



FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

To: File for BLA STN# 125562/0

From: Yonggang Wang, Ph.D., Visiting Associate, CBER/OBRR/DHRR/LPD

Through: Michael C. Kennedy, Ph.D., Team Leader, CBER/OBRR/DHRR/LPD

Cc: Thomas J. Maruna, RPM, CBER/OBRR/DBA/LRPM/HFM-380
Tracy Tilghman, RPM, CBER/OBRR/DBA/LRPM/HFM-380

Applicant: Emergent BioSolutions (Former Cangene Corporation)

Product: Anthrasil™; Anthrax Immune Globulin Intravenous (Human) [AIGIV]

Subject: Final Memo: Original BLA, assigned CMC topics - Assay Validation and Stability Studies

RECOMMENDATIONS:

This original BLA is recommended for approval, based on evaluation of assigned topics, with the following Post Marketing Commitments:

1. Cangene commits to (b) (4) [REDACTED] This change will be submitted, with validation data, as a CBE-30 by March 25, 2016.
2. Cangene commits to (b) (4) [REDACTED] The validation report will be submitted to CBER as a CBE-30 by March 25, 2016.

EXECUTIVE SUMMARY:

This review is limited to specific areas of the Chemical, Manufacturing, and Control issues of this BLA, particularly the following sections:

1. Analytical Methods and Assay Validation Studies.
All the analytical methods and assays, except (b) (4) [REDACTED], were found to be validated and documented appropriately and acceptable for the testing of (b) (4) [REDACTED] and final products. A PMC is generated in order to improve the product quality (b) (4) [REDACTED]
2. Stability Studies:

Two materials were tested in this stability study, i.e., Drug Substance and Drug Product. The dating period was evaluated based on the data from real-time, accelerated and stress condition studies and summarized as follows:

- 1) (b) (4)
- 2) For **Drug Product** stored at ≤ -15 °C, a dating period of **72 months** was proposed based on 60 months stability data from (b) (4) lots, of which (b) (4) were manufactured consecutively, and found to be acceptable. One (b) (4) has a predicated stability failure time of (b) (4) for (b) (4) content, and additional information is requested for further evaluation.

BACKGROUND INFORMATION:

This original BLA submission was received on July 25, 2014. AIGIV is an immune globulin product obtained from fractionated pooled source plasma from donors immunized with Anthrax vaccine adsorbed (AVA) vaccine (BioThrax). This hyperimmune product contains polyclonal antibodies that neutralize the lethal toxin of B. anthracis and indicates for the treatment of toxemia associated with inhalational anthrax. AIGIV is manufactured and formulated with the same method as for other Cangene’s hyperimmune IGIV product, i.e., WinRho SDF, HepaGam B and VIGIV. The final product is supplied in 50 ml (b) (4) glass vials with no less than 60 Units/Vial activities based on Tissue Neutralization Assay, and is frozen and stored at ≤ -15 °C.

CMC REVIEW SUMMARY:

This submission contained the following validation protocols and final reports which were assessed in this review (Table1):

Table 1. List of Analytical Method and Assay reports.

Standard Test Method	Pharmacopodia	Method	Validation Reports
500206	(b) (4)	(b) (4)	VAL_MV_B54_v1_ADD004
501023	(b) (4)	(b) (4) Protein Assay	MV_0044_rep_v2
501295	(b) (4)	Quantitation of Maltose in Hyperimmune Preparations (b) (4)	MV_0054_rep_v3
500054	(b) (4)	(b) (4)	MV_0068_rep_v2
500174	(b) (4)	(b) (4)	VAL_MV_175_rep_v1
500151a	(b) (4)	TnBP Quantitation and Limit Assay	Limit: MV 38, MV 38B Quantitation: MV 39, MV 39B
500156a	(b) (4)	(b) (4)	Limit: MV 36, MV 36B Quantitation: MV 37, MV 37C
520100	(b) (4)	Appearance by Visual Inspection	Not applicable
500174	(b) (4)	(b) (4)	VAL_MV_175_rep_v1
501016	(b) (4)	(b) (4)	MV 61; MV 61D
520127	(b) (4)	(b) (4)	MV0229

501003	(b) (4)	(b) (4)	MV 4, 4A, 4B, 4F, 4I
520033	(b) (4)	(b) (4)	MV_0160_rep_v3
500173	(b) (4)	(b) (4)	MV_0152
520123.01	(b) (4)	(b) (4)	MV_0227
501032	(b) (4)	(b) (4)	VAL MV 22
501001	(b) (4)	pH Measurement	Not applicable
501295	(b) (4)	Quantitation of Maltose in Hyperimmune Preparations (b) (4)	MV_0054_rep_v3
520001	(b) (4)	General Safety CFR 610.11 (Biologics)	Not applicable

REVIEW OF ASSAY VALIDATIONS:

All the analytical methods listed above except potency (b) (4) were previously developed for the assay of the human plasma, (b) (4) or finished product samples for hyperimmune product, such as, WinRho SDF, HepaGam B and VIGIV, and re-validated for the purpose of AIGIV product.

1. Potency assay – Validation protocol MV_B53, B54 and STM500206 (b) (4) for Detection of Bacillus Anthracis PA-Specific IgG”.

Two methods were adapted in the potency assay: TNA and (b) (4). Review of (b) (4) method is deferred to Miriam Ngundi (OVR). TNA method is used to determine the potency activities, and (b) (4) method is used to quantify *B. Anthracis* PA-specific antibodies in both human plasma, in-process and finished product samples, and to demonstrate certain consistency of manufacturing.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2. Total Protein: Validation protocol MV_0044_rep_v2 and STM501023 (b) (4) Assay”.

This test method was previously validated for the detection of total proteins for the following products: WinRho SDF, Varicella Zoster Immune Globulin, VIG, HepaGam B, and is currently validated to qualify the total protein in-process and finished AIGIV product samples. The samples were prepared with the maximum concentration of excipients expected in the matrix and spiked to cover the range of the calibration curve (b) (4)

- (b) (4)

3. Excipients: Maltose Validation Report MV_0054_rep_v3, and STM 501295 “Quantitation of Maltose in Hyperimmune Preparations by (b) (4)

This validation report covers the method of determination of maltose content by (b) (4)

- (b) (4)

4. Excipients: Polysorbate 80 Validation Report MV_0068_rep_v2, and STM 500054 “(b) (4) of PS80.”

This validation report covers a (b) (4) method in measuring the amount of PS80 present in solution. The in-house standards are from multi-compendial grade PS80.

- (b) (4)

5. Purity Assay: Validation Report MV_175_rep_v1, and STM 500174 (b) (4)

(b) (4)

[Redacted]

6. Tri-n-Butyl Phosphate (TnBP) STM 500151

(b) (4)

[Redacted]

7. Triton X-100 Validation Report MV_0235_rep_v2, and STM 500156 “TX-100 Quantitation and Limit Test)

(b) (4)

[Redacted]

8. Appearance STM 520100

This is a visual inspection procedure in line with (b) (4) The presence

3 pages determined to be not releasable: (b)(4)

(b) (4)

16. pH Measurement

The (b) (4) determination of pH is a compendia method, as outlined in (b) (4) (b) (4) Determination of pH.

17. General Safety

This method follows (b) (4) and is compliant with the Code of Federal Regulations (CFR) 610.11 Biologics.

REVIEW OF PRODUCT STABILITY:

The purpose of these stability studies is to provide guidance for assessing the proposed storage conditions and establishing the shelf life, without sacrificing the specified product's potency, purity and quality. Two types of materials are included in this stability studies, i.e., Drug Substance and Drug Product.

1. Drug Substance (Bulk Product)

(b) (4)

[Redacted content]

1 page determined to be not releasable: (b)(4)

2. Drug Product (Final Container Product)

Stability Concept and Protocol:

AIGIV final product is filled into 50 mL (b) (4) glass vials with 20 mm (b) (4) bromobutyl rubber stopper, aluminum seals and 20 mm plastic flip-off cap, and stored at ≤ -15 °C. Each vial contains ≥ 60 Units of activity as determined by TNA potency assay. The filled volume is calculated based on a target of (b) (4) U/vial. For real-time stability studies, the (b) (4) are placed in a stability program with full ICH (Q1A) testing frequencies, i.e., 0,3,6,9,12,18,24 months and annually thereafter up to (b) (4) months. (b) (4)

(b) (4). For accelerated stability studies, (b) (4) lots were tested. The following test parameters are included:

- Appearance (Clear or slightly opalescent colorless liquid, free of foreign particles)
- (b) (4)
- Bacterial Endotoxin (b) (4)
- Sterility (meets 21 CFR 610.12 requirements)
- Potency – TNA (≥ 60 U/mL)
- Potency – (b) (4)
- pH- Neat (5.0-6.5)
- pH- (b) (4) (5.0-6.5)

Since June 15, 2005, totally (b) (4) filling lots were produced, of which (b) (4) lots are stockpiled in SNS. The selection of lots for stability studies are as follows:

- (b) (4) lots with stability data up to 60 months were selected for shelf life determination, which are (b) (4)
- (b) (4) lots with 24-54 months data were selected for supporting analysis, which are (b) (4)
- The remaining (b) (4) lots not being included in this study are:
 - (b) (4) lots are not stored at SNS, which are (b) (4) (not for market purpose).
 - (b) (4) lot was quarantined as a result of an out of specification (OOS) potency result at (b) (4) months, which is (b) (4).
 - (b) (4) lots were filled based on volume, which are (b) (4)
 - (b) (4) most recent lots with stability data less than 2 testing time points, which are (b) (4).
- For accelerated studies, the lots were selected from the remaining (b) (4) lots.
- Lot (b) (4) was selected for (b) (4) studies: For (b) (4)

Reviewer's comments: The remaining (b) (4) lots not being included in this study have a

stability date more than 72 months, except the one with less than 2 testing time points and (b) (4) (this lot was not intended for market purpose). The individual lots stockpiled at SNS will have different shelf life as has done for VIGIV product. Currently the lot with the longest dating period of VIGIV has been approved for (b) (4). In this BLA submission, an initial shelf life of 60 months is requested.

(b) (4)

^a Filled based on volume

^b TNA potency specification of (b) (4) U/vial

^c Lot was filled into a (b) (4) vial rather than 50 mL vial, and will not be stocked in SNS.

Stability Results:

a) Real Time Stability:

The data from (b) (4) “shelf life determination” lots and (b) (4) “supporting analysis” lots were plotted and shown in Figure 2 and 3, respectively. All parameters are relatively stable and no deviation was noticed except the total protein level for lot (b) (4), which originally contained more than (b) (4) total proteins. For another (b) (4) lots, (b) (4) which are not included for shelf life determination, all parameters monitored up to 72 to (b) (4) months met the acceptance criteria.

b) Accelerated Stability:

Potency –TNA and (b) (4) have a trend of increase over time which might be due to assay variation. Although there is no OOS within 6 months test intervals, the 95% confidence interval intersected with the acceptance criteria at 5.2 months indicating ACA might be one of the limit factor in determination of shelf life over time.

c) Stress Stability:

All parameters monitored up to 60 months met acceptance criteria. Out of trend value was noticed for this single lot at 9 months without clear reason being identified (b) (4) [REDACTED]. Nevertheless the data after 9 months returned to normal range indicating a possibility of testing error or variation.

d) Regression analysis:

The failure time for individual monitored parameters was estimated using (b) (4) software per ICH guideline Q1E for 6 “shelf-life determination” lot (Table 4). None of the parameters predicate a failure within proposed initial shelf life of 72 months. In addition, the analysis indicated that the following critical parameters have the same slopes within (b) (4) lots, i.e., (b) (4) [REDACTED], potency – TNA, total protein, pH- (b) (4) [REDACTED], and (b) (4) [REDACTED].

Reviewer’s comments: Regression analysis based on the real time stability studies supported the proposed initial shelf life of AIGIV, which is 72 months at (b) (4) [REDACTED]. A one year extrapolation of the long-term stability (60 months) is available from [REDACTED] lots. Since most of the supporting lots do not have 60 months data available, the prediction of shelf life can’t be used to extrapolate up to 72 months. However the same slope for most of the parameters indicates the consistency of the stability among batches manufactured in different times. The limit factor influencing the long term stability will be potency-TNA (predicated failure time (b) (4) [REDACTED]), which is the same case as for VIGIV products. Please note though that with the accumulation of the data close to the (b) (4) [REDACTED] the prediction may change. Nevertheless the (b) (4) [REDACTED] is still above (b) (4) [REDACTED] – the targeted long-term stability time. It is very likely that the same strategy applied to VIGIV will be used to extend the (b) (4) [REDACTED] lots stockpiled at SNS with individual shelf life.

(b) (4) [REDACTED] (filled on 09/24/2010) has a predicated failure time of (b) (4) [REDACTED] for parameter of (b) (4) [REDACTED]. No reason was indicated. (b) (4) [REDACTED]. The next testing point is 60 months under reduced testing plan, and this lot will be asked to be tested again in 2015. In addition, a full testing plan should be considered for this lot.

(b) (4)

(b) (4)

Figure 2. Drug Product Real-Time Stability Analysis - (b)(4) selected lots (The inner and outer dotted lines are 95% CLs for the regression line and for the individual points; the dotted blue line indicated the limit of specification).

(b) (4)

3 pages determined to be not releasable: (b)(4)

(b) (4)

INFORMATION REQUEST SENT TO THE SPONSOR:

The following IR was sent to the sponsor on Nov. 5 2014:

1. *There is a formatting issue with the page 30 in your file of STM 500206, where the text was overlaid and covered by a graph. Please correct the error and provide an updated file.*

Sponsor's response: The error was corrected and a new file was supplied.

2. *Please specify the microplate being used in your (b) (4) potency assay.*

Sponsor's response: The (b) (4) are used. The corresponding section was updated with (b) (4) description.

3. *A (b) (4) was qualified to be used in STM 501016, but it was not used in STM 520127. Please explain why a (b) (4) is not necessary in STM 520127, although the same type of (b) (4) are used in both STM 501016 and STM 520127 methods. In addition, please indicate if a life time for the (b) (4) has been defined, if not, please provide your justification.*

Sponsor's response: The sponsor stated that the life-time is not defined and will be replaced when the system suitability test failed. Approximately (b) (4) method (STM 520127) provides more conservative and consistent (b) (4) results in comparison to the current (b) (4) method (STM 501016). The LLOD for (b) (4) for both methods and for (b) (4) respectively.

Reviewer's comments: A (b) (4) is usually applied in order to (b) (4) do not have to be used. An (b) (4)

4. Please predict when the legacy method STM501016 will be replaced by the new method STM 520127, and estimate the impact of this method change on your ongoing stability studies.

Sponsor's response: STM 520127 will be implemented upon approval of this BLA application and no impact is anticipated for the ongoing stability studies.

Reviewer's comments: These two methods have different detection limit and sensitivity, which will potentially impact the test results and variation.

5. Please provide the following documents:

- a. Cangene Method Validation Addendum # B53-A Report.
- b. Method Validation No. MV_034 for method STM 501500.
- c. Method Validation No. MV_0152 for method STM 500173.
- d. Method Validation No. MV_0160 for method STM 520033.

Sponsor supplied the corresponding documents for review.

The following IR was sent to the sponsor on Nov. 7 2014:

1. Please provide the SOP and validation report for your (b) (4). Please indicate if this (b) (4) method has been calibrated with one of the following (b) (4), and the limit of assay sensitivity is below (b) (4). If so, please provide all the available data for AIGIV lots testing measured in units of the (b) (4). If not, please provide a timeline for when Cangene can supply this data.

Sponsor's response: The (b) (4) test STM 520123 was validated in MV_0227 used a commercially supplied (b) (4). A calibration of this commercial standard against (b) (4) was performed with a calibrated ratio of (b) (4). Both the commercial standard and (b) (4) are valid references for use in the assay. All AIGIV lots originally tested using a pre-validated version of the (b) (4) was retested with the new methods. A table of retest assays' results were provided (table 5). The LLOQ is (b) (4).

In initial discussion with the FDA, it was proposed that potentially acceptable (b) (4) reference IGIV product. Using the mean Cangene test results for Lot (b) (4)

1400mU/dose, i.e., 20 mU/kg.

