

From: Maruna, Thomas
Sent: Monday, October 06, 2014 12:01 PM
To: Allison Kennedy (akennedy@ebsi.com)
Cc: Fisher, Robert; Ngundi, Miriam
Subject: Information Requested: BLA 125562/0 - Please Respond by October 15, 2014

Importance: High

Cangene Corporation [Emergent Biosolutions]
Attention: Ms. Allison Kennedy
October 6, 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:

1. In Document: 3.2.S.4.1 Specification, Specification for Drug Substance, you use (b) (4) results to (b) (4) however you have not provided specification limits to determine when drug substance (b) (4) is not acceptable. Please provide the specification limits for AIGIV (b) (4) in manufactured drug substance or justify why a (b) (4) specification is not needed to control the process or product.
2. Section 3.2.P.8.1 Stability Summary and Conclusions, Specification for stability indicates that the potency by TNA acceptance criteria for stability testing are lot specific and are reported in either mU/ml or U/vial. Please clarify why the limits are lot specific and how those limits are derived. Please justify how product stability is assured in the different lots when the specifications are variable and lot specific.
3. The following comments pertain to Method Validation Report – Document VAL_MV_B55_rep_v8_ADD002 – Anthrax Toxin Neutralizing Assay (TNA) for Potency Determination of Plasma (b) (4) Purified Immunoglobulin Test Articles.
 - 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) or indicate where the reports can be found.

- ii) Table 1-2, page 5, does not indicate which applicable product(s) (liquid formulation, (b) (4) were used to generate the data listed. For each type of sample to be tested using this method, please provide a summary that includes the validation parameter, acceptance criteria and supporting data.
 - iii) The Validation Summary in Table 1-2 does not include the assay range. Please provide the upper and lower limits of quantitation based on the precision and accuracy of the assay.
 - iv) The Validation Summary in Table 1-2 does not include the concentration of samples tested for specificity. Also, the validation acceptance criteria require “Average (b) (4) not significantly different” between responses. Please provide the concentration of samples used to assess specificity and the level of significance for the acceptance criterion.
 - v) Table 1-2 Sample Stability presents the data for short term stability and freeze-thaw stability for (b) (4) finished product. Please include the concentrations of the samples used for stability testing and specify the storage conditions tested.
 - vi) Table 3-4, page 11 lists recombinant (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.
4. The following comments pertain to SOP #87.040.0016.RR – Appendix I of Document MV_B55_rep_v8_ADD002 Qualification/Validation Report
- i) On page 32, section 4.2.1, we note that either (b) (4) is to be used to prepare culture medium. Please provide data that support the interchangeability of these reagents.
 - ii) On Page 47, Section 6.4.1, plasma samples are (b) (4)
 - iii) On Page 47, Sections 6.4.2: (b) (4)

Please include in the SOP (b) (4)

- iv) On page 47, section 6.5, you state that for plasma samples (b) (4)

Please provide the validation data that support the equivalence of the dilution options or clarify in the SOP the criteria for selecting the dilution scheme.

- v) We note that you have not provided the storage conditions and sample preparation for (b) (4). Please add this information in the SOP.

- vi) On Page 52, section 6.9.2 and Page 53, section 6.10.2: After addition of (b) (4) for one of the Reference Standard dilution series. The criterion of a minimum (b) (4) is reached for one of the Reference Standard dilution series is not specific enough since dilutions run from (b) (4). Please state in your SOP the specific dilution (b) (4) that has to have a minimum (b) (4). Provide the steps taken if a (b) (4) does not meet the criterion.

- 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.

- ix) On Page 55, you state that (b) (4) samples require (b) (4), respectively, in order to generate a reportable value. Please indicate how the variability among the replicates is controlled.

The following comments pertain to the Toxin Neutralization Assay (TNA) for Quantitation of Anthrax Immune Globulin (AIG) in Non-Clinical Rabbit Serum Samples.

5. The following comments pertain to Method Validation Report: Document MV.120 – Toxin Neutralization Assay (TNA) for Quantitation of Anthrax Immune Globulin (AIG) in Non-Clinical Rabbit Serum Samples
 - i) Please provide the following:
 - a) SOP used for the validation of the routine use of the assay
 - b) Qualification protocols with acceptance specifications for all critical reagents
 - c) Assessment of robustness of the assay including (b) (4)

- d) Criteria for long-term assay stability
 - ii) Table 8:1 presents the data to support precision. Please describe the method used to estimate precision. In general we recommend a variance component analysis to correctly estimate the precision due to various sources of variability.
 - iii) In order to determine whether an assay is adequate for the intended use, incurred samples should be run as part of the validation. Please justify why incurred samples were not included in the validation
6. The following comments pertain to Method Validation Addendum Report: Document VAL_MV_120_rep_v2_AD01 – Toxin Neutralization Assay (TNA) for Quantification of Anthrax Immune Globulin (AIG) in Non-Clinical Rabbit Serum Samples
- i) In Table 1:1, no acceptance criterion is provided for selectivity assessment in sera from infected animals or serum containing PA. Please indicate the criteria against which the validation was judged for selectivity in sera from infected animals or sera containing PA.
 - ii) In Table 3:3 (Method Summary), (b) (4) [REDACTED] are different in the two documents. Please justify the changes in the assay operating parameters and the system suitability from the method validated versus that described in the SOP.

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

7. The following comments pertain to 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
- i) Please provide the following:
 - a) SOP used for the validation of the routine use of the assay.
 - b) Qualification protocols with acceptance specifications for all critical reagents
 - d) Assessment of robustness of the assay including (b) (4) [REDACTED]
 - e) Criteria for tracking long-term assay stability
 - ii) Accuracy and precision data provided in the Appendix I (page 30) show NRV results reported (non-reportable value) at all the concentrations including 1200 mU/ml. Please provide the reason for each missing data point.
 - iii) Please provide information of how NRV data are handled during the analysis of accuracy and precision

- iv) In order to determine whether an assay is adequate for the intended use, incurred samples should be run as part of the validation. Please justify why incurred samples were not included in the validation

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

- 8. The following comments pertain to 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
 - i) Please provide the following:
 - a. SOP used for the validation of the routine use of the assay. Please include (b) (4) and all assay suitability criteria
 - b. Qualification protocols with acceptance specifications for all critical reagents
 - c. Demonstration of robustness including (b) (4)
 - d. Criteria for tracking long-term assay stability
 - ii) Accuracy and precision data provided in the Appendix I (page 33) show NRV results reported at all the concentrations including the ULOQ (b) (4). Please provide the reason for each missing data point.
 - ii) Please indicate how replicates with NRV were handled in the analysis of accuracy and precision
 - iii) In order to determine whether an assay is adequate for the intended use, incurred samples should be run as part of the validation. We note that you have not provided any data from incurred test samples. Please justify why incurred samples were not included in the validation

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 October 15, 2014 referencing the date of this request.

If Cangene is unable to respond by October 15th, 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}
Lieutenant, U.S. Public Health Service
Senior Regulatory Management Officer

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