

From: Maruna, Thomas
Sent: Tuesday, October 14, 2014 9:59 AM
To: Allison Kennedy (akennedy@ebsi.com)
Cc: Fisher, Robert; Melhem, Randa; Reed, Jennifer; Mahmood, Iftekhar; Ngundi, Miriam
Subject: Information Requested: BLA 125562.0 - Please Respond by October 31, 2014 & November 3, 2014

Importance: High

Cangene Corporation [Emergent Biosolutions]
Attention: Ms. Allison Kennedy
October 14, 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:

CMC – Response due October 31, 2014

1. Please submit complete batch records for Human Anthrax Immune Globulin Drug Substance bulk lots (b) (4).

Nonclinical – Response due October 31, 2014

2. Please submit a table indicating the pre-study PA (b) (4) and/or TNA screening results for each animal in study 828. Please indicate if any test results were initially invalid and repeat testing was performed.
3. Please submit a SAS xpt file containing the following information for each animal in study 828:
 - a) Animal ID number
 - b) Delivered spore dose
 - c) Dose of AIGIV or placebo administered
 - d) Challenge day (A, B, C, or D)
 - e) Challenge date/time
 - f) Treatment date/time (or study time)

- g) Euthanasia date/time

Clinical Pharmacology – Response due October 31, 2014

4. The review of the POPPK report has identified several deficiencies:
- a) The POPPK analysis needs to be recalculated and resubmitted using combined data from all species (rabbits, monkeys, and humans). Please justify a human dose based on this analysis. Please ensure that you analyze the data without fixing the exponent (you can use the fixed exponent for comparative purposes). Please follow the Heptavalent equine-derived botulinum antitoxin analysis pattern (BLA 125264).
 - b) It seems that throughout the POPPK analysis the focus was to justify a 420 U dose in humans rather than trying to find out other suitable doses (besides 420 U). Therefore, attempts should be made to evaluate if other doses are more suitable or optimal than 420 U.
 - c) In addition, based on the POPPK results, an exposure-response model should be developed and applied linking response (survival) to exposure (AUC) using logistic regression type of analysis. Please follow the Heptavalent equine-derived botulinum antitoxin analysis pattern (BLA 125264).
 - d) The exposure-response analysis graph should include simulations indicating human survival up to 99%. The simulations also should predict NP-015 doses (in Table format) that would produce 80%, 85%, 90%, and 95% probability of survival in the human population exposed to anthrax.
5. Modeling and Simulation of NP-015 to Support Dosing in Obese Subjects:
- a) Obesity is associated with physiological changes and most of the time obesity impacts the PK of a drug. There are also instances when obesity has no impact on the PK of drugs, but this can only be determined after conducting a PK study. The modeling and simulation of NP-015 assumes that there is no impact of obesity on the PK of NP-015. This assumption may or may not be correct. **Therefore, a PK study of NP-015 in obese subjects is needed for supporting the dose of NP-015 in this population. The study can be a phase 4 required clinical protocol.**
6. Modeling and Simulation of NP-015 to Support Dosing in Pediatric Subjects:
- Your current approach to support dosing in pediatric population is not acceptable. It is not clear how you estimated the CL of NP-015 in pediatrics based on age (Table 4.3.2). Based on body weight, you estimated the CL of NP-015 using a fixed exponent 0.75 across all age groups. This is an incorrect approach. Fixed exponent 0.75 on CL will substantially over-estimate the CL of a drug in children <5 years of age especially, in neonates and infants. Your current method has overestimated the clearance in children <5 years of age and any dose selection based on these CL values may overestimate the dose of NP-015 and may cause toxicity in this age group.

- b) Please calculate your CL values based on age dependent exponents (exponent 0.75 can be used in children >5 years of age) and then select the dose based on these calculated CL values. Please see the references below for age dependent exponents to predict CL across pediatric age groups.
 - i. Mahmood I, Staschen CM, Goteti K. [Prediction of Drug Clearance in Children: an Evaluation of the Predictive Performance of Several Models](#). AAPS J. 2014 Oct 2. [Epub ahead of print]
 - ii. Mahmood I. [Dosing in children: a critical review of the pharmacokinetic allometric scaling and modelling approaches in pediatric drug development and clinical settings](#). Clin Pharmacokinet. 2014;53(4):327-46.
 - iii. Mahmood I. Pharmacokinetic allometric scaling in pediatric drug development; Pine House Publishers, 2013.
- e) Please also modify and stratify your age groups from 2-12 years into two age groups, 2 to 5 years and >5 to 12 years.
- f) For a given age group an average known weight can be used. For example, for neonates 1 to <3 months old average weight may be 5 kg. Please use an average body weight of 70 kg for adult subjects.
- g) Please design your required phase 4 clinical protocol for pediatric PK study on the pattern of Heptavalent equine-derived botulinum antitoxin (BLA 125264).

Please respond to these comments.

7. Population PK (POPPK) in rabbits:

The estimated clearance (CL) of NP-015 in rabbits by POPPK analysis indicates that CL in unexposed rabbits (0.177 mL/hr/kg) and exposed rabbits (0.478 mL/hr/kg) is substantially different from non-compartmental analysis (0.474 mL/hr/kg in non-exposed rabbits by averaging CL from 5, 15, and 30 U/kg dose, and 1.19 mL/hr/kg in exposed rabbits (GLP Study No. 1207-100005104). Please explain this discrepancy between POPPK and non-compartmental analysis when same data were used.

This discrepancy may be due to the model misspecification (3 compartment vs 2 compartment model). Probably, this difference is also due to the use of so-called allometry (fixed exponents on CL and Volume). The weight range of rabbits is so narrow that incorporation of any kind of allometric function may distort the results. Statistically, the model may appear sound but the parameter values are incorrect. The narrow weight range is the reason that the weight does not appear as a covariate in the POPPK model hence, any kind of allometric exponent may introduce error in PK parameter estimates. In other words, allometric concept should not be included in this analysis.

8. Population PK (POPPK) in humans:

The estimated clearance (CL) of NP-015 in humans by POPPK analysis is comparable to non-compartmental analysis. It is not clear if the weight appeared as an influential covariate on CL and V (although an allometric function in terms of fixed exponents was used). Like rabbits, the weight range in humans is also narrow and allometric function should not be used either as fixed exponents or as estimated exponents.

The exponents of allometry do not have biological or physiological meaning and will vary depending on the data. West et al's work (as cited in the POPPK report by Pharsight) has been misunderstood by the pharmacometrics community and they seem to be quite unaware about the heavy criticism (unrealistic mathematical model) of West et al's manuscript. Over the years, dozens of papers have been published by experts of allometric scaling that belie West et al's fixed exponent concept and notion that the exponents of 0.75 and 1.0 are universal and have biological meaning.

In short, when weight range is narrow one should not use allometric function (fixed or estimated) because this may give wrong parameter estimates and cannot be detected by simple statistical analysis.

Facilities, Manufacturing & Product Quality – Response due November 3, 2014

Environmental Analysis

9. You requested exemption from the requirement to prepare an environmental assessment under 21 CFR 25.31 (c) because AIGIV is a biological product that occurs naturally in the environment. However, you did not include in your request that no extraordinary circumstances exist (21 CFR 25.15 (a)). Please amend your request.

Facilities/Equipment: Containment

10. AIG and AIGIV are manufactured in the same facilities, using the same equipment/rooms and similar procedures as other FDA approved hyperimmune products. Please provide detailed description of facilities/equipment/procedures that are new and have not been submitted, reviewed and approved in association with other product submissions.

Cleaning of equipment

11. Please provide the acceptance criteria for the following metrics: (b) (4)

[REDACTED]
[REDACTED] for the equipment used for the manufacture of AIG and AIGIV.

(b) (4)
[REDACTED]

13. (b) (4)

(b) (4)

(b) (4)

e) (b) (4)

(b) (4)

(b) (4)

Manufacturing Process

16. In section 3.2.P.3.3 Description of Manufacturing Process and Process Controls, you stated that the manufacturing areas used for of AIGIV are shared with other human immune globulin (IgG) or contract manufacturing products. Please list the other products and clarify if the same equipment is shared as well with justification.

Post-licensure Labeling Operation

17. Please provide additional information/SOPs to support your statement that “labeling/packaging process will be performed at the SNS under CGMP controls, including Packaging Instructions, line approval and clearance, component-product reconciliation and quality assurance release.” Please clarify which party would govern

and approve this process (such as Cangene QA personnel or SNS personnel. Please justify why you think whomever is in charge of this process is the appropriate party in your response.

Process Validation

18. In *PV.HYP.02.13* you state that the set mixing time is (b) (4) ; however you reported that the set mixing time is (b) (4). Please clarify when this was changed and the reasons for the change.
19. Please provide the schedule for requalification of the mixing tanks and the most recent data to support that the mixing vessels are functioning as intended.

Sterile Filtration

20. You provided a summary of the filter validations which consisted of extractables testing, compatibility of the filter with the product and validation for microbial retention. The validation was executed by (b) (4) using representative hyperimmune drug substances (similar formulation to AIGIV), which were processed, formulated and filtered in accordance to routine manufacturing conditions.
- a) Please provide the date of execution of the filter validation study(ies), and clarify whether the validation reports were submitted, reviewed and approved in other submissions – please list the STN number(s) and date(s) of approval.
 - b) Please provide a comparison of the AIG drug substance with the representative hyperimmune drug substances used in the validation studies to justify that the studies and results are valid for AIGIV manufacturing.
 - c) Please clarify if the sterilization of the sterilizing filter is performed in-house or by the vendor and submit the most recent re-validation sterilization report.

Aseptic Process Simulations (APS)

21. You provided in this submission the initial media fill simulations in 2005. You have provided in STN 103649/5654 media fill simulations following the upgrade of the facility (which was not provided in this BLA submission). It appears that the media simulations were run at different speeds in the initial (2005) and the recent (2013) media fills. Please provide the data of parameters for the current filling operations.
22. You reported that the media fills are performed at low speed or high speed, however during the recent biennial inspection (July 2014), the inspector noted that the line speed for the media fills was not documented and thus speed could not be verified. Please explain.
23. In addition, you reported that media simulations are performed under worst case condition, yet as noted during the July 2014 inspections, addition of stoppers during filling is not always simulated and the documentation of the media fills is completed on autoclavable paper (and transcribed later to batch records) instead of filling directly into

the batch record as done during routine manufacturing. Please clarify why these practices would be considered worst case.

24. Please clarify why (b) (4) fill volume is representative of the (b) (4) AIGIV filled volume.
25. You stated that for AIGIV filling operations is (b) (4), with a specification of (b) (4) filling time and a maximum filling speed of (b) (4). In addition you stated that for the media fills, (b) (4). However the data presented for the 2005 validation show the filling time is a maximum of (b) (4) and there is no documentation of a (b) (4). The media fill studies performed to qualify the upgrade to the filling suite showed that the 50mL vials run was performed (b) (4). Please state clearly what your procedure for media fills is, and why you consider that the media fills are performed under worst condition, and are representative of the routine manufacturing operations.

Filling Equipment

26. Has the qualification of the filling machine been reviewed and approved in other submissions – please provide the STN and approval date. This study was performed in 2005 and it is not clear if any changes have been implemented and whether these changes have been reported and approved by FDA. Please list all the changes and the submissions STN numbers and approval dates.
27. Please specify the number of vials filled in each water run, and whether the samples were collected from the beginning, middle and end to ensure consistency throughout the filling process.
28. You state in section 6.2 of report 3.2.P.3.5 Process Validation and/or Evaluation (1) that The filling accuracy therefore brackets the predicted fill volumes for the AIG products is @ (b) (4). However the AIGIV volume is @ (b) (4); please explain.

Capping Machine

29. Has the qualification of the capper including the displaced stopper detection system and RSF been submitted and reviewed by FDA in association with other submissions? Please provide the STN number(s) and approval date(s). Otherwise provide the qualification report(s).

Labeler for the 50mL vial size

30. Report IQ/OQ#0281-5 does not provide any data to support the change. Please explain and submit the document that provides that information.
31. Has the qualification of the capper (b) (4) (50mL vial) been reviewed and approved in other submissions – please provide the STN and approval date. This study was performed in 2005 and it is not clear if any changes have been implemented and

whether these changes have been reported and approved by FDA. Please list all the changes and the submissions STN numbers and approval dates.

32. Please state the requalification frequency for this equipment and provide the SOP that describes the requalification frequency and procedure.
33. You stated that the print heads deteriorate over time, please state the frequency and procedure for re-qualification and maintenance of the labeler to ensure that it is functioning within specifications.
34. Please clarify whether the qualification and requalification of (b) (4) has been submitted and reviewed by the Agency. Please list the STN number and approval date. Otherwise provide the qualification report(s).
35. You stated that the (b) (4) labeling machine stamps expiry date, lot number, and/or potency on unvarnished part of a label; however for the AIGIV label, only the lot number is stamped. Please explain.
36. You also stated that the (b) (4) labeling machine can print 1-3 lines; however, the AIGIV label has several lines and logo printed. Please explain.
37. In the IQ/OQ (EQ_0058) you reported that the maximum acceptable reject rate is (b) (4) of the total number of vials labeled per vial size. However, in the PQ report, the maximum allowed reject rate is (b) (4) Please clarify.

Follow-up questions to the information provided in amendment 125562/0/1
Container Closure Integrity Testing

38. Drug Substance: You stated in your response to 04 Sep 2014 information request that you have implemented CAPA to address the cracking of the (b) (4) Have you performed a prospective study using a surrogate to simulate the storage of the drug substance to determine if the CAPAs implemented worked. Please justify your response.
39. Drug product: In your response to the 04 Sep 2014 information request, you did not provide data or risk assessment to demonstrate that CCIT performed on (b) (4) media filled vials (frozen/thawed) is representative or worst case for (b) (4) product filled vials (frozen/thawed). Please provide supportive information.

Shipping Validation
Ground Shipping

40. In your response to the information request you stated that the (b) (4) truck has a temperature set point of is (b) (4). However the validation reports of the (b) (4) trucks state that the truck has a setpoint of (b) (4) which is outside the -15°C. Please explain.

41. The reports provided for the validation of the trucks has expired in 2011. Please clarify if you receive and approve the re-validation reports.
42. You have provided reports of actual shipping during winter (Jan2010) and spring (Apr2010) for AIGIV and BAT. However, if you plan to ship in the summer, you need to provide validation during summer shipping. Please provide data.

Air Shipping

43. During our telecon, we discussed that the actual shipping performed does not support a (b) (4) summer shipping conditions, as the product was stored in the freezer for (b) (4), and you agreed that this is the case. However this issue was not addressed in your response, and you did not propose additional studies to support the (b) (4) shipping time. Please explain and provide supportive information.

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 31, 2014 and November 3, 2014 respectively, referencing the date of this request.

If Cangene is unable to respond the proposed dates, please suggest an alternative date to respond.

The action due date for these files is March 25, 2015.

If you have any questions, please contact me.

Very Respectfully,

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

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