Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: March 7, 2013

To: To File (BLA STN 125462/0)

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Applicant: Cangene Corporation

Product: Botulism Antitoxin Heptavalent (A ,B, C, D, E, F, G) - (Equine)
Trade name: N/A

Subject: Final Review : Process Validation and Raw Materials

Recommendation

The recommendation is for approval with the following PMCs listed below.

CMC PMCs (Cangene committed to these PMCs on March 6, 2013)

1. Cangene commits to ----------(b)(4)----------, and submitting a concurrent validation for ----------(b)(4)----------. A modified SOP and/or batch record limiting -----(b)(4)----- will be submitted as a CBE30 within 60 days of approval.

2. Cangene commits to re-validating the maximum hold time for the ----------(b)(4)----------, within 1 year of approval. The validation will be performed with at least 3 lots of each solution held at the maximum time requested. The validation study report will be submitted as a PMC-Final Study Report within 60 days of completion.

3. Cangene commits to re-validating the hold time for ----------(b)(4)----------. The validation will be performed with the next ----------(b)(4)---------- lots, which will be held at the maximum time requested. The validation study report will be submitted as a PMC-Final Study Report within 60 days of completion.

4. Cangene commits to perform a process validation study prior to the manufacture of any new lots of BAT bulk drug substance. The process validation will include at least two lots, one of which may be a simulated batch manufactured with normal or low anti-botulinum titer equine plasma. If normal equine plasma is used, a feasible biological endpoint such as tetanus, rabies, or West Nile Virus antibody measures can be used in lieu of botulinum neurotoxin neutralization levels for the purpose of monitoring biological activity in the simulated bulk drug substance. The process validation protocol (including equipment requalification) will be submitted as a Postmarketing Study Correspondence at least 60 days prior to execution of the process validation, and the final validation report will be submitted within 60 days of completion as a Prior Approval Supplement.

Executive Summary (Process Validation and Raw Materials)

Cangene Corporation submitted a BLA on September 20, 2012 for Botulism Antitoxin Heptavalent (A ,B, C, D, E, F, G) - (Equine), BAT. BAT is a clear to slightly opalescent, colorless to pale yellow sterile liquid containing enzymatically modified and purified equine-derived gamma immune globulin (IgG) antibodies to the seven known botulinum toxin types (A, B, C, D, E, F and G). The drug product is formulated with 10% maltose and 0.03% polysorbate 80.

BAT is supplied in clear -(b)(4)- glass vials (20 or 50 mL) with --------(b)(4)---------- rubber stoppers (20 mm), aluminum seals and plastic flip-top caps. Each vial contains approximately ---(b)(4)-- purified $(Fab')_2$/Fab fraction per vial. Potency is expressed in units (U) based on the amount of toxin-specific neutralizing antibodies to each toxin serotype as determined by the Mouse Neutralization Assay (MNA). Filling is based on target potency per vial, expressed in U.

Botulism Antitoxin Heptavalent contains no preservatives and is intended for single use by intravenous infusion. Prior to use, the product is diluted one in ten (1/10) with 0.9% Sodium Chloride Injection (USP).

Manufacturing Process

Plasma

For the -(b)(4)- scale manufacturing process, Phase A plasma was collected by the US Department of Defense (DoD) at BioWhittaker Inc. between 1993 and 1996 and was used to manufacture 18 Drug Substances. Beginning in -(b)(4)-, Phase B plasma was collected from Auburn University, followed by Lake Immunogenics. For the -(b)(4)- manufacturing process, Phase B Plasma from Lake Immunogenics and Auburn University was used. All horses are tested for Equine Infectious Anemia (EIA) prior to acquisition and annually thereafter, and quarantined for a minimum of 21 days. The horses are immunized with one of seven known purified *C. botulinum* toxoids, toxin complexes treated with formaldehyde to inactivate the toxin, types, designated as A, B, C, D, E, F, and G. Cangene targets approximately -----(b)(4)------ titers, based on serotype, to maintain average titer targets for manufacturing. Plasma is collected into sterile bags containing sodium citrate as anticoagulant and tested for adventitious agents: Equine herpes virus-1 (EHV-1), Reovirus (REO-3), Rabies, Equine arteritis virus (EAV-1), Bovine viral diarrhea virus (BVDV), West Nile Virus (WNV), Eastern Equine Encephalitis Virus. The plasma is held for -(b)(4)- from the last bleed date prior to use.

Solvent Detergent Treatment

Plasma is treated with -(b)(4)- TnBP (solvent) and -(b)(4)- Triton X-100 (detergent) at -(b)(4)----------.

--(b)(4)-- **and Clarification**

----------(b)(4)----------

Cation Exchange Chromatography (----(b)(4)----**)**
----------(b)(4)----------

Pepsin Digestion
The intermediate-purity IgG is then digested by pepsin, which cleaves the monomeric IgG into the F(ab')2 and Fab/F(ab')2 related fragments. This removal of the Fc portion of the equine IgG despeciates the product minimizing the potential for immunogenic reactions.

--(b)(4)--
----------(b)(4)----------

Anion Exchange Chromatography (-(b)(4)-)
The anion exchange column, ----------(b)(4)----------

Nanofiltration (--(b)(4)--)
The virus filtration is initiated in Manufacturing Suite ----------(b)(4)----------
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-(b)(4)--
----------(b)(4)----------

----------(b)(4)----------
----------(b)(4)----------

----------**(b)(4)**----------
----------(b)(4)----------

----------(b)(4)---------- ------
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----------(b)(4)----------
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Blending

Botulism Antitoxin Heptavalent drug product contains seven monovalent serotypes (A-G) blended together to deliver a target potency per vial, expressed in units (U).

Table 1 Heptavalent Potency Target Specifications

Assay	Potency Target (Units/vial)
Serotype A	(b)(4)
Serotype B	
Serotype C	
Serotype D	
Serotype E	
Serotype F	
Serotype G	

----------(b)(4)----------
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----------(b)(4)----------
----------(b)(4)----------

Filling

----------(b)(4)----------
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-----(b)(4)-----
----------(b)(4)----------
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No major deficiencies have been found with the process validation section and the control of raw materials. ----------(b)(4)---------- ------

----------(b)(4)----------

---. The Agency requested PMCs regarding a re-validation of the hold times of -------(b)(4)--------, a re-validation of the ----------(b)(4)----------
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-----, and a validation of more conformance lots when production is started again. The recommendation is for the approval of this BLA with the proposed PMCs.

CMC Review Assignments

Douglas Frazier: stability, assay validation
Malgorzata Norton: process validation and raw materials
Michael Kennedy: nonhuman primate efficacy studies
Robert Fisher: Viral clearance/guinea pig efficacy studies
Anthony Lorenzo: DMPQ (facilities)

Supplement Review Summary (since midcycle)

1. General Information
    a. Process Flow Chart (please see attachment)

2. List of raw materials

Table 4 Control of Materials used in the (b)(4) Scale Manufacture of Botulism Antitoxin Drug Substance – (Equine)

Raw Material	Process Step	Function	Grade
Tri-n-butyl Phosphate (TnBP)	Solvent Detergent Treatment	(b)(4)	
Triton X-100 (TX-100)	Solvent Detergent Treatment		
(b)(4)			
Pepsin	Despeciation (Pepsin Digestion)	(b)(4)	
(b)(4)			
Maltose Monohydrate	Formulation	(b)(4)	
Polysorbate 80	Formulation		
Water for Injection	All		
(b)(4)			

3. Controls of Critical Steps and Intermediates
    a. Critical Quality Attributes

Eight (8) Pages Determined to be Non-Releasable: (b)(4)

[--(b)(4)--]

Information Request (IR) (Sent December 21, 2013; Response received January 18 (eCTD sequence 0006) and February 5 (0008) and 21 (0010), 2013

13. Please confirm which process scales you intend to license.
    Cangene stated that it intends to license ----------(b)(4)----------. The -(b)(4)- scale is considered their "commercial" manufacturing process, and will be used for future production of BAT; however, there is material in the SNS for the -(b)(4)- scale, which also needs to be licensed.

14. Please submit a table indicating which adjuvant was used to produce the anti-sera for each monovalent bulk.
    Cangene provided the requested table. They also mentioned that from September to December 2006, Lake Immunogenics trialed formulation and administration of an adjuvant containing ------(b)(4)------ Freund's Incomplete Adjuvant to enhance the immune response to different toxin serotypes and the use of this adjuvant has not been previously reported in the IND.
    ----------(b)(4)----------, *these horses remained on the program receiving only Freund's Incomplete Adjuvant.*

15. Please provide a timeline of process changes during the -----(b)(4)------ process and a chronological listing of all monovalent bulks as they relate to the time of the change.
    Cangene provided the requested table.

16. Please provide a complete list of deviations, which occurred during the H-BAT manufacturing process at all scales. Please include: date of deviation, brief explanation, root cause, and CAPA.
Cangene provided the list of deviations. I reviewed the deviations occurring within the last 4 years. It appears that proper CAPAs have been implemented and follow up of the CAPAs should be performed on inspection.

17. Please explain what procedure is in place if the alert limit is reached for each in-process specification?
Cangene explained that first a laboratory investigation is performed. If the alert limit is found not to be due to a laboratory error, a deviation is opened.

The answer is satisfactory.

18. Please describe the maltose endotoxin deviation and what increased testing is being done.
Cangene explained the investigation which was initiated for the OOS levels (--(b)(4)--) of endotoxin present in post formulated product for BAT lot 10804533 (OOS 1242). An investigation (QAIRc-0341) was initiated where additional testing of the maltose lot in question confirmed contamination of the material. The lot of maltose was quarantined. The investigation looked further into other BAT lots using the same lot of maltose and one other lot was found (lot ---(b)(4)--). The root cause was a maltose originating from ----------(b)(4)----------

The corrective and preventative actions taken were to ----------(b)(4)----------, and changes were made to the requirements for dispensing released maltose to production to include sampling maltose from the container used for production -----(b)(4)----- subsequent to a manufacturing run.

The answer is satisfactory.

19. Please provide clearer pictures of figures in report L.194.05.060, (e.g. Figure 3).
Cangene provided the clearer pictures of the figures. The answer is satisfactory.

20. Please describe the containers in which the plasma is aliquoted and shipped back to Cangene. Please provide this shipping validation.
Cangene described the containers which are ----------(b)(4)---------- designed for the collection, storage and shipment of plasma prior to fractionation. It is a ----------(b)(4)----------. Cangene contracts an independent company -----(b)(4)-----, for delivery of -(b)(4)- equine plasma to Cangene's manufacturing facility in Winnipeg. -----(b)(4)----- employs a qualified carrier, --(b)(4)-, for transport of the -(b)(4)- equine plasma to Winnipeg using ----------(b)(4)----------. There is no internal validation report for the plasma shipment. The documentation of -----(b)(4)----- as a supplier and --(b)(4)-- as a carrier has been reviewed under Cangene's audit program. The adequate shipment of plasma is confirmed by Cangene with verification of the shipment against the controlled document, including verification that the trailer tamperproof seal is intact prior to unloading the plasma, a copy of the temperature chart records for the trailer is obtained and confirmed to be maintained at -(b)(4)-

for the trip duration, and the shipment quantity. Temperature excursions during shipment are documented and investigated under the Deviation management system. This answer is satisfactory.

21. Please provide a table of all the mixing speeds and times with a reference to their respective validation protocols. Please provide the results of mixing validations for all your mixing steps for the maximum speed and time with an assessment of product impact.
Cangene provided a table of the mixing speeds and times with references to the respective validations. The answer is satisfactory.

22. Please comment on the sampling errors encountered with the -------(b)(4)------- chromatography column samples for -(b)(4)- testing. Please describe how the samples were contaminated with the -(b)(4)-. Please provide all other occurrences of such sampling errors and the CAPAs.
Cangene commented on the sampling errors for -(b)(4)- testing in cleaning validation samples of the -------(b)(4)-------- columns. The sampling errors were due to potential contamination of the samples with ----------(b)(4)---------- . The CAPA implemented was to let the ---------(b)(4)---------- before sampling. Cangene also mentioned other -(b)(4)- excursions in -(b)(4)- cleaning samples which were due to -------(b)(4)-------- ----------. The CAPA implemented was to implement ---------(b)(4)---------- ----------. This answer is satisfactory.

23. Please set a time range limit on the process parameters which do not have one, e.g., plasma pooling time, -(b)(4)- duration, clarification filtration, etc., and provide a table listing these parameters and process time limits.
Cangene set ranges for processing times based on the validation data based on 3 sigma calculations from the -(b)(4)- runs. The ranges are acceptable since the limits were covered by data from the validation batches.

[--(b)(4)--]

24. What is the process in place if you experience -(b)(4)- membrane fouling?
Cangene responded that alert levels for processing times were committed in the response to question 23 and an increase over those times is an indication of membrane fouling. Excursions exceeding the alert limits will be documented under the Deviation management system. As part of the investigation, additional samples will be taken to identify the source of fouling and impact to product. In addition to the alert limit for processing times, the following procedures are in place for monitoring the

performance of the -(b)(4)- membranes: ----------(b)(4)----------. This answer is satisfactory.

25. Please set the equilibrated column hold times for each column.
Cangene set the equilibrated hold times based on 3 sigma calculations of the trended mean from -(b)(4)- runs.

[--(b)(4)--]

26. Your -(b)(4)- IgG purity has been mainly above -(b)(4)- in most runs, please comment on the tightening of this specification from -(b)(4)-
Cangene recommended the tightening of the -(b)(4)- purity to -(b)(4)-, which is approximately 2 standard deviations from the average purity of -(b)(4)-. This answer is satisfactory.

27. Please set a maximum time of pepsin digestion.
Cangene set the maximum time of pepsin digestion based on 3 sigma calculations from the mean of -(b)(4)- runs.

[--(b)(4)--]

28. Please explain the origin of the precipitate in the -(b)(4)- step.
----------*(b)(4)*----------

29. Please provide a validation for the -(b)(4)- hold time of the Drug Substance Hold prior to aliquoting.
Cangene provided the hold time validation PV_5014_rep_v1, "Hold for Bulk Formulated ---(b)(4)----------"(date of report approval: December 19, 2012). The validation contained
----------*(b)(4)*----------

30. Please direct us to the eCTD document section where we may find the following validation reports: PV_5025, PV_5028, PV_5029.
    a. *PV_5025 was submitted for ----------(b)(4)----------.*
    b. *PV_5028 (approved December 21, 2012) and PV_5029 (approved December 21, 2012) were submitted for the number of uses of the ----------(b)(4)----------, respectively. We*

did not agree that -(b)(4)- uses was fully validated and requested Cangene to limit the number of uses to -(b)(4)- for each column. If Cangene intends to increase the number of uses, they may submit additional data for review.

31. Has a leachables and particle shedding study been performed with product on the ---------(b)(4)---------- sterile filter?
    Cangene stated that the particle shedding study has been performed (the particle shedding study is acceptable), but a leachables study has not been performed. An extractables study has been performed under worst-case conditions using model solvents (----------(b)(4)----------). In all cases, the extracts have been shown to be non-toxic. This answer is satisfactory.

32. Please direct us to the document where we may find the pre-determined acceptance criteria for the parameters measured in report PD_740_BAT_08_018_rep_v1, "Additional characterization of the -(b)(4)- Anion Exchange Chromatography Step".
    Cangene stated that the fractional factorial design consisted of -(b)(4)- runs, including -(b)(4)- runs executed at the manufacturing targets (centre points). The design allowed evaluation of the four parameters at high and low conditions. The acceptance criterion for this study was that all runs had comparable purities and recoveries to the center-point runs. This answer is satisfactory.

Response received and February 5 (eCTD sequence 0008) and 21 (0010), 2013

Additional data were submitted in the February 5, 2013 response. One of the reports, PV_5007 was for the "Mixing and Hold Times for Solutions in Large Liquid Preparation (LLP) ---(b)(4)--- BAT Process" (approved January 28, 2013). The report did not contain the hold times validation for the buffers as stated in the title and instead referenced report PV_5033 (approved August 26, 2008), which was provided after a request on February 21, 2013. Report PV_5033 intended to support a -(b)(4)- hold time for these solutions; however, the validation contained missing data and TNTC microbial counts for some -(b)(4)- hold timepoints. We request that Cangene re-validate the hold times for the following solutions: --(b)(4)----------

Ten (10) Pages Determined to be Non-Releasable: (b)(4)