

From: Maruna, Thomas
Sent: Thursday, September 04, 2014 11:14 AM
To: Allison Kennedy (akennedy@ebsi.com); 'smcgregor@ebsi.com'
Cc: 'adyer@ebsi.com'; Melhem, Randa
Subject: Information Requested: BLA STN 125562/0 - Please Respond by September 15, 2014

Importance: High

Cangene Corporation [Emergent Biosolutions]
Attention: Ms. Allison Kennedy
September 4, 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:

Container Closure

Drug Substance

1. You stated that in the commercial process, AIG will be routinely stored at (b) (4) in (b) (4) for a maximum of (b) (4) (validated hold time). You then added that in cases where longer hold time is anticipated the AIG bulk can be (b) (4)
 - a. Will both containers - (b) (4) be used for the storage of the bulk? If you are requesting approval for storage of the (b) (4) bulk in the (b) (4) – please provide the validated procedure for (b) (4), the validated storage time and the validated procedure for (b) (4) and transfer to the mixing tank in preparation for mixing, sterile filtration and filling.
 - b. There seems to be an issue with the (b) (4). Please submit the corrective/preventive measures taken to alleviate/minimize cracking, and evidence that these actions are successful.

Drug Product

2. You provided several studies to demonstrate integrity of the container closure of the frozen vials; however the procedures used, and the results obtained do not assure container closure integrity.

Please provide additional information, justifications and/or propose to perform additional CCIT to demonstrate integrity of the container closure throughout the shelf life of the product.

- PQ#1125, (b) (4) Fill/Freeze/Thaw (b) (4) 20mm Serum Stoppers and 50cc (b) (4) Vials) (approved 16 Aug 2005). This study demonstrates that 50mL vials can support a fill volume of (b) (4); however, it does not demonstrate the suitability of the container closure as no container closure integrity testing was performed after freezing and thawing.
3. PQ#1123, Closure integrity Tests (b) (4) 20mm Serum Stoppers and 50cc (b) (4) Vials), (approved 13 Oct 2005). Cangene performed (b) (4) using the same lot of 50 mL glass vials, 20mm neck diameter and the same lot of 20 mm bromobutyl stoppers and the following was noted:

- (b) (4)
 - (b) (4)
- a. Please describe the positive control to demonstrate that the testing method as performed will allow (b) (4) in a compromised container closure. Please describe the studies performed to demonstrate the sensitivity of the method (critical leak).
- b. Please describe the conditions for testing the integrity of container closure, and justify why these conditions were used, and how they relate to the conditions under which the product is stored and shipped.
4. VAL_PV_0090_rep_v1, Closure Integrity Testing for Frozen Product Vials (b) (4) 20mm Serum Stoppers and 50cc (b) (4) Vials) (approved 04 May 2009). In this study CCIT (b) (4) was performed using (b) (4). Please address the following:

- a. This study, like previous study (PQ#1123) does not provide a positive control to determine the suitability of the method for detecting a leak. In addition, it is not clear whether the stoppered vials (b) (4). Also it is not clear what is meant when you stated that the vials were (b) (4). The study is already completed and the time should be fixed unless more than one trial was performed. Please explain.
- b. Please clarify whether the testing was performed (b) (4) and for how long. Please justify why these conditions were used, and how they relate to the conditions under which the product is stored and shipped.
- c. Please provide the (b) (4) testing procedure.
- d. The AIGIV contains (b) (4), and this study used (b) (4) filled vials. Please provide a risk assessment that was performed where you came to the conclusion that the volume will not have an impact on the freezing and will not impact the container closure. Please justify why the (b) (4) vials are representative of (b) (4) filled vials.

Implementation of a Positive Control

5. You reported that you implemented the use of positive controls and a (b) (4) challenge in the method of validation for container closure under protocol **PV_0275**.
 - a. Please provide PV_0275 protocol and results.
 - b. Please justify why you consider the study – (b) (4) is sufficient to demonstrate validity of the method. Please describe the negative control used.
 - c. Please describe the (b) (4) testing procedure used.
 - d. Please clarify if you tested this CCI method (b) (4) using positive controls and negative controls for vials that have been frozen and thawed (to simulate the manufacturing process). Please provide the results and justifications.
 - e. Please clarify if you implemented the use of CCIT at expiration to demonstrate integrity through-out shelf life? Please justify your response.

Consolidated Report

6. Please provide *PV_0120, Qualification of the Container Closure; AIG Hyperimmune Product*; consolidated report referencing validations for preparation and sterilization of stoppers; sterilization / depyrogenation of vials; container closure integrity.

Residual Seal Force (RSF)

7. You reported that residual seal force (RSF) of the elastomeric closures is routinely executed by (b) (4). Please clarify if you qualified/validated the method, and what are the acceptance criteria? Please justify your response.

Shipping

8. You reported that you ship to the US by ground transportation, and to other countries by air. You provided simulated and actual shipping for both. The reports provided do not provide the temperature mapping of the containers to demonstrate that dataloggers placed in the loads during shipping record temperature data representative of the product temperature throughout the loads. Please provide additional information and justification to support that the shipping processes consistently maintain the product temperature between -15°C and (b) (4) under worst case conditions.

Ground Transportation

9. VAL-PQ_2244_rep_v1, (b) (4) *Shipping Custom Crate (approved 01 Sep 2009)* provides the protocol and data for the qualification of the crates to maintain temperature of the shipped 50mL vials when stored at ambient temperature (b) (4) and elevated temperature (b) (4).

The results reported show the time it took for the temperature to be > -15.0°C as recorded by the different dataloggers monitoring air and product temperatures for maximum and minimum loads. This validation report provides the results of one run/load/temperature, and it is not evident that the temperature is consistent throughout the load considering there is quite a wide time range for maintaining temperature depending on the location of the datalogger. In addition, there does not seem to be consistent correlation between the results of the Air and Vial dataloggers to allow the use of the data recorded by the air datalogger to predict the product temperature during routine shipping.

- a. Please clarify if you performed additional studies to confirm your conclusions. Please provide data and justification.
 - b. Please clarify if you performed a comprehensive temperature mapping of minimum and maximum loaded crates to determine worst case locations; and clarify if you have performed studies to demonstrate a correlation between the air and product datalogger recordings. Please provide data and justifications.
10. You have also provided PQ report PQ_2302_rep_v1, ≤-15°C *Product Shipping using (b) (4) Custom Crate (approved 15 Dec 2010)* which documented the use of the custom crates and (b) (4) transport trucks (b) (4) trucks with validated

temperature of (b) (4) under actual shipment conditions, over winter (Jan2010) and spring (Apr2010) temperature conditions for both the Anthrax Immunoglobulin (AIGIV) and the Botulinum immunoglobulin (BAT).

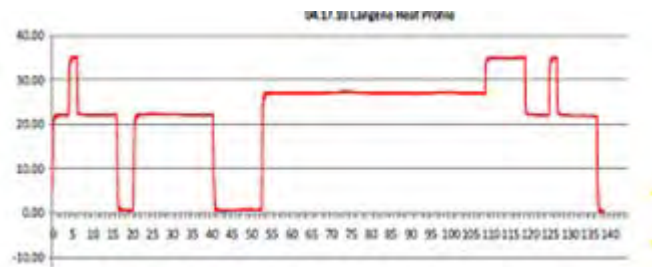
The data collected by the dataloggers show that the crates and (b) (4) trucks can maintain temperature for the duration of the shipment (winter and spring conditions). However additional information is needed to clarify the following points:

- a. Would this temperature hold during summer shipping? Please justify.
- b. It is not clear whether the datalogger recordings are representative of the product temperature; and it is not clear why the dataloggers were placed in the (b) (4) in the actual shipment, while the dataloggers were placed in the (b) (4) in VAL-PQ_2244_rep_v1, please explain.
- c. Please state the fill volume and size of the vials (AIGIV and BAT) shipped.
- d. Please state the (b) (4).
- e. Please provide the temperature mapping of the crates and truck to assure consistent temperature throughout.

Qualifications for Air Shipments

11. You stated that the frozen AIGIV and BAT are shipped frozen to other countries using validated (b) (4) shipping container (b) (4) and provided VAL_PQ_2260_rep_1, (b) (4), at $\leq -15^{\circ}\text{C}$ (approved 23 Jul 2010). The study was performed by the supplier (b) (4) to simulate the air shipment temperature cycle (max and min vial loads) to an overseas destination from Cangene Corporation, under worst case conditions: summer conditions (Fig) and extended times (b) (4)

Fig: Summer Conditions



(b) (4)

(b) (4) to get the temperature profile inside the container.

- a. Please provide data to demonstrate that the dataloggers are placed in worst case locations (cold and hot spot for both the min and max loads).

The temperature profiles for the max and min loads are quite different:

- b. For the min load, it looks that the center datalogger marked a temperature very close to the limit in the initial (b) (4). The loading of the vials in the shipper should be adjusted to prevent the temperature spike. Please provide a risk assessment, data and justifications.
- c. It is clear from the graphs that the recorded temperature fluctuates with the simulated temperature cycle – thus if the temperature is below zero, there is a possibility that the temperature (max load, (b) (4)) may drop below (b) (4), thus causing stopper integrity issues. Please provide a risk assessment and data to assure that the temperature of the shipment will not drop below (b) (4).

12. In addition to the simulated shipping, you provided *PQ_2286_rep_v1*, (b) (4) *Shipping Qualification $\leq 15^{\circ}\text{C}$ (approved 27 Aug 2010)*, which describes actual shipping to UAE.

In this study you stated that the shipment of (b) (4) vials of BAT with the load divided over (b) (4)

During the study all temperature readings were maintained between (b) (4) meeting the acceptance criteria of -15°C to (b) (4) for the overseas shipment. Please address the following:

- a. Please provide the location of the (b) (4) data loggers and provide justification that they are representative of the load (max and min temperature).
- b. The study showed that the extra (b) (4) in storage did not lead to a change in temperature recorded by the dataloggers – please clarify at what temperature was the container stored, and does this represent worst case storage. Please justify your response.

- c. In this study you tried to address the spike in temperature during loading, by (b) (4), but the temperature in the (b) (4) was (b) (4), and the temperature spike still occurred. Please provide a risk assessment and proposed remedies with justifications.

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 September 15, 2014 referencing the date of this request.

If Cangene is unable to respond by September 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}

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