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

Date: December 19, 2012

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: (Midcycle) Review : Process Validation and Raw Materials

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Recommendation

An information request with the questions outlined below.

Information Request (IR)

1. Please confirm which process scales you intend to license.
2. Please submit a table indicating which adjuvant was used to produce the anti-sera for each monovalent bulk.
3. 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.
4. 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.
5. Please explain what procedure is in place if the alert limit is reached for each in-process specification?
6. Please describe the maltose endotoxin deviation and what increased testing is being done.
7. Please provide clearer pictures of figures in report L.194.05.060, (e.g. Figure 3).
8. Please describe the containers in which the plasma is aliquoted and shipped back to Cangene. Please provide this shipping validation.
9. 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.

10. 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.
11. 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.
12. What is the process in place if you experience -(b)(4)- membrane fouling?
13. Please set the equilibrated column hold times for each column.
14. 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)-.
15. Please set a maximum time of pepsin digestion.
16. Please explain the origin of the precipitate in the ---(b)(4)--- step.
17. Please provide a validation for the -(b)(4)- hold time of the Drug Substance Hold -------(b)(4)------.
18. Please direct us to the eCTD document section where we may find the following validation reports: PV_5025, PV_5028, PV_5029.
19. Has a leachables and particle shedding study been performed with product on the ---------(b)(4)--------- ---------- sterile filter?
20. 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".

Executive Summary

Cangene Corporation submitted a BLA on September 20, 2012 for Botulism Antitoxin Heptavalent (A ,B, C, D, E, F, G) - (Equine), [H-BAT]. H-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.

H-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).

At the time of the midcycle review, no major deficiencies have been found with the process validation section and the control of raw materials. There were a few deviations that the FDA was informed about during the IND review of this product and appear to be resolved. Some of the manufacturing process parameters and certain specifications appear more broad than necessary and may be asked to be tightened before approval. The -------(b)(4)------ scales appear comparable, except for the F(ab)'2 content, which has ----------(b)(4)---------- scale due to change in pepsin type and digestion parameters. An information request will be sent to obtain more information about the process validation.

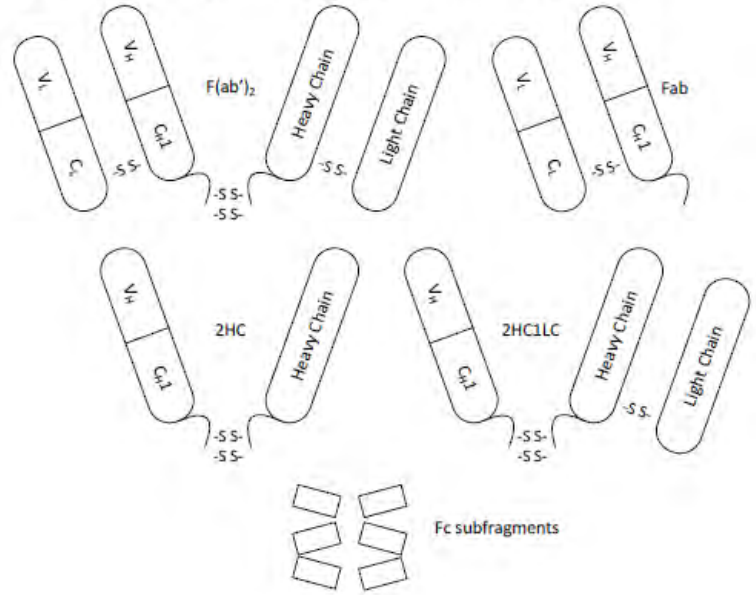
CMC Review Assignments

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

1. General Information
    a. Process Flow Chart (please see attachment)
    b. Name, address, and responsibility of each manufacturer (please see attachment)
2. Botulism Antitoxin - Equine (Drug Substance)
    a. eBAT (or H-BAT) Drug Substance is an immunoglobulin (Ig) product produced from equine plasma by pepsin digestion of the gamma immune globulin (IgG) monomer to yield a purified fraction containing dimeric antigen binding fragments (F(ab′)2) with a molecular weight of approximately 100 kDa, monomeric antigen binding fragments (Fab) with a molecular weight of approximately 50 kDa and F(ab′)2 related fragments (i.e. small amounts of fragments comprised of two heavy chains (2HC) and fragments comprised of two heavy chains/one light chain (2HC1LC)). IgG as measured as a process related impurity by ------(b)(4)-------
    ----------.

Figure 2 Schematic Representation of IgG Fragments Generated by Pepsin Digestion



    b. Botulism Antitoxin Drug Substance is manufactured by a general process that is identical for seven (7) monovalent antitoxin serotypes (A-G) which are subsequently processed, by blending, into Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine; eBAT NP-018).
    c. Each eBAT Drug Substance antitoxin serotype is a clear to opalescent, colorless to pale yellow liquid in an aqueous buffer (--(b)(4)--) containing equine derived antibody fragments that are targeted against one of the seven serotypes. The fragments are derived from digesting intact equine IgG monomers with the enzyme pepsin, resulting in F(ab′)2, Fab and F(ab′)2 related fragments. The purpose of the digestion is to remove the Fc region from the intact equine IgG monomer, rendering it less immunogenic in humans.
    d. Cangene Corporation (Cangene) has been manufacturing eBAT Drug Substance since 2004, ----------(b)(4)----------, to accommodate an increased requirement for eBAT NP-018 delivery to the Center for Disease Control and Prevention (CDC) Strategic National Stockpile (SNS).
    e. The process validation is done at the -(b)(4)- scale, which is Cangene's "commercial" manufacturing process, and Cangene submitted a comparability study (740_BAT_07_040_v2) to show that the H-BAT manufactured at the -(b)(4)- scale is comparable to the -(b)(4)- scale.

f. The manufacturing process is identical for all seven antitoxin serotypes (A, B, C, D, E, F and G). Each serotype bulk is manufactured as a stand-alone manufacturing run, each with its own batch record and separated by line clearance activities, yielding a formulated monovalent antitoxin specific bulk drug substance.

g. The manufacturing process for each monovalent bulk consists of three (3) critical purification steps:

   i. The immunoglobulin (IgG) fraction is purified from the plasma by cation exchange chromatography, using --------(b)(4)-------.

   ii. The intermediate-purity IgG is then digested with pepsin, which cleaves the monomeric IgG into the F(ab')2, Fab and F(ab')2 related immune globulin fragments (also termed F(ab′)2/Fab fragments).

   iii. The despeciated product is applied to an anion-exchange column, which binds the pepsin and residual digested proteins/peptides.

h. There are two (2) orthogonal viral inactivation/removal steps:

   i. Solvent Detergent (SD) inactivation step

   ii. ------------------------------(b)(4)--------------------------- virus filtration step

i. Bulk hold

   i. H-BAT drug substance is stored at ---------------------(b)(4)-------------------- --.

j. Reprocessing

   i. There are no reprocessing procedures for the Drug Substance (monovalent bulk).

k. Filling, Storage, and Transportation (DMPQ)

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

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l. Control of Materials

   i. Starting plasma

      1. Phase A and Phase B

         a. ----------------------(b)(4)--------------------

            i. Phase A Plasma, was collected by the US Department of Defense (DoD) at BioWhittaker Inc. (Walkersville, MD) between 1993 and 1996. ---------------------(b)(4)------------------ ------------------------------------.

ii. ------(b)(4)-------, starting plasma for the -(b)(4)- scale, Phase B plasma, was collected from Auburn University initially, followed by Lake Immunogenics.

b. For the -(b)(4)- manufacturing process, Phase B Plasma, sourced from Lake Immunogenics (Ontario, New York) and Auburn University (Auburn, Alabama).

2. Horses
   a. All horses used in production are, to the greatest extent possible, of North American (US or Canadian) origin.
   b. tested for Equine Infectious Anaemia (EIA) prior to acquisition, and annually thereafter, and are quarantined for a minimum of 21 days following acquisition to confirm they are free from infectious diseases.
   c. The health of each animal is monitored closely and recorded, with regular worming and vaccination programs in place managed through supplier standard operating procedures (SOP).
3. Botulism Toxoid and Toxin
   a. Toxoid - purified *C. botulinum* toxin complexes ----------(b)(4)----------
   b. The source of both botulism toxoid and toxins during Phase A Plasma production was the ----------(b)(4)---------- with the exception of the Type C toxoid which was obtained from ---(b)(4)---
   c. The group at the ----------(b)(4)---------- that produced toxoid and toxin for Phase A Plasma is the current group known as ------(b)(4)------ which is the source of all toxoid and toxin for Phase B Plasma production.

Table 3 Strains of *C. botulinum* used to Produce Toxins

Toxin Type	Strain
Type A Toxin Complex	(b)(4)
Type B Toxin Complex	
Type C Toxin Complex	
Type D Toxin Complex	
Type E Toxin Complex	
Type F Toxin Complex	
Type G Toxin Complex	

4. Horse immunization and equine plasma collection
   a. Performed in line with cGMP for human plasma collection
   b. botulism toxoid (with or without adjuvant) and botulism toxin (with or without adjuvant) administered to invoke the greatest response from the horse/ amended as required to increase or sustain antibody titers. Cangene targets approximately -(b)(4)- higher titers, based on serotype, to maintain average titer targets for manufacturing.

Table 29 Average Titer Target for Pheresis

Serotype	Average Titer Target for Pheresis (IU/mL)
A	(b)(4)
B	
C	
D	
E	
F	
G	

b. Plasma is collected into sterile bags containing sodium citrate as anticoagulant
c. bags of plasma are assessed as being essentially free of blood cells and have no evidence of hemolysis.
d. Tested for adventitious agents
    i. 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
e. Plasma held for -(b)(4)- (from last bleed date) prior to use.

ii. Pepsin

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

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

iii. TNBP

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

iv. Triton-X

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

v. ----------(b)(4)----------

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

m. Complete list of raw materials

Table 4 Control of Materials used in the 1000 L Scale Manufacture of Botulism Antitoxin Drug Substance – (Equine)

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

1. Controls of Critical Steps and Intermediates

n. Critical Quality Attributes

Nine (9) Pages Deteremined to be Non-Releasable: (b)(4)

m. Control of Excipients
    i. Maltose

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

    ii. Polysorbate 80

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

n. Control of the Drug Product
    i. Specifications (Lot release)
    ii. See attachment

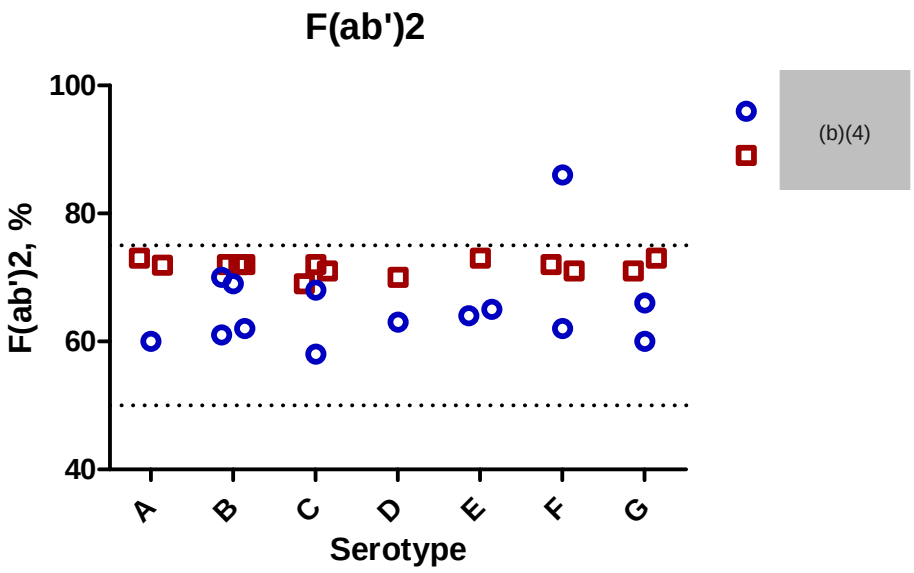
3. Batch Analysis
    a. Change in Plasma Source
        i. (3.2.P.5.4) pg 48 of 63
        ii. During the -(b)(4)- campaign. Phase A vs. Phase B Plasma, 2 serotypes compared A and B. Data appear comparable except differences in potency seen, Cangene attributes these to the mouse neutralization assay (MNA), ---(b)(4)----.
    b. Change in Peak Collection for Cation Exchange Chromatography step
        i. (3.2.P.5.4) pg 53 of 63
    c. During the -(b)(4)- campaign, Start of Phase B plasma, ----------(b)(4)---------- ----------, which allowed for the entire peak to be recorded. The point of stop

collection changed to point at which absorbance profile decreases and plateaus to allow for compete product collection. Data appear comparable.

c. Change in Grade of Pepsin used for digestion of Equine IgG
   i. (3.2.P.5.4) pg 53 of 63
   ii. The -(b)(4)- process pepsin contained ----------(b)(4)----------. The grade of pepsin was replaced with a ----------(b)(4)---------- ----------.
   iii. All the -(b)(4)- drug substance and drug products were made with pepsin with -(b)(4)- (including Lot 2060401 used in clinical and non-clinical studies)
   iv. The -(b)(4)- monovalent bulks were made with the ----------(b)(4)---------.
   v. Data appear comparable.

d. Increase in Scale of Manufacture Including Optimization of Pepsin Digestion (Despeciation) Step
   i. (3.2.P.5.4) pg 54 of 63
   ii. The % F(ab′)2 and % Fab and F(ab′)2 related fragment is statistically different in the product manufactured at ----------(b)(4)----------. The average % F(ab′)2 has ----------(b)(4)----------. This change is associated specifically with the optimization of the pepsin digestion step
   iii. The pepsin digestion step was optimized for the ----------(b)(4)---------- ---------- ---------- ---------- ----------.

4. Comparability of the ----------(b)(4)---------- scale (740_BAT_07_040_v2)
   a. Written in 2009
   b. Two (2) -(b)(4)- finished product lots produced, one with Phase A plasma and one with a blend of serotypes produced with Phase A and Phase B.
   c. Six (6) -(b)(4)- finished lots produced from Phase B plasma, -(b)(4)- monovalent bulks.
   d. Lots made from both scales appear comparable except for F(ab')2 content which is higher for the -(b)(4)- bulk due to an optimized pepsin digestion step.



   e. It appears that the F(ab')2 specification may be tightened.

Three (3) Pages Determined to be Non-Releasable: (b)(4)