

From: Maruna, Thomas
Sent: Friday, November 21, 2014 2:04 PM
To: Allison Kennedy (akennedy@ebsi.com)
Cc: Tilghman, Tracy (Tracy.Tilghman@fda.hhs.gov); Ngundi, Miriam; Fisher, Robert; Pierce, Leland Ross
Subject: Information Requested: BLA 125562/0 - Please Respond by December 1, 2014
Importance: High

Cangene Corporation [Emergent Biosolutions]
Attention: Ms. Allison Kennedy
November 21, 2014
Sent by email

Dear Ms. Kennedy:

We are reviewing your July 25, 2014 biologics license application (BLA) indicated for the treatment of adult and pediatric patients with toxemia associated with inhalational anthrax for the following:

STN	Name of Biological Products
BL 125562	Anthrax Immune Globulin Intravenous (Human)

We determined that the following information is necessary to continue our review:

The following comments pertain to the document "Response to FDA Information Request Dated October 6, 2014". The original CBER comment is in bold. Additional comments regarding your responses are in plain text. Cangene should maintain the CBER comment numbering to facilitate review of responses.

CBER Comment 3.i

On Page 4 you state that this report summarizes the original validation MV B55 and all associated addendums/amendments. Please provide the complete validation reports listed in Table 1-1 that support assay performance using the current SOP for the three applicable products indicated on page 9 (liquid formulation, (b) (4) and pooled plasma/donor plasma samples) or indicate where the reports can be found.

On page 7 of 42 of your response, you state B55-B, B55-F and VAL_MV_B55_rep_v8 validation reports support the assay performance for the quantitation of liquid formulated AIGIV bulk/finished product samples. While Method Validation #B55 supports assay performance for samples in concentration range (b) (4), Validation Reports B55-B, B55-F and VAL MV B55 rep v8 do not adequately support assay validation for samples ranging from (b) (4)

- i) Please clearly describe how repeatability and intermediate precision, dilutional linearity and robustness of the assay were assessed for samples in (b) (4) range.
- ii) Please justify how validation, for samples ranging (b) (4) were bridged to the re-optimized levels of (b) (4) used in the later validation studies.
- iii) Please provide data to support the stability of the assay from the time of validation to the analysis of AIGIV for lot release and stability testing.

CBER Comment 3.vi.

Table 3-4, page 11 lists (b) (4)

as the only critical reagents. We consider the following reagents/materials to be critical for TNA assay performances: (b) (4)

Please provide the qualification protocol with acceptance criteria for each of the above critical reagents.

On page 16 of 42 of your response you state that different lots of (b) (4) have been observed to be more consistent than (b) (4) and have not affected performance of the assay. You also state that provided that new lots of (b) (4) meet supplier specifications, they are used at the validated fixed concentration in the assay without further qualification.

This statement is in contradiction to your summary of Method Validation #B55-F where you state that changes to the method include an (b) (4) required. (b) (4) is a critical reagent in potency determination since (b) (4) directly interacts with your product. Please develop a protocol that will be used to qualify new lots of (b) (4). Please indicate when the SOP will be in place for use.

On page 16-17 of 42, you state that a new reference/internal control is assayed as an unknown against the current reference standard or against a CDC reference a minimum of (b) (4) times and averaged to obtain a potency value. Please describe the performance characteristics that are assessed during qualification of the new reference to ensure that the introduction of the new reference does not alter the precision or accuracy of the assay.

CBER Comments 4.vii. and 4.viii.

vii. On Pages 54-55, section 7.2.2: you list the key suitability criteria for the assay. Please justify how the current suitability criteria adequately control the assay performance with regard to the reference standard curve and the similarity of the reference curve to the test sample curve. Please also describe how the limits for the internal control were derived.

viii. Please describe how the estimate of potency is calculated.

Page 21 of 42 indicates that, to assess similarity between test sample (TS) or internal control (IC) curve and reference standard (RS) curve, curve fit parameters A, B, D and G are constrained to the same values determined for the RS and the Chi-Square analysis is performed on the

constrained TS or IC curve. Please provide the acceptance criteria for A, B, D and G parameters of the RS and for Chi-Square of TS versus RS.

**CBER Comment 5.i.b. Regarding the Toxin Neutralization Assay (TNA) for Quantitation of Anthrax Immune Globulin (AIG) in Non-Clinical Rabbit Serum Samples:
[Please provide] Qualification protocols with acceptance specifications for all critical reagents**

In your response on pages 23-25 of 42 you refer to QDrPA. Please explain what is meant by QDrPA and how it differs from rPA.

**CBER Comment 5.i.d. Regarding the Toxin Neutralization Assay (TNA) for Quantitation of Anthrax Immune Globulin (AIG) in Non-Clinical Rabbit Serum Samples:
[Please provide] Criteria for long-term assay stability**

On page 27 of 42 you state that no specific long-term assay stability criteria were defined in the method SOP 87.040.0008 or the initial validation protocol, and long-term assay stability is ensured by the combination of the different aspects that either have been evaluated in validation addendum studies (sample stability) or are being tracked on a recurring basis (reference standard stability).

Sample stability studies do not provide sufficient data to assure assay stability during the life-time of the assay. Long-term assay stability is assessed by tracking the potency of the reference standard or internal control standard throughout the life of the assay. Please provide data, from tracking of reference standard or internal control standard, that support the stability of the assay from validation to the analysis of the rabbit serum samples used in the PK studies.

**CBER Comment 7.i.e Regarding the Method Validation Report: Document VAL_MV_134_rep_v1 – Toxin Neutralization Assay (TNA) for Quantification of Anthrax Immune Globulin (AIG) in Non-clinical Monkey Serum Samples:
[Please provide] Criteria for tracking long-term assay stability.**

On pages 34 of 42, you state that no specific long-term assay stability criteria were defined in either SOP 87.040.0048 or the initial validation protocol, and long-term assay stability is assured by the combination of the different aspects that either have been evaluated in validation addendum studies (sample stability) or are being tracked on a recurring basis (reference standard stability). Please provide data, from tracking of reference standard or internal control standard, that support the stability of the assay from validation to the analysis of the monkey serum samples used in the PK studies.

**CBER Comment 8.i.d. Regarding the Method Validation Report: Document VAL_MV_143_rep_v1 – Toxin Neutralization Assay (TNA) for Quantification of Anthrax Immune Globulin (AIG) in Clinical Human Serum Samples
[Please provide] Criteria for tracking long-term assay stability.**

On pages 39 of 42, you state no specific long-term assay stability criteria were defined in the clinical TNA method SOP 87.040.0050 or the validation protocol, and long-term assay stability is assured mainly by the on-going verification of the stability of the AIG reference standard (#29-00324) used in the method. Please provide data, from tracking of reference standard or internal control, that support the stability of the assay from the time of validation to the analysis of clinical human serum samples used in the PK studies.

Additional comments

The following comments pertain to Method Validation #B55 – Method Validation Final Report (Anthrax Toxin Neutralization Assay)

- A. For the assessment of inter-assay precision, page 8 of 26, please provide assay validation design including number of replicates, analysts and days over which the assays were performed. Please describe the method used to estimate the precision due to the various sources of variability.
- B. Please provide the concentrations of the reference standard, internal control standard, rPA and rLF used for the validation study.

The following comments pertain to Method Validation #B55-B – Method Validation Final Report

- C. Based on your executive summary on page 3 of 4, this study report was a result of four amendments.
 - a. Please provide the assay design (replicates, analysts and day) used during the validation
 - b. Please provide the concentrations of reference standard, internal control standard, rPA and rLF used for the validation study
 - c. Please describe the method used to analyze the data
- D. In section 1.3 on page 3 of 4, and Table 4 on page 4 of 6, the tables are titled “Accuracy Determination of the Anthrax (b) (4) – Liquid Formulation Excipients”. Please confirm whether these data were generated using TNA method or are (b) (4) data.

The following comments pertain to Method Validation #B55-F – Method Validation Final Report

- E. Please provide the assay design, concentrations of reference standard, internal control standard, rPA and rLF used for the validation, and the method used for data analysis

The following comment pertain to SOP # 87.040.0008.00 – Toxin Neutralization Assay (TNA) for Quantification of Anthrax Immune Globulin (AIG) in Non-clinical Rabbit Serum Samples

- F. In section 6.3, please include in your SOP the number of cell passages, post revival, that are needed before performing an assay, and the maximum number of passages allowed before the cells are terminated.

The following comments pertain to SOP # 87.040.0048.00 – Toxin Neutralization Assay (TNA) for Quantification of Anthrax Immune Globulin (AIG) in Non-clinical Monkey Serum Samples

- G. In Section 4.2.5 on page 6 of 31, please include in your SOP the qualification of rPA and rLF when a new lot of the toxin components are received or justify why cytotoxicity activities on (b) (4) cells determined by the supplier would be comparable to those measured by your assay.
- H. In sections 6.2 and 6.3 on pages 14 and 16 of 31, respectively, you recommend to terminate the cell line (b) (4). Section 5.2, page 11 of 31 indicates that different working cell bank cultures are prepared at different passage numbers. Please justify why time and not passage number is used to determine cell line termination.
- I. On page 25 of 31, Sections 7.2.4 and 7.2.5, if the lower portion of the reference standard curve fails to yield a lower asymptote, the lower asymptote is fixed to the (b) (4) value of the assay (b) (4) Control (no toxin). Similarly, if the upper asymptote fails to yield an asymptote, the upper asymptote is fixed to the (b) (4) value of (b) (4) Control (b) (4) with toxin)
- For the curve asymptotes to be fitted to the Control (b) (4) specifications of the Controls should be independent of the fitted curve asymptotes. Please provide specifications of (b) (4) values for (b) (4) Control and (b) (4) Control (b) (4).
 - (b) (4) control (no toxin) and (b) (4) control (b) (4) cells with toxin) as defined on page 19 of 31 correspond to the highest and lowest measurable (b) (4) respectively. Please justify how (b) (4) Control (no toxin) and (b) (4) control (b) (4) cells with toxin) ODs are fixed as the curve's lower and upper asymptotes, respectively.

The following comments pertain to SOP # 87.040.0050.00 – Toxin Neutralization Assay (TNA) for Quantification of Anthrax Immune Globulin (AIG) in Clinical Human Serum Samples

- J. Please describe the difference between rPA and QDrPA as used in the SOP.
- K. In Sections 6.2 and 6.3, cell lines are to be terminated (b) (4). Please justify why time and not passage number is used to determine cell line termination if different working cell banks are prepared at different passage number.
- L. On page 24 of 33, Sections 7.2.4 and 7.2.5, if the lower portion of the reference standard curve fails to yield a lower asymptote, the lower asymptote is fixed to the (b) (4) value of the assay (b) (4) Control (no toxin). Similarly, if the upper asymptote fails to yield an asymptote, the upper asymptote is fixed to the (b) (4) value of (b) (4) Control (b) (4) with toxin)

- a. For the curve asymptotes to be fitted to the Control (b) (4), the Control (b) (4) specifications should be independent of the fitted curve asymptotes. Please provide specifications of (b) (4) values for (b) (4).1 Control and (b) (4) Control (b) (4).
- b. (b) (4) control (no toxin) and (b) (4) control (b) (4) cells with toxin) as defined on page 19 of 33 correspond to the highest and lowest measurable (b) (4) respectively. Please justify how (b) (4) Control (no toxin) and (b) (4) control (b) (4) cells with toxin) (b) (4) are fixed as the curve's lower and upper asymptotes, respectively.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your responses as an amendment to this file by December 1, 2014 referencing the date of this request.

If Cangene is unable to respond by December 1, 2014, please propose an alternative date to respond.

The action due date for these files is March 25, 2014.

If you have any questions, please contact me.

Very Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP)^{CM}

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