



**U.S. FOOD & DRUG  
ADMINISTRATION**

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**To:** BLA File STN 125683/0

**From:** Bradley Dworak, Ph.D., Consumer Safety Officer, Reviewer, OCBQ/DMPQ/BI

**Through:** Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/BI

**CC:** Sarah Lee, RPM, OCBQ/DMPQ/ARB  
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Jennifer Reed, Ph.D., Chair, OMPT/CBER/OTAT/DPPT/PDB

**Applicant:** Grifols Therapeutics LLC, Clayton, NC; License #1871

**Site:** Clayton, NC 27520 FEI #1050373

**Product:** Immune Globulin Subcutaneous (Human), 20% (b) (4)

**Intended Use:** Intended for the treatment of adult and pediatric patients 2 years of age or older with primary immunodeficiency (PI) including but not limited to congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

**Subject:** Final review memo

**Action Due:** July 9, 2019

Title	Concurrence	Signature/Date
Bradley Dworak, Ph.D., Reviewer OCBQ/DMPQ/MRB1	Concur	
Deborah Trout, Team Lead OCBQ/DMPQ/MRB1	Concur	
John A. Eltermann, Director OCBQ/DMPQ	Concur	

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I. **Reviewer Recommendation – Approval**

Approval is recommended pursuant to the information provided in the original submission and amendments, provided that there are no outstanding issues remaining with the product office.

The following inspectional consideration is recommended:

Incident 971692 involved a scenario where the (b) (4) exceeded the limit (b) (4). The (b) (4) was identified. The firm does not recognize this deviation has having any past history. However, the firm indicates that deviations 813964 and 818188 involved results of (b) (4) respectively. It is uncertain if the same (b) (4) was identified. Please verify that this deviation is indeed not a historic re-occurring issue.

CBER understands that the recommendation may or may not be taken (based on risk and available resources), and is not requesting documentation to be submitted as evidence of completion

## **II. Executive Summary**

This Initial BLA eCTD (sequence 0001) submission was received by CBER on July 9, 2018 from Grifols Therapeutics LLC located in Clayton, North Carolina. The submission is intended to introduce and market Immune Globulin Subcutaneous (Human), 20% (IGSC 20%, (b) (4) ) in 5mL, 10mL, 20mL, and 50mL vials.

This review has been prioritized according to risk/benefit. The IGSC 20% manufacturing process is based upon the approved process for manufacture of Immune Globulin Injection (Human), 10% (Gamunex-C) but includes an additional (b) (4) step to increase the protein concentration from 10% to 20%. The (b) (4) and thus outside the scope of this review.

(b) (4). The manufacturing process includes a (b) (4)

Other changes include those to the container closure system. (b) (4) 50, 100, 200 and 400-mL vials are used for the existing 10% product Gamunex-C. For this 20% product, 4 vials of smaller quantity (5, 10, 20, and 50mL) are used. Thus, media fill studies were included with the submission to validate filling on these containers.

The firm formally requests a categorical exclusion for this product.

An inspection waiver for all the facilities of GDS was granted by DMPQ management.

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### **III. Supporting Information**

To support this initial BLA, the firm provided the following information under the scope of DMPQ review:

- Product Description
  - Intended Use
- Submission summary
- Chemistry, Manufacturing, and Controls (CMC)
  - Description of Manufacturing Process
  - Drug Product Stability
  - Facilities and Equipment
    - Descriptions
    - Flow diagrams
      - Waste
      - Personnel
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- Verification and Validation
  - Equipment used for (b) (4)
  - Manufacturing process
  - Facility qualification
  - Cleaning studies
  - Media Hold Challenges
  - Container/Closure Systems
  - Media Fill Studies

#### **Reviewer Comment**

Regional information (including executed batch records, method validation, and lot release protocols) was not provided in the BLA. Some other sections needed clarification including batch numbering, filling, storage, and shipping, microbiological attributes, CCI testing, and (b) (4) validation. An IR was sent out to the firm before the filing meeting (see IR #1 dated August 15, 2018 in IR section below).

## **IV. Product Description and Characterization**

### **a. Manufacturing Process**

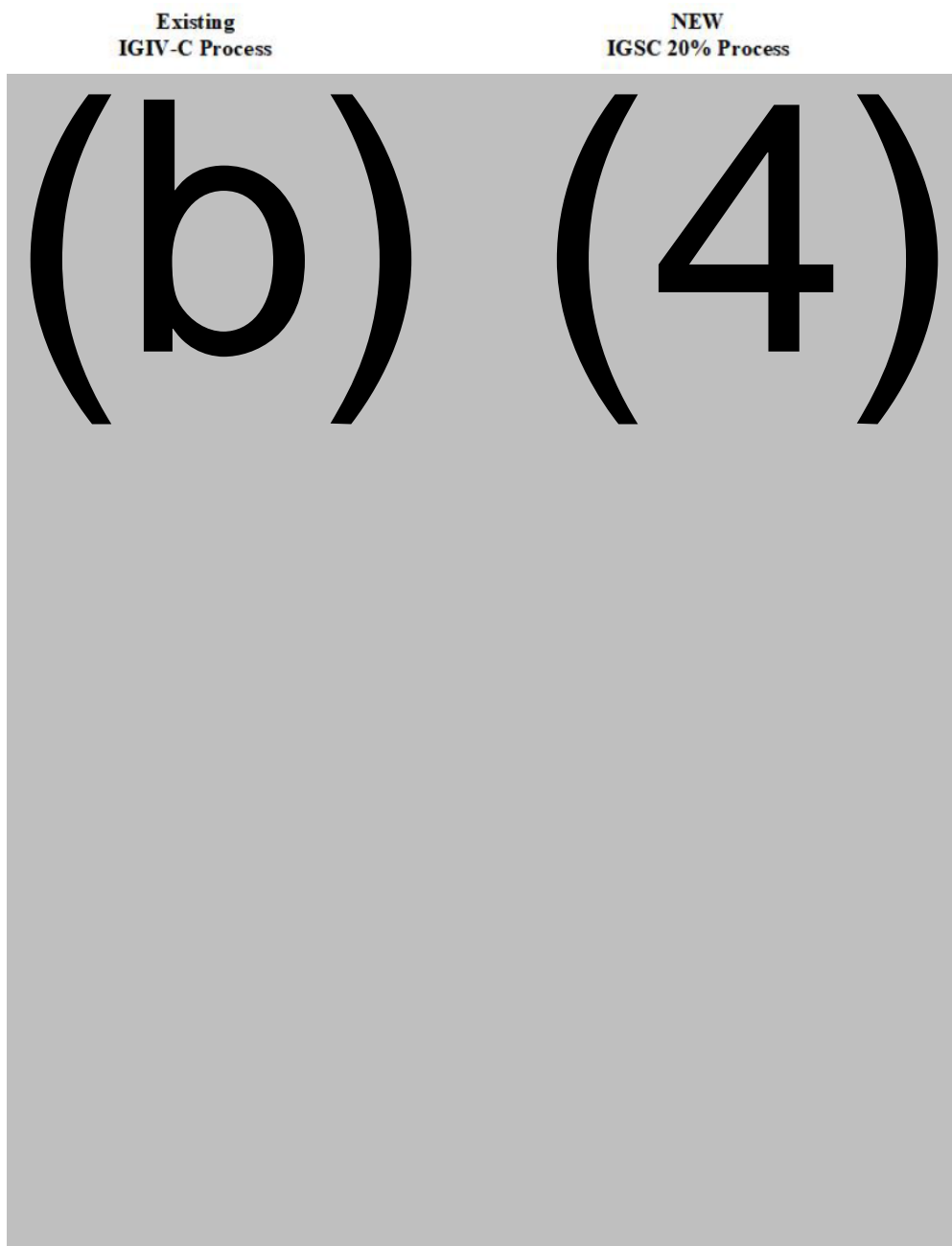
#### **i. Description**

The upstream manufacturing process for this product uses the (b) (4) process for the licensed process for Immune Globulin Injection (Human), 10%. In order to reach a 20% protein concentration, the solution undergoes an additional (b) (4) step with a (b) (4). The (b) (4) is done in a (b) (4) dedicated processing area in the (b) (4) facility, Building (b) (4). This area of the building has been modified to provide a Class (b) (4) environment.

After (b) (4), adjustments of the concentrated solution are performed as necessary to attain a protein solution of 18% to 22% and a pH of 4.1 to (b) (4) using glycine. Polysorbate 80 is added to achieve a target concentration of

25µg/mL for enhanced stability/extended shelf-life. All batches undergo an additional (b) (4) as part of the routine filling operations. Aseptic filling is done followed by low pH incubation for (b) (4)

ii. [Process flow diagram and comparison to existing IGIV-C process](#)



iii. (b) (4)

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

(b) (4)

viii. (b) (4)

(b) (4)

V. **Intended Use**

Intended for the treatment of adult and pediatric patients 2 years of age or older with primary immunodeficiency (PI) including but not limited to congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

<b>Reviewer Comment</b> <b>IFU Risk Analysis</b> No risk identified from a DMPQ perspective.
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VI. **Facility Information**

a. Location

Manufacturing facilities are outlined in the table below:

Facility Name / Address	Registration Number
Grifols Therapeutics LLC (GT) (b) (4)	FEI: (b) (4)

b. Establishment Info

i. (b) (4)



(b) (4)

ii. (b) (4)

iv. Flow and facility diagrams

Flow diagrams that were reviewed consisted of the following:

- Product flow
- Finished product flow
- Personnel flow
- Waste flow
- Material flow
- Raw material flow
- Differential pressure

Facility diagrams that were reviewed included:

- Area Classification
- HEPA filter locations

#### Reviewer Comment

Product flow indicates that product is (b) (4)

(b) (4). No issues were identified with the flow diagrams. HEPA filters were identified in the associated rooms for the (b) (4) area. Rooms (b) (4) associated with the (b) (4) were identified as Grade C.

Results of the differential pressure and room classifications can be found below.

## VII. Facility Qualification

### a. Manufacturing rooms handled by (b) (4)

(b) (4)

(b) (4)

(b) (4)

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

f. (b) (4)

## IX. Environmental Assessment

Per 21 CFR 25.15(d), GDS is requesting a categorical exclusion from the preparation of an environmental assessment under the 21 CFR 25.31(c): “Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.”

The firm states that the substances (human plasma and its derivatives) associated with production occur naturally in the environment. Approval of this application does not alter significantly the concentration these substances, its metabolites, or degradation products in the environment. To our knowledge, no extenuating circumstances exist which would preclude the application of this categorical exclusion.

### Reviewer Comment

This response is acceptable.

## X. Process Validation (qs-0318.pdf)

### a. Description

The process validation consisted of a complete manufacturing process that followed a comprehensive set of approved manufacturing SOPs and BPRs. A total of (b) (4) validation runs were conducted. The review focused on the results that immediately follow (b) (4) since this is the last process step that is (b) (4) to the existing approved process (post IGIV-C 10%). (b) (4)

i. (b) (4)

[Redacted]

[Redacted]

(b) (4)

**Reviewer Comment**

The process of (b) (4) has been demonstrated to provide passing results according to the acceptance criteria and process steps above. This process validation appears to be adequate.

c. **Final Formulation Step**

Acceptance criteria and results:

Parameter	Acceptance criteria	(b) (4)
% protein	18 – 22 %	
(b) (4)		
(b) (4)		

**Reviewer Comment**

According to the proposed labeling the firm intends to market the product as containing a protein concentration of 20%. However, the acceptance criterion for protein concentration is 18-22% permitting the possibility of a lower protein concentration (ex. the final formulation of (b) (4) resulted in a value of (b) (4) than the stipulated value of 20%.

On December 10, 2018 I alerted the PO chair Jennifer Reed of this issue via email, as well as DMPQ management verbally at the internal mid-cycle meeting on December 13, 2018. Ms. Reed forwarded the email to her supervisor Dr. Dorothy Scott on December 10, 2018 for further consideration. I was advised by DMPQ management that this is not a DMPQ review issue.

**d. Sterile Filtration Step**

Acceptance criteria and results:

- (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

f. Fill, Stoppering, Overseal, and Incubation Step

Sterile (b) (4) is aseptically filled into prepared vials (5mL, 10mL, 20mL, or 50mL) and the filled vials are stoppered and an overseal is applied.

The final product is then incubated for (b) (4) at a pH of 4.1 to 4.8

- (b) (4)

**Reviewer Comment**

According to the PO chair, the product office requires 2 dedicated (b) (4) pathogen removal steps for plasma-derived protein products. The firm has chosen to use caprylate and this low pH incubation step. According to the PO this incubation time is sufficient.

g. Final Container Testing Step

Results of the final container testing is indicated in the table below:

Run/Batch #	Appearance See description	Volumetric Fill Check Min labeled vol	Protein Concentration 18-22%	Sterility No Growth	Endotoxin (LAL) ≤ 5.0 EU/ml
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(b) (4)

The results for all (b) (4) final container batches (b) (4) final container batches (5mL, 10mL, 20mL, and 50mL (b) (4)) indicate compliance according to the acceptance criteria and are as follows:

i. Acceptance criteria and results

- Visual appearance
  - Clarity: clear or slightly opalescent, during storage it may show formation of (b) (4) or small amount of visible particulate matter
  - Color: colorless or pale yellow, (b) (4)
- Volumetric fill check: all results were at or above minimum labeled volume
- Sterility: no growth

- Bacterial endotoxin: Acceptance criteria is (b) (4), all results were (b) (4)

#### h. [Deviation #971692](#)

(b) (4)

#### i. [Deviation #1022698](#)

(b) (4)

#### Reviewer Comment

Although the final results for (b) (4) were within acceptable limits, the firm did not indicate what type of investigation was conducted into why the OOS occurred and a possible follow up actions. They should state how they handled the OOS. Also, none of the runs conducted were without a deviation.

[IR #3 December 12, 2018] All (b) (4) of your process validation runs included at least one incident/deviation regarding (b) (4). Incident #971692 in Run (b) (4) reports an OOS for (b) (4) and #1022698 indicates that the values for (b) (4) (b) (4) Runs (b) (4) are missing. It is unclear to us if a run can be conducted without an incident or deviation. Also, it appears to us that an OOS should be listed as a deviation and not as an incident. Please provide an explanation as to why these incidents are not reported as deviations and why investigations and corrective actions are not being conducted to prevent these future OOSs and non-reporting incidents from occurring.

## XI. Container Closure System

### a. [Description](#)

A table of the various container sizes, stopper, and overseal configurations is given below:

Vial Size	Parameter	Glass Vial	Stopper	Overseal
5 mL	Vendor	(b) (4)	(b) (4)	(b) (4)
5 mL	Description	5 mL (b) (4) with 20 mm neck finish (tubing)	20 mm (b) (4) chlorobutyl gray (b) (4)	20 mm lacquered aluminum overseal with plastic flip-cap



10 mL	Vendor	(b) (4)	(b) (4)	(b) (4)
10 mL	Description	10 mL (b) (4) with 20 mm neck finish (tubing)	20 mm (b) (4) chlorobutyl gray (b) (4)	20 mm lacquered aluminum overseal with plastic flip-cap
20 mL	Vendor	(b) (4)	(b) (4)	(b) (4)
20 mL	Description	20 mL (b) (4) with 20 mm neck finish (molded)	20 mm (b) (4) chlorobutyl gray (b) (4)	20 mm lacquered aluminum overseal with plastic flip-cap
50 mL	Vendor	(b) (4)	(b) (4)	(b) (4)
50 mL	Description	50 mL (b) (4) with 32 mm neck finish (molded)	32 mm (b) (4) chlorobutyl gray stopper (b) (4)	32 mm lacquered aluminum overseal with plastic flip-cap

**b. COA Results for Glass Vials**

Schematic diagrams of the dimensions of the container closure components were provided. (b) (4) batch for each of the glass vials were tested and found to be within specifications for filling volume, filling (b) (4), glass (b) (4)

**c. COA Results for (b) (4) 20-mm stopper**

A total of (b) (4) batches were tested and the results for are as follows:

(b) (4)

All results are in compliance with the acceptance criteria.

**d. COA Results for (b) (4) 32-mm stopper**

A total of (b) (4) batches were tested and the results for are as follows:

(b) (4)

All results and vials are in compliance with the acceptance criteria.

**XII. Media Fill Studies**

A total of (b) (4) qualification studies were done for the following container closure configurations:

(b) (4)

**a. Protocol**

(b) (4)

All test cases were successfully completed, and all requirements met.

**b. History of approved vials and lines**

Pre-existing qualification studies have been done for these vials and background information is included in the IR response for April 26, 2019 set of IRs.

**c. (b) (4)**

(b) (4)

(b) (4)

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

There were no contaminated vials from all media fill validation runs. All filled containers passed nutritional adequacy.

### **XIII. Batch Records**

The batch records CB-000-78-001008 (b) (4), *Formulation of 20% IGSC*, (b) (4) and CB-000-78-001009 Sterile Filtration of 20% IGSC, (b) (4) were reviewed for completeness of documentation.

### **XIV. Information Requests**

#### **a. August 15, 2018**

Responses received on August 21, 2018 as Amendment #4.

#### **1. Please submit the following information or location where these items may be found within the submission:**

##### **a. [3.2.S.2.2] Batch numbering and pooling scheme;**

##### **[Firm's response]**

A copy of the standard operating procedure (SOP) describing the batch numbering system for in process and final container products is provided in the current amendment in CTD section 3.2.S.2.2.

Please note that information regarding plasma pooling, pool size and (b) (4) is provided in manufacturing method GTI\_MM-000002 already provided in the original submission in CTD section 3.2.S.2.2. A standard (b) (4) batch size corresponds to (b) (4) of plasma.

As described in the manufacturing method GTI\_MM-000001 already provided in the original submission in CTD section 3.2.S.2.2, a targeted batch size of (b) (4)

. For ease of review, the following link to the purification manufacturing method submitted in Sequence 0000 is provided.

##### **Reviewer Comment**

This response is acceptable.

##### **b. [3.2.S.2.2] Filling, storage, and shipping;**

##### **[Firm's response]**

Please note that the (b) (4) for IGSC 20% is the Sterile (b) (4) solution. The final formulated IGSC 20% (b) (4) solution is (b) (4) sterile filtered into a (b) (4) prior to use according to a validated method to form the Sterile (b) (4). The Sterile (b) (4) solution may be (b) (4) for not more than (NMT) (b) (4) days and at NMT (b) (4) days at (b) (4) temperature for a total of NMT (b) (4) days total (b) (4) prior to aseptic filling into individual product vials. The aseptic filling process is considered part of the drug product manufacturing process and details are provided in CTD section 3.2.P.

Data supporting the stability of the Sterile (b) (4) solution during (b) (4) prior to aseptic filling were provided in the original submission in CTD section 3.2.S.7.3.

Information regarding shipping is not applicable for IGSC 20% as all processing from plasma pooling through sterile filtration of the (b) (4) is performed at the (b) (4) site. Although sterile filtration (b) (4) and information is already provided in manufacturing method GTI\_MM-000001, additional detail was added to the following overview document for clarity. A copy of the updated overview document is provided in the current amendment in CTD section 3.2.S.2.2.

**Reviewer Comment**

This response is acceptable.

**c. [3.2.P.2.5] Microbiological Attributes;**

**[Firm's response]**

Information regarding microbiological attributes of the drug product were provided in Section 3.2.P.2.5 of the summary document provided in CTD section 3.2.P.2 of the original submission (Sequence 0000).

Please note that IGSC 20% is provided as a sterile drug product and does not contain any antimicrobial preservatives. Sterility testing is performed on each batch prior to release according to the methodologies described in the (b) (4) and comply with the current edition in force. The post-approval stability protocol for the drug product includes sterility and container closure integrity testing at initial time point (Time 0) and at product expiry (24 months) to support sterility and container integrity is maintained throughout the product's shelf-life.

Although microbiological attribute information was previously provided, additional detail was added to the following overview document for clarity. A copy of the updated overview document is provided in the current amendment in CTD section 3.2.P.2.

**Reviewer Comment**

This response is acceptable.

**d. [3.2.P.2.5] CCI testing;**

**[Firm's response]**

As stated in Section 3.2.P.2.5 (page 3) of the overview document provided in CTD section 3.2.P.2, reports summarizing the container closure integrity studies for each vial size are provided in CTD section 3.2.A.1.

As an additional measure, all IGSC 20% batches filled in 20 mL and 50 mL vials are 100% container integrity tested using the same (b) (4) method already FDA approved for other liquid products manufactured at the (b) (4) site. A report summarizing the performance qualification (PQ) study performed for the (b) (4) was provided in CTD section 3.2.A.1 of the original submission.

Please note that study report QS-10917 was previously submitted and approved by FDA for (b) (4)

**Reviewer Comment**

This response is acceptable.

**e. [3.2.P.2.5] Filter validation for (b) (4)/nano filtration;**

**[Firm's response]**

Nanofiltration of IGSC 20% is performed during (b) (4) processing as part of the of the (b) (4) (3.2.S) manufacturing process and is not applicable to the drug product. Nanofiltration is performed using a (b) (4). Details regarding the nanofiltration process is provided on page 9 of manufacturing method GTI\_MM-000001 provided in the original submission.

Grifols performed a process validation (PV) study to demonstrate the specified process parameters were achieved during nanofiltration using the commercial process. A separate pathogen safety study was performed to evaluate the capacity of the nanofiltration process to remove and/or inactivate deliberately spiked infectious viruses.

As part of the current amendment, the following (b) (4) validation report from the vendor (b) (4) is provided in CTD section 3.2.S.2.5 and provides further information regarding the nanofilter.

Please note that this is the (b) (4) nanofilter already FDA approved for use with (b) (4). As described in the submission, the (b) (4) IGSC 20% processes are (b) (4) from plasma pooling through the nanofiltration step.

**Reviewer Comment**

This response is acceptable.

**f. [3.2.R] Executed batch records for drug substance and drug product;**

**[Firm's response]**

A complete set of executed batch records are provided in CTD section 3.2.R as requested.

**Reviewer Comment**

This response is acceptable.

**g. [3.2.R] Method validation package;**

**[Firm's response]**

Since comprehensive method and method validation information was provided in the original submission for the drug substance (CTD sections 3.2.S.4.2 and 3.2.S.4.3) and drug product (CTD section 3.2.P.5.2 and 3.2.P.5.3), an additional method validation package was not provided in CTD section 3.2.R.

To facilitate review, the original submission provided an overview in CTD section 3.2.P.5.2 and 3.2.P.5.3 which provides a roadmap of the testing performed for drug product release and the associated method validation studies.

**Reviewer Comment**

This response is acceptable.

**h. [3.2.R] Lot Release Protocol template;**

**[Firm's response]**

A copy of the Lot Release Protocol template for IGSC 20% is provided in CTD section 3.2.R.

**Reviewer Comment**

This response is acceptable.

**b. December 12, 2018**

Received on January 3, 2019

1. Your acceptance criterion of (b) (4) for the temperature verification for the (b) (4) room is not correct and differs from the criterion in the IQ of (b) (4). Please correct this value. Also, please explain why an acceptance criterion of (b) (4) would be a satisfactory tolerance for a stipulated (b) (4) room.

**[Firm's response]**

Previously submitted study report QS-0518 provides a summary of the IQ, OQ and PQ studies performed during the qualification of (b) (4) that serves (b) (4) Storage Room (b) (4). As requested, Table 6-1 in the PQ section of the report has been revised to correct the typographical error which incorrectly stated an acceptance criterion as (b) (4). The correct acceptance criterion for the temperature of Room (b) (4)

Please note that the (b) (4) acceptance criterion is the minimum acceptable temperature for Room (b) (4) which is controlled with a temperature setpoint of (b) (4). The room is identified as the "(b) (4) Storage Room" as the name reflects the (b) (4) temperature setpoint. As shown in the previously submitted study report QS-0218 summarizing the temperature mapping data for Room (b) (4) temperatures are consistently maintained around the (b) (4) setpoint and all data met the (b) (4) acceptance criterion.

**Reviewer Comment**

The firm revised the table to reflect the (b) (4) acceptance criterion. Their response indicates that the temperature can be held at the setpoint of (b) (4) with minimal deviation. Thus, their response is acceptable.

2. The cleaning validation process of the (b) (4) does not include (b) (4) sampling of the (b) (4). Please provide an explanation of how you further ascertain that the (b) (4) are devoid of any remaining residues and operate correctly after your cleaning procedure. For example, a (b) (4) test would indicate any (b) (4).

**[Firm's response]**

As noted, the CV study protocol did not include a requirement for (b) (4) sampling of the (b) (4). Confirmation of continued correct (b) (4) operation and an indication of possible (b) (4) is monitored under a useful lifetime study for the (b) (4). The study requires that (b) (4) are tested for each (b) (4) run. At this time, data for (b) (4) runs are available under the study protocol. A summary of the currently available data is provided in the following table below. The lifetime study results will be reviewed and summarized in an interim report after data are available for (b) (4) runs.

(b) (4)

#### Reviewer Comment

The firm's strategy to monitor correct (b) (4) operation is to monitor for any trends in the (b) (4) levels and (b) (4) levels. After (b) (4) runs, (b) (4) remains at (b) (4) and (b) (4) levels are consistent. An interim report will be available after (b) (4) runs. This response is acceptable.

3. All (b) (4) process validation runs included at least one incident/deviation regarding (b) (4). Incident #971692 in Run (b) (4) reports an OOS for (b) (4) and #1022698 indicates that the values for (b) (4) of the (b) (4) of Runs (b) (4) are missing. It is unclear to us if a run can be conducted without an incident or deviation. Also, it appears to us that an OOS should be listed as a deviation and not as an incident. Please provide an explanation as to why these incidents are not reported as deviations and why investigations and corrective actions are not being conducted to prevent these future OOSs and non-reporting incidents from occurring.

#### [Firm's response]

According to Grifols procedures, an incident is any event, issue or unexpected result that represents a failure to meet a predetermined product quality requirement, a process performance parameter or a quality system requirement. Therefore all deviations are captured as incidents. When an excursion with the potential to impact product quality



occurs, an incident is initiated to document the event and the subsequent investigation, supporting documentation, cause conclusion, product impact assessment and any corrective actions, as applicable.

The (b) (4) action level excursion and ‘missing’ (b) (4) data described in Incidents 971692 and 1022698 were investigated by Grifols according to procedure. The summaries provided in study report QS-0318 provided a brief overview of the deviations and the disposition of the incidents. Additional details are provided below for the investigation and assessment of each incident.

#### Incident 971692

An incident was issued when the (b) (4) sample result of (b) (4) for Run (b) (4) failed to meet the action level of (b) (4) (Table 13 in QS-0318). Please note that the acceptance criteria cited in Table 13 of study report QS-0318 incorrectly states the acceptance criteria as (b) (4). The correct expression is (b) (4). This sample is collected as part of the (b) (4) steps and represents the (b) (4) for the currently licensed IGIV-C process. However, since additional (b) (4) and final formulation steps are performed for IGSC 20%, this sample is referred to as the (b) (4) sample for the IGSC 20% process. Regardless of the end drug product (IGIV-C or IGSC 20%), the action level for samples collected at this step for both processes is (b) (4).

A comprehensive investigation was initiated to investigate the excursion which included a review of the following documentation:

- Batch Production Records & Standard Operating Procedures
- Incident Historical Review
- CIP & SIP Reports
- Environmental Monitoring Data
- (b) (4)
- Downstream (b) (4) and Final Container Results

The investigation did not identify a definitive root cause for the excursion; therefore, no corrective action was taken. However, the investigation did identify that the manual cleaning of the (b) (4) of the (b) (4) system may have been a contributing factor for the OOS. As a preventive action, intensive cleaning of the (b) (4) and associated equipment (b) (4) was performed using (b) (4).

The product impact assessment focused on the additional downstream data available for the batch. After the completion of the additional (b) (4) and formulation steps for IGSC 20%, samples were collected from the (b) (4) final container drug product. All downstream test results for (b) (4), sterility, (b) (4) met all acceptance criteria.

The completed investigation concluded that the OOS had no impact to the safety, quality or sterility of the batch and the batch was dispositioned as ‘accept without restrictions’.

#### Reviewer Comment

The firm indicates that manual cleaning may have been a contributing factor for the OOS although the investigation did not identify a definitive root cause. A preventative action was taken by undergoing intensive cleaning of the (b) (4) and associated equipment. This response is acceptable.

#### Incident 1022698

An incident was issued when the final formulation (b) (4) samples for IGSC 20% Runs (b) (4) were not tested as required within (b) (4). The process validation samples were delivered to the test laboratory on 9/18/2017 and 9/25/2017 respectively, along with other routine IGIV-C samples. On 10/23/2017 an incident was issued when the test results for the IGSC 20% final formulation samples were not available. A review determined that an EM technician inadvertently placed the samples in the 2 to 8°C incubator used for retain sample storage. The samples were retrieved from the incubator and were tested for (b) (4) 10/23/17. Both samples yielded a result of (b) (4). Due to the extended timeframe between sample collection and testing, the (b) (4) results are considered not valid and were therefore not reported in Table 16 of study report QS-0318.

The assessment concluded that the incident was due to operator error due to misinterpretation of the sample table used for sample handling. As a preventative action, the sample table was revised to provide additional clarity.

An evaluation of the remaining (b) (4), sterility, (b) (4) data for the batches was performed. The available data demonstrate that the batches were manufactured under an acceptable level of (b) (4) control and confirms the cleanliness of the batches from a (b) (4) perspective. There is no adverse effect on the quality or safety of the batches as a result of the invalid test results and the batches were dispositioned as 'accept without restrictions'.

#### Reviewer Comment

The firm indicates that this incident was due to operator error regarding placement of the sample handling. The firm revised the sample table to provide additional clarity for sampling handling. Therefore, this response is acceptable.

#### c. March 15, 2019

Received on March 20, 2019 (sequence 0027)

1. Please provide SOP CS-000-AB-001005, Process Outline for the IGSC 20% Manufacturing Process (b) (4).

#### [Firm's Response]

The firm submitted the requested SOP.

#### Reviewer Comment

The information gained was that the (b) (4) storage hold time is up to (b) (4) at 2-8°C until ready to be transferred from Room (b) (4) to Room (b) (4).

d. April 26, 2019

Received on May 6, 2019

1. Are the final drug product vials received “ready to use”?

**[Firm’s response]**

No. The final drug product vials (5 mL, 10 mL, 20 mL and 50 mL) used for IGSC 20% are not ‘ready to use’. The vials are received (b) (4) prior to use for sterile pharmaceutical applications.

2. Have (b) (4) studies for the final drug product vials been done?

**[Firm’s response]**

All four final drug product vial sizes used for IGSC 20% (5 mL, 10 mL, 20 mL and 50 mL) are existing qualified and licensed vials for other plasma-derived products at the (b) (4) site. The following table provides a listing of the previous FDA submissions and approvals for the vials.

Vial Size	Vendor	Glass Type	Neck Finish	Product	Fill Line	STN	Date of Approval
5 mL	(b) (4)	(b) (4) (tubing)	20 mm	GamaSTAN	(b) (4)	BL 101134/5612	5-Feb-18
10 mL		(b) (4) (tubing)	20 mm	HyperRAB		BL 101144/5724	5-Feb-18
20 mL		(b) (4) (molded)	20 mm	Plasbumin		BL 101138/5611	17-Apr-17
50 mL		(b) (4) (molded)	32 mm	Plasbumin		BL 101138/5616	18-Sep-17

Data supporting the (b) (4) achieved by the established (b) (4) procedures was reviewed by FDA as part of the supplements submitted to each dossier listed (above). In addition, the (b) (4) processes used for Fill Line (b) (4) (20 mL) and Fill Line (b) (4) (50 mL) were reviewed by FDA during a pre-approval inspection on (b) (4) (FEI (b) (4))

**Reviewer comment**

The firm has satisfactorily demonstrated that these vial sizes and corresponding fill lines have prior FDA approval and thus (b) (4) studies are not required in this submission.

3. Regarding your response to IR #11 question #3 received on January 3, 2019, please indicate the specific (b) (4) that was/were identified from the investigation of Incident #971692.

**[Firm's response]**

The (b) (4) identified from the investigation of Incident #971692 was (b) (4).

**Reviewer Comment**

This (b) (4) is (b) (4) and found in (b) (4). It is (b) (4) and found particularly among (b) (4). We asked for the complete investigation. Please see IR dated May 7, 2019.

4. Regarding your (b) (4) study, please describe the worst-case parameters determined from information provided in the questionnaire. Also, explain how these worst-case parameters were used to determine the appropriate conditions used in the scaled-down study such as (b) (4) conditions.

**[Firm's response]**

The process parameters that will be used for sterile filtration of IGSC 20% during routine production as well as worst-case parameters were provided to (b) (4) in a questionnaire used to design the bacterial retention study.

Since IGSC 20% is sterile filtered (b) (4) during aseptic filling, production parameters for (b) (4) filtrations are shown. Parameters that may vary within the established ranges such as (b) (4) or may be affected by equipment set points such as sterilization time/temperature were tested under worst-case conditions during the retention study. Since the IGSC 20% formulation was already established parameters such as product (b) (4) were not challenged during the study. The study considered both (b) (4) conditions to represent the temperatures experienced during routine production.

A summary of the routine process parameters and the parameters used during the retention study is provided in the following table.

(b) (4)

(b) (4)

**Reviewer comment**

The process parameters that represent worst-case appear to be incorporated into the scaled-down simulation. These include time of (b) (4) steril

5. Regarding the (b) (4) used for the final concentration of the protein:

a. What is the lifespan of the (b) (4)

**[Firm's response]**

The lifespan of the (b) (4) used for the final concentration of the protein is being evaluated under an approved study protocol LTS-0117. The protocol has a maximum lifetime target of (b) (4) runs pending acceptable results. The required testing and acceptance criteria for the study are summarized in the following table.

(b) (4)

**Reviewer comment**

As (b) (4) protein concentration is checked (b) (4) this approach seems adequate.

b. How are the (b) (4) stored?

**[Firm's response]**

The (b) (4) are stored (b) (4) located in Processing Room (b) (4) for both short-term (between runs) and long-term (campaign runs). If the (b) (4) system is stored for more than the established (b) (4) is cleaned using the validated cleaning cycle described in study report *QS-8417 Qualification and Cleaning Validation of the (b) (4), in Building (b) (4)* before re-use. The validation report can be found in eCTD section 3.2.A.1 of the original application.

**Reviewer comment**

The (b) (4) are stored in a (b) (4) between runs and cleaned if the (b) (4) This approach appears adequate.

e. May 7, 2019

Received on May 10, 2019

Please provide the complete investigation and summary results into Incident #971692 including, but not limited to, your review and assessment of the following: batch production records, SOPs, incident history, (b) (4) reports, EM data, (b) (4) and assessment, downstream (b) (4) and final container results.

**[Firm's response]**

The firm provided the complete investigation into this incident.

#### Reviewer Comment

I reviewed the reports from the complete investigation for the (b) (4). One thing I did notice in Attachment 1 is that they have had two other deviations of exceeding the limit of (b) (4). Deviations 813964 and 818188 indicated a result of (b) (4) respectively. Not sure if they were from the same (b) (4) or not. Also interesting is that in Attachment 3 they specify that the latest deviation 971692 is not based on history but from the previous deviations I would think it has been a historical issue.

I discussed this issue with the team lead and made a decision to make this an (b) (4):

Incident 971692 involved a scenario where the (b) (4) exceeded the limit (b) (4). The (b) (4) was identified. The firm does not recognize this deviation has having any past history. However, the firm indicates that deviations 813964 and 818188 involved results of (b) (4) respectively. It is uncertain if the same (b) (4) was identified. Please verify that this deviation is indeed not a historic re-occurring issue.