



Memorandum

To: BLA STN 125683/0 File

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Through: Michael C. Kennedy, Ph.D., Team Leader, PDB/DPPT/OTAT/CBER
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CC: Candido Alicea, RPM, DRPM/OTAT/CBER

Applicant: Grifols Therapeutics LLC, Clayton, NC

Product: Immune Globulin Subcutaneous (Human), 20% Solution for Injection
Proposed trade name: XEMBIFY®

Subject: CMC Review: Original BLA – (b) (4) Drug Product Specifications, Analytical Procedures and their Validation Studies – assigned to the Product Office

Recommendation

Approval

Executive Summary

This Discipline Review memorandum covers assigned CMC sections of the Original Biologics License Application (BLA) submission from Grifols Therapeutics LLC for their Immune Globulin Subcutaneous (Human), 20% Solution for Injection (IGSC) product, XEMBIFY®, for the treatment of primary humoral immunodeficiency, which was received by FDA CBER on 9-JUL-2018. The CMC sections I reviewed were the (b) (4) Drug Product Specifications, Analytical Procedures and their Validation Studies that are usually assigned to the Product Office for review, which included: Appearance, (b) (4) Polio Potency, Measles Antibody Potency, (b) (4) The abovementioned specifications, analytical procedures and validation studies, and the sponsor's responses to information requests that I reviewed appeared to be adequate and acceptable.

Background Summary

FDA CBER received on 9-JUL-2018 this Biologics License Application (BLA) from Grifols Therapeutics LLC (dated 9-JUL-2018) for their Immune Globulin Subcutaneous (Human), 20% (IGSC) product, XEMBIFY®, for the treatment of primary humoral immunodeficiency. The IGSC 20% manufacturing process is based on the currently licensed process used for the Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified (IGIV-C) product, Gamunex-C®, but includes an additional (b) (4) step to increase the protein concentration to 20%. The (b) (4) for IGSC 20% also includes the addition of polysorbate 80 to enhance the stability of the final drug product over its shelf-life.

Jennifer L. Reed, Ph.D. of PDB/DPPT/OTAT is the chair of this BLA submission. My CMC review focused on the following assigned (b) (4) Drug Product Specifications, Analytical Procedures and their Validation

Studies: Appearance, (b) (4), Polio Potency, Measles Antibody Potency, (b) (4)
The other (b) (4) Drug Product Specifications, Analytical
Procedures and their Validation Studies such as: Sterility, Pyrogen, pH of (b) (4) Protein Solution, Diphtheria Potency,
Protein Composition, Protein Concentration, (b) (4), Polysorbate 80,
(b) (4) Caprylate, Volumetric Fill Check, Immunoglobulin A (b) (4) were reviewed by
several assigned reviewers of DBSQ/OCBQ (see their Discipline Review memos). Osmolality, (b) (4)
were reviewed by Dr. Reed (see her Review memo). LACBRP/
DBSQ/OCBQ also reviewed the (b) (4) for in-support
testing purposes. Varsha Garnepudi of QAB/DBSQ/OCBQ reviewed the lot release protocol template.

Supplement Review Summary

IGSC 20% is a liquid preparation of human normal immunoglobulin intended for subcutaneous administration; the product has a protein concentration of 200 mg/mL, of which $\geq 98\%$ is IgG. The manufacturing process for IGSC 20% starts with the pooling of human (b) (4) Plasma. (b) (4)

; this IGSC 20% (b) (4) is aseptically filled into the appropriate glass vials, stoppered, and overseals applied. The sealed product vials are then incubated for (b) (4) at a pH of 4.1 to 4.8 prior to labeling and packaging. The product is then stored at 2-8 °C. Four fill sizes of 5 and 10 mL (in (b) (4) clear glass vials), 20 and 50 mL (in (b) (4) clear glass vials) will be made available. The formulation for the IGSC 20% final drug product was developed based on the knowledge acquired from the formulation of Grifols' currently licensed IGIV-C, 10% product, Gamunex-C®. The IGSC 20% formulation contains 10-40 µg/mL polysorbate 80 (PS80, as a stabilizer), 0.16 to 0.26 M glycine, pH 4.1 - 4.8, and a total protein content of 180-220 mg/mL.

Manufacture, aseptic filling, labeling, packaging, in-process and most of the lot release testing of IGSC 20% are performed at the (b) (4) facility.

A. Proposed (b) (4) Drug Product Specifications

The proposed (b) (4) Drug Product (DP) specifications were based on a total of (b) (4) lots of IGSC 20% produced and tested between 2014 and 2017. An additional (b) (4) final container lots were produced for stability studies.

I compared the proposed (b) (4) DP specifications of IGSC 20% with those of IGIV-C 10% (see Current files in STN 125046 folder) and three IGSC products made by other manufacturers. As of the writing of this review memo, there are 3 US-licensed IGSC products: CSL Behring's Hizentra (STN 125350), Baxalta/Shire/Takeda's Cuvitru (STN 125596) and Octapharma's Cutaquig (STN 125668).

Table 1: Proposed Specification for IGSC (b) (4) compared to those of IGIV-C (b) (4), other IGSCs

Test	Method SOP No./ Reference	IGSC 20%	IGIV-C 10%	Other IGSCs
Sterility	CS-000-BB-064 (b) (4)	No growth	No growth	None (Hizentra, Cuvitru, Cutaquig)

Table 2: Proposed Specifications for IGSC Drug Product compared to those of IGIV-C Drug Product, other IGSCs

Test	Method SOP No./ Reference	IGSC 20%	IGIV-C 10%	Other IGSCs
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Appearance	CS-000-BB-057 Visual Inspection (b) (4)	Clarity: clear or slightly opalescent During storage it may show formation of (b) (4)	Clarity: clear to opalescent Color: Colorless to pale yellow	Hizentra has separate release and end-of-shelf life specifications for appearance; Cuvitru has release specification for appearance; Cutaquig has release specifications for appearance and clarity

		(b) (4) Color: Colorless or pale yellow (b) (4)		
Diphtheria Potency	CS-000-BF-019 (b) (4) CFR	(b) (4)	(b) (4)	(b) (4) (Hizentra); (b) (4) (Cuvitru); (b) (4) (Cutaquig)
Glycine	CS-000-BC-036 (b) (4) Grifols (b) (4) /CFR specification: (b) (4)	0.16-0.26 M	0.16-0.24 M	N/A (Hizentra, Cutaquig); 0.20-0.30 M (Cuvitru)
(b) (4)				
Identity by (b) (4)	(b) (4)	Main component is gamma globulin	Main component is gamma globulin	(b) (4); Main component is IgG (b) (4); (b) (4)
Immunoglobulin A (IgA)	CS-000-BF-036 (b) (4)	(b) (4)		
(b) (4)				
Measles Potency	CS-000-BF-034 Neutralization Test (b) (4) CFR	(b) (4) x CBER Reference for a 20% IgG solution*	(b) (4) x CBER Reference (b) (4)	(b) (4) CBER (Hizentra); (b) (4) x CBER Ref Lot (b) (4) (Cuvitru); (b) (4) (Cutaquig)
(b) (4)				
pH of (b) (4) Protein Solution	CS-000-BC-012 pH (b) (4) Grifols (b) (4) /CFR: (b) (4)	4.1 to 4.8	(b) (4) 4.0 to 4.5 (shelf-life)	4.60 - 5.20 (Hizentra); 4.6 to 5.1 (Cuvitru); 5.0 - 5.5 (Cutaquig)
Polio Potency	CS-000-BF-034 Neutralization Test (b) (4) CFR	(b) (4) x CBER Reference for a 20% IgG solution*	(b) (4) x CBER Reference (b) (4)	(b) (4) CBER (Polio (b) (4) (Hizentra); (b) (4) x CBER Ref Lot (b) (4) (Cuvitru); (b) (4) (Polio (b) (4) (Cutaquig)
Polysorbate 80	CS-000-BC-023 (b) (4) Method Grifols	10-40 µg/mL	(b) (4)	8-30 mg/L (Hizentra); (b) (4) (Cuvitru); (b) (4) (Cutaquig)
Protein Concentration	CS-000-BC-052 (b) (4) Method (b) (4)	18-22%	9.0-11.0%	(b) (4) (Hizentra); (b) (4) (Cuvitru); (b) (4) total protein, (b) (4) mg/mL IgG (Cutaquig)
Protein Composition	CS-000-BC-200 (b) (4) CFR (b) (4) IgG	≥ 98% gamma globulin	Minimum 98% gamma globulin	≥ 98.0% (Hizentra); NLT 98% (Cuvitru); ≥ 96% (Cutaquig)
Pyrogen	CS-000-BB-125 Rabbit Pyrogen Test USP/CFR	Must comply	USP/21 CFR 610.13 (b)	(b) (4) (Hizentra); (b) (4) (Cuvitru); (b) (4) (Cutaquig)
(b) (4) Caprylate	CS-000-BC-028 (b) (4)	(b) (4)	Maximum 216 µg/mL	(b) (4)

	Grifols			(b) (4)
Sterility	CS-000-BB-064 (b) (4) CFR(b) (4).	No growth	(b) (4)/21 CFR 610.12	No microbial growth detectable (vials/ syringes)(Hizentra); No growth (Cuvitru); Sterile (Cutaquig)
Volumetric Fill Check	CS-000-BC-007 Volumetric Method (b) (4)	Minimum stated volume	Minimum stated volume	None (Hizentra, Cuvitru, Cutaquig)
(b) (4)				
Packaged Final Container				
(b) (4)		Main component is gamma globulin	Main component is gamma globulin	(b) (4) Main component is IgG (b) (4)
Protein Concentration	CS-000-BC-052 (b) (4) Method (b) (4)	None	Confirmed as (b) (4)	(b) (4) (Hizentra); (b) (4) (Cuvitru); (b) (4) (Cutaquig)

(b) (4) United States Pharmacopeia (USP) – based on the current editions

*The words, “for a 20% IgG solution”, was added later for clarification (see response to Information Request no. 23, Amendment 29, STN 1256830.29, received 1-APR-2019)

Reviewer’s Comments: (1) For the majority of the specifications, the proposed specifications for IGSC 20% appeared to be similar or not significantly different from those set for the other IGSC products. Also, a few IGSC 20% specifications were just (b) (4) of what were set for IGIV-C 10%, which are acceptable where applicable. However, no specifications for (b) (4) were set for IGSC 20%. Two out of the 3 US-licensed IGSC products have set specifications for (b) (4) (see DP specifications of (b) (4))

(2) In addition, no specification was set for Osmolality for both IGSC 20% and IGIV-C 10%. Of the 3 US-licensed IGSC products, only Cuvitru has a set Osmolality specification (b) (4) mOsmol/kg).

(3) The (b) (4) specification of IGSC 20% also seemed to be set quite low compared to that of IGIV-C 10% and slightly lower than the specifications of the other IGSC products.

(4) The wording of the Appearance specification could be improved, particularly, the term (b) (4)

An Information Request (IR) was sent to the firm on 18-SEP-2018 regarding the missing specifications (mentioned above in the Reviewer’s Comments), however, Dr. Dorothy Scott, Branch Chief, PDB/DPPT/OTAT, decided not to include (b) (4) in the IR. To discuss the IR further, Dr. Reed and Dr. Scott had a teleconference with the firm on 1-OCT-2018 (see teleconference summary in Product Correspondence STN 125683/2.0, received 2-NOV-2018). The sponsor provided responses to the IR in STN 125683/2.0, which contained the following revised proposed specifications and justifications (see Table 3 below):

Table 3: Summary of Revised Proposed Specifications for IGSC 20% (compared with other IGSCs)

Assay (Method)	Initial Proposed Specification	Revised Proposed Specification	Justification for Proposed Specification	Specifications of Other IGSCs
(b) (4)	(b) (4)			
Osmolality (CS-000-BC-032)	None	280 to 404 mOsmol/kg	(b) (4)	None (Hizentra); (b) (4) mOsmol/kg (Cuvitru); None (Cutaquig)
(b) (4)				

(b) (4)

3. **Polio Potency – Specification for drug product:** (b) (4) x CBER Reference (for polio (b) (4) virus)

Method (CS-000-BF-034): (b) (4)

Reviewer's Comments: (1) The polio and measles antibody neutralization tests are combined in this one method SOP, because the assay principle is the same. However, the method SOP version (version 24.0, effective 25-SEP-2017) that was submitted for this current BLA still mentions poliovirus (b) (4). For Gamunex-C, Grifols has already (b) (4) the use of poliovirus (b) (4) and only uses poliovirus (b) (4) in the Poliomyelitis Neutralization Test (STN 125046/1545, submitted 13-NOV-2017, approved 15-MAR-2018), therefore, this should also apply to the IGSC 20% product. An Information Request (no. 29) was sent to the sponsor on 22-MAY-2019 to request for the most recent version of the method SOP that should not contain any mention of poliovirus (b) (4) and to confirm that their Polio Potency specification applies to testing anti-poliovirus (b) (4) antibodies only. The sponsor provided the latest version of the method SOP (version 26.0, dated 12-DEC-2018) and confirmed that they only test for anti-poliovirus (b) (4) antibodies. I checked the version 26.0 method SOP and confirmed that all references to poliovirus (b) (4) have been removed (see STN 125683/0.38, received 31-MAY-2019).

(2) An Information Request (no. 23) was sent to the sponsor on 24-MAR-2019 by Dr. Reed asking for clarification of the Polio Potency specification on whether the (b) (4) x CBER Reference" refers to the product that has been (b) (4). The sponsor confirmed that the Polio Potency specification of (b) (4) x CBER Reference applies to the IGSC 20% product that is (b) (4) during analytical testing. The (b) (4) protein reference (CBER Lot (b) (4)) obtained during testing is (b) (4).

In order to provide additional clarity, Grifols updated the wording for both Polio and Measles Potency specifications by adding the words, "for a 20% IgG solution" (see STN 125683/0.29, received 1-APR-2019).

Method Validation (GTI_AMVP-000041): The sponsor performed validations of their method SOP:

Accuracy/ Specificity: (b) (4)

Passed.

Linearity/ Range: (b) (4)

Passed.

Precision (Intermediate Precision): (b) (4)

Passed.

Precision (Repeatability): (b) (4)

Passed.

Reviewer's Comments: Overall, the method validation study design appears to be adequate and acceptable. The method validation study data appears to be acceptable, even if the sponsor did not provide any robustness study data. Small variations in performing the test method could have been evaluated for robustness. On the other hand, this test method is already being used to test Polio Potency of other Immune Globulin products like IGIV-C 10% and IGIM-C (in process materials and clinical lots).

4. Measles Potency – specification for drug product: (b) (4) x CBER Reference for a 20% IgG solution

Method (CS-000-BF-034): (b) (4)

Reviewer's Comments: (1) Lot (b) (4) and the (b) (4) test methods have been reviewed in a previous Trans-
BLA submission (see STNs 101134/5446 and 125046/1000, approved 14-DEC-2011).

(2) The polio and measles antibody neutralization tests are combined in this one method SOP, because the assay principle is the same. The sponsor provided the latest version of the combined method SOP (CS-000-BF-034, version 26.0, dated 12-DEC-2018) in response to IR no. 29 that was sent on 22-MAY-2019 (see STN 125683/0.38, received 31-MAY-2019).

Method Validation (GTI_AMVR-000013): The sponsor performed validations of their method SOP:

Accuracy: (b) (4)

Passed.

Linearity: (b) (4)

Passed.

Range: (b) (4)

Passed.

Precision (Intermediate Precision): (b) (4)

Passed.

Precision (Repeatability): (b) (4)

Passed.

Specificity: (b) (4)

. Passed.

Detection Limit and Quantitation Limit: (b) (4)

Passed.

Reviewer's Comments: Overall, the method validation study design appears to be adequate and acceptable. The method validation study data appears to be acceptable, even if the sponsor did not provide any robustness study data. Small variations in performing the test method could have been evaluated for robustness. On the other hand, this test method is already being used to test Measles Potency of other Immune Globulin products like IGIV-C 10%, IGIM-S/D, and IGIM-C (in process materials and clinical lots) and the plasma pools (e.g., (b) (4) Pool).

5. (b) (4)

Reviewer's Comments: Since this test is based on a (b) (4) method, only verification was needed (i.e., not a full validation) to demonstrate that they could perform the test as described. The method validation study data appear to be acceptable, however, the sponsor did not perform any robustness studies.

6. **Appearance - Specification for drug product:** Clarity: Clear or slightly opalescent. During storage it may show formation of a small amount of visible particulate matter; Color: Colorless or pale yellow (revised from what was submitted in Original BLA, removed (b) (4))

Method (CS-000-BB-057): (b) (4)

Additional Information: As part of routine procedures, Grifols removes any vials where particles are observed during the 100% visual inspection performed prior to lot release of all liquid products. At this time, Grifols has observed (b) (4)

Reviewer's Comments: (b) (4) was originally included in the DP Appearance specification to align with the (b) (4) for subcutaneous immune globulin. Grifols agreed to remove (b) (4) from the specification to reflect the actual product appearance of IGSC 20% lots made to date.

Method Validation (N/A): Inspection according to standard procedure

APPENDIX

Supporting documents submitted in this BLA (STN 125683/0, received 9-JUL-2018)

- a. Cover Letter (dated 9-JUL-2018)
- d. Section 1.11.1 Quality Information Amendment
- e. Section 2.3 Drug Substance
- f. Section 2.3.P.5 Control of Drug Product
- g. Section 3.2.S.2.3 Control of Materials
- h. Section 3.2.S.5 Reference Standards or Materials
- i. Section 3.2.P.5.1 Specifications – GTI_PS-000083 Specifications for Finished Product Immune Globulin Subcutaneous (Human), 20% (version 1.0, effective 01-JUN-2018)
- j. Section 3.2.P.5.2 Analytical Procedures
- k. CS-000-BF-049 Determination of (b) (4) (b) (4) According to (b) (4) (v.9.0, effective 15-SEP-2017)
- l. CS-000-BB-057 Determination of Product Appearance with Color Evaluation by Visual Comparison – QC Sterility Lab (v.20.0, effective 25-AUG-2017)
- m. CS-000-BF-051 Detection of (b) (4) (v.18, effective 15-SEP-2017)
- n. CS-000-BF-061 Determination of (b) (4) (v.7.0, effective 6-MAY-2016)
- o. CS-000-BF-034 Poliomyelitis and Measles Neutralization Test in (b) (4) (v. 24.0, effective 25-SEP-2017)

- p. Section 3.2.P.5.3 Validation of Analytical Procedures (dated 24-MAY-2018)– *many typographical errors on this page (e.g., QOAS, instead of QCAS, (b) (4) validation report is incorrectly linked to (b) (4) validation report)*
- q. QCAS-2017-101 Validation of Determination of (b) (4) According to the (b) (4) for IGSC, 20% Drug Products (approved 8-AUG-2017)
- r. QCAS-2017-093 Validation of Detection of (b) (4) (approved 8-AUG-2017)
- s. QCAS-2014-127 Validation of Determination of (b) (4) According to the (b) (4) 20% IGSC (approved 17-DEC-2014)
- t. GTI_AMVR-000013 Validation of Measles Neutralization Test in (b) (4) (approved 3-MAY-2018)
- u. GTI_AMVP-000041 Validation of Poliomyelitis Neutralization Test in (b) (4) for IG-S/D, 10% IGIV-C, IG-C, and IGSC 20% (approved 28-MAR-2018)
- v. Section 3.2.P.5.6 Justification of Specifications
- w. BA-RTEC-000082 IGSC 20% Justification of Specifications (3-MAY-2018)
- x. Section 3.2.P.6 Reference Standards or Materials
- y. Qualification of the Standard, (b) (4) (18-MAY-2018) – for (b) (4)
- z. GTI_STDR-000003 (b) (4) Polio (b) (4) Standard Qualification Report (23-APR-2018)
- aa. GTI_STDR-000004 (b) (4) Measles Standard Qualification Report (23-APR-2018)

Supporting documents submitted in this BLA (STN 125683/2.0, received 2-NOV-2018)

- a. Cover Letter (dated 1-NOV-2018)
- b. Section 1.12.11 Basis of Submission Statement (dated 30-OCT-2018) – *contains the summary of teleconference held on 1-OCT-18 between the firm and FDA to discuss the DP specifications as well as the proposed revised specifications*
- c. Section 1.12.11 Attachment 1: Test data from (b) (4) IGSC 20% lots – (b) (4), Osmolality, (b) (4)

Supporting documents submitted in this BLA (STN 125683/0.27, received 27-MAR-2019)

- a. Cover Letter (dated 27-MAR-2019) – Response to IR no. 21
- b. Section 1.12.11 Basis for Submission – Response to IR # 21
- c. Attachment 1 – FDA Information Request #21 (19-MAR-2019)
- d. Section 2.3.P Quality Overall Summary, Drug Product
- e. GTI-PS-000083 Specifications for Finished Product Immune Globulin Subcutaneous (Human), 20% (28-FEB-2019)
- f. Section 3.2.P.5.2/3.2.P.5.3 Analytical Procedures and Validations (IGSC 20%)(24-MAY-2018)
- g. CS-000-BB-057 Determination of Product Appearance with Color Evaluation by Visual Comparison – QC Sterility Lab (01-MAR-2019)
- h. CS-000-BC-032 Osmolality by (b) (4) (27-FEB-2019)
- i. CS-000-BF-035 (b) (4) for Immunoglobulin Products (27-FEB-2019)
- j. CS-000-BF-069 (b) (4) Assay Using an (b) (4) Assay (27-FEB-2019)
- k. GTI_AMVR-000052 Validation Summary Report for Osmolality by (b) (4) for 20% IGSC (21-JAN-2019)
- l. GTI_AMVR-000064 Validation of Test Method (b) (4) for Immunoglobulin Products” for 20% IGSC (27-FEB-2019)
- m. GTI_AMVR-000052 Validation Report for (b) (4) Assay Using an (b) (4) Assay (27-FEB-2019)
- n. Batch Analysis (GTI_PS-000083)(14-FEB-2019)
- o. BA-RTEC-000082 IGSC20% Justification of Specifications (07-MAR-2019)

Supporting documents submitted in this BLA (STN 125683/0.28, received 29-MAR-2019)

- a. Cover Letter (dated 29-MAR-2019) – Response to IR no. 19 Revise the Lot Release Protocol
 - b. Section 1.12.11 Basis for Submission – Lot Release Protocol
- Final Review STN 125683/0 ML Virata-Theimer

- c. Attachment 1 – Information Request no. 19 for Lot Release Protocol
- d. IGSC20 CBER Protocol Template GTI_032719

Supporting documents submitted in this BLA (STN 125683/0.29, received 1-APR-2019)

- a. Cover Letter (dated 1-APR-2019) – Response to IR no. 23 Clarification of Polio Potency Spec
- b. Section 1.12.11 Basis for Submission – Response to IR # 23 Clarification of Polio Potency Spec
- c. Attachment 1 – Information Request # 23
- d. GTI-PS-000083 Specifications for Finished Product Immune Globulin Subcutaneous (Human), 20% (29-MAR-2019)

Supporting documents submitted in this BLA (STN 125683/0.30, received 1-APR-2019)

- a. Cover Letter (dated 1-APR-2019) – Response to IR no. 24 (b) (4) SOP Questions
- b. Section 1.12.11 Basis for Submission – Response to IR # 24 for (b) (4) SOP
- c. Attachment 1 – Information Request # 24
- d. Attachment 2 – Biological Control (b) (4) IGIV-C (b) (4) Control Biological Control Qualification Report (version 00, dated 12-FEB-2007)
- e. Attachment 3 – Biological Control (b) (4) Qualification Report (version 1.0, dated 30-JUL-2015)
- f. Attachment 4 – Biological Material (b) (4) Qualification Report (version 00, dated 4-APR-2008)
- g. Attachment 5 – Biological Material (b) (4) Qualification Report (version 00, dated 4-APR-2008)

Supporting documents submitted in this BLA (STN 125683/0.38, received 31-MAY-2019)

- a. Cover Letter (dated 30-MAY-2019) – Response to IR no. 29 Polio Method SOP
- b. Section 1.12.11 Basis for Submission – Response to IR no. 29 Polio Method SOP (dated 30-MAY-2019)
- c. Attachment 1 – Information Request # 29
- d. CS-000-BF-034 Poliomyelitis (b) (4) and Measles Neutralization Test in (b) (4) (v. 26.0, effective 12-DEC-2018)

References:

STN 125046 Current files in the EDR
 STN 125350 DP Specifications (May 2018)
 STN 125596 DP Specifications (October 2018)
 STN 125668 DP Specifications (October 2018)