

From: Maruna, Thomas
Sent: Monday, November 17, 2014 3:30 PM
To: Allison Kennedy (akennedy@ebsi.com)
Cc: Fisher, Robert; Campbell, Karen M; Pierce, Leland Ross
Subject: Information Requested: BLA 125562/0 - Please respond by requested dates

Importance: High

Cangene Corporation [Emergent Biosolutions]
Attention: Ms. Allison Kennedy
November 17, 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:

Clinical: Responses due by December 15, 2014 unless otherwise indicated.

1. Regarding your submitted synopsis of contingency postmarketing requirement (PMR) field study protocol AX-003:
 - a. We request the PMR be split into two components:
 - i. Field study to confirm efficacy, safety, and the appropriateness of the recommended dosing regimen in persons exposed in a “broad [anthrax] exposure event scenario.”
 - ii. A requirement to periodically submit and analyze cumulative data from use of AIGIV in sporadic systemic anthrax cases.
 - b. Please submit a draft protocol or protocols by 15 December 2014.
 - c. Please submit a draft case report form (CRF) or forms by 12 January 2015.
 - d. Please submit with the draft field study protocol proposed relative timelines at this time in relation to initiation of the protocol for completion of enrollment, completion of data collection, and for submission of the final study report. We

request calendar date timelines be submitted for the collection, analysis, and submission of the final study report for the component of the PMR dealing with sporadic anthrax cases.

- e. Please include in both the sporadic and broad exposure study designs a mechanism for studying the use of more than one dose of the product in comparison to use of a single dose.
- f. Please consider for both components of the PMR including international healthcare providers who may administer AIGIV to patients with inhalational anthrax located overseas.
- g. As previously requested, please include a pediatric pharmacokinetic protocol as part of your PMR, designed according to the pattern of Heptavalent equine-derived botulinum antitoxin (BLA 125264).
- h. Please consider sampling a subset of patients for lethal factor (LF) before and after administration of AIGIV and exploring the relationship between changes in LF levels in relation to the time of administration of AIGIV and to changes in PA levels in individual patients.
- i. Serious adverse events (SAEs), adverse reactions, and suspected adverse reactions should be recorded, analyzed, and reported. Recording and reporting of adverse events that do not fall into one or more of the aforementioned categories need not be reported.
- j. Please change the secondary endpoint to the frequency of serious suspected adverse reactions plus serious adverse reactions.
- k. Please add exploratory endpoints consisting of cause-specific mortality, duration of ICU stay, duration of mechanical ventilation, need for dialysis, maximum increase from baseline in SOFA score, and duration of hospitalization.
- l. Please include in the protocol provision for independent assessment by the sponsor of the relatedness of all serious adverse events.
- m. Please define the total of serious suspected adverse reactions plus serious adverse reactions as all SAEs for which any one or more of the following criteria are met:
 - i. SAEs for which the onset was during or within 24 hours of the end of AIGIV infusion.
 - ii. SAEs considered by the healthcare provider or the sponsor to be possibly, probably, or definitely related to administration of AIGIV.

- iii. SAEs for which the healthcare provider's causality assessment was missing or indeterminate.
 - n. Please include plans to compare the observed mortality rate to historical controls and to compare the demographics and other pertinent patient characteristics to historical controls.
 - o. Please analyze both efficacy and safety outcomes by age, sex, body mass index, race, and ethnicity.
2. Please indicate whether the following individuals who were administered AIGIV for injectional anthrax were discharged from the hospital: patients (b) (6) [REDACTED] Please provide your response by 15 December 2014.
 3. In reviewing the regulatory history of AIGIV, we note that the planned clinical development program originally included a 2nd pre-licensure clinical trial, AX-002. This trial was to have enrolled a total of 36 subjects: 12 to be given a single dose and 24 to be given a multi-dose regimen. Please indicate why AX-002 was not conducted. Please provide your response by 30 November 2014.

Lot Release Template: Responses due December 15, 2014

1. On page 1, Please change the title of the product from "Varicella Zoster Immune Globulin (Human)" to "Anthrax Immune Globulin Intravenous (Human)"
2. On page 2, there are spelling errors, Anti-A Haemagglutinis' and 'Anti-B Haemagglutinis' needs to be changed to: 'Anti-A Hemagglutinins' and ' Anti-B-Hemagglutinins'
3. On page 5: Sterility, please add the method type, for example: (b) (4) .
4. On page 5: Sterility, Please add the (b) (4) [REDACTED] test date.
5. The sterility test qualification was carried out using ^{(b) (4)} [REDACTED] vials/media type, which relates to ^{(b) (4)} [REDACTED] vials for 'tested quantity'. On page 5: sterility, ^{(b) (4)} [REDACTED] vials are shown for 'tested quantity'. Please confirm that ^{(b) (4)} [REDACTED] vials will be used, and clarify this discrepancy.

CMC: Response due December 15, 2014

1. Please provide unredacted copies of batch records for Anthrax Immune Globulin Drug Substance bulk lots (b) (4) [REDACTED] and for filled lot (b) (4) [REDACTED] .

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 as noted above referencing the date of this request.

If Cangene is unable to respond by the requested dates, 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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Very Respectfully,

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

Lieutenant, U.S. Public Health Service

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