of the appearance of Alyglo DP was (b) (4) (b) (4) however, the original verification data was still used to support the validity of the method. An information request was submitted on September 1, 2023 to seek additional verification data; as a response to the information request, GCBP performed a new verification study and submitted the verification results (validation report: GC-REP-20094) in Amendment 0.73.

In the report, (b) (4) lots of DPs were analyzed for their clarity and coloration by (b) (4) analysts to demonstrate the precision (repeatability and intermediate precision) of the method; the results from (b) (4) analysts were the same: (b) (4)

All met the specification for clarity and coloration (b) (4)

Conclusion

Based on the information provided, the appearance method for Alyglo DP is adequately described and verified for its intended use.