OBE/DE Review Memo

Date: February 28, 2013

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To: Robert Fisher, MD, Chair, BLA Review Committee
CBER/OBRR

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FDA STN: BLA 125462.0

Subject: Review of the Pharmacovigilance plan (PVP) for Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) (Equine) indicated for the treatment of symptomatic botulism following documented or suspected exposure to botulism neurotoxin (BoTN) serotypes A, B, C, D, E, F or G.

Applicant: Cangene Corporation (Lic # 1201)

Product: BAT [Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) (Equine)]
Pharmaco-therapeutic group (ATC Code): Immune sera and Immunoglobulins (ATC code: J06AA04)

Proposed Indication: Treatment of symptomatic botulism following documented or suspected exposure to botulism neurotoxin (BoTN) serotypes A, B, C, D, E, F, or G.

Submission: BLA 125462/0 (Original application) and 125462.03

Submitted to FDA: September 20, 2012

First Action due: March 23, 2013

Material reviewed: Section within BLA 125426.0 pertaining to the of the pharmacovigilance plan (PVP) version 1.0 and 125462.03

1. Introduction

a. Botulism

Botulism is a rare but serious illness characterized by flaccid paralysis of muscles caused by neurotoxins produced by the *Clostridium Botulinum* bacteria. The botulism toxins act by entering neurons and preventing the release of acetylcholine from voluntary motor nerve endings and autonomic cholinergic neuromuscular junctions. Motor muscle contraction can only resume when a new axon not exposed to the toxin is generated leading to lengthy recovery time. Botulism neurotoxins are highly potent and lethal and have been designated as potential biological weapons. There are various types of botulism based on the port of entry such as food-borne, wound, intestinal colonization (infant and adult) inhalation and iatrogenic botulism. Symptoms occur within 8 to 36 hours of exposure but can occur as early as 6 hours or as late as 10 days. Untreated, botulism has a mortality rate of 50%. With intensive supportive care, mortality rates drop to 3-5%. About 100 cases occur every year in the US and about 1,000 worldwide. The main therapy relies on intensive care unit support with mechanical ventilation if needed and administration of equine antitoxin. Timely administration of antitoxin may arrest the progression of paralysis and decrease the duration of the illness.

b. Product information

BAT is an antitoxin consisting of F(ab')2, and Fab plus F(ab')2 related immune globulin fragments derived from horses immunized with a specific Clostridium botulism toxoid and toxin serotype. BAT is a sterile antitoxin solution prepared from pooled plasma obtained from horses immunized with Clostridium botulism toxoid and toxin serotypes A to G. The F(ab')2, and Fab plus F(ab')2 related immune globulin fragments derived from pepsin digestion of the Fc portion of whole IgG molecules. The final heptavalent product is obtained by blending the seven antitoxin serotypes A-G. BAT is a sterile solution formulated with 10% maltose and 0.03% polysorbate 80 (PS80) for IV administration and contains trace amounts of tri-n-butyl phosphate (TnBP), Triton X-100 (TX-100) pepsin and, impurities from the BAT manufacturing process. BAT contains approximately --(b)(4)-- of purified F(ab')2 and Fab plus F(ab')2 related immune globulin fragments and is supplied in either 20 or 50 mL glass vials. The vial size (20 mL or 50 mL) and fill volume (10 to 22 mL) vary between product lots however, each vial contains a minimum potency of >4,500 Units (U) serotype A antitoxin, >3,300 U serotype B, >3,000 U serotype C, >600 U serotype D,>5,100 U serotype E antitoxin, >3,000 U serotype F, and >600 U serotype G.

c. Regulatory history

The original BLA application was received on September 20, 2012. There are currently no available US licensed product to treat botulism except for Botulism Immune Globulin Intravenous Human (BabyBIG or BIG IV) which is a human immunoglobulin product used to treat botulism caused by botulism neurotoxin (BoTN) serotypes A and B in patients less than one year of age (infant botulism).

Since the evaluation of new treatment options for botulism using controlled human efficacy trials is unethical and unfeasible, the sponsor submitted the equine BAT biological license application (BLA) for review under the "Animal Rule" (21 Code of Federal Regulation (CFR) 601 Subpart H) (1). The "Animal Rule" states that in selected circumstances the Food and Drug Administration (FDA) may grant marketing approval based on adequate and well-controlled animal studies when the results of these studies established that the biological product is reasonably likely to produce clinical benefits in humans. 21 CFR section 601.91 states: "…the applicant must conduct postmarketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Such postmarketing studies would not be feasible until an exigency arises".

d. Blood Product Advisory Committee (BPAC) meetings

BAT is the first and only CBER product to be reviewed under the "Animal Rule" to date. The current status of the BAT BLA review was presented at the Blood Advisory Committee Meeting (BPAC) on February 12-13, 2013.

e. Objectives of the review

The purpose of this review is to determine whether the sponsor's proposed pharmacovigilance plan is adequate to monitor the safety of the product after licensure in accordance to FDA regulations.

2. Material reviewed

- **a.** Adverse events characteristic of the pharmacological class (125462.0 section 1.7)
- **b.** BAT Pharmacovigilance Plan (125462.0) version 1.0 and amendment 125462.08
- **c.** CBER's clinical review
- **d.** Medical literature
- **e.** Blood Products Advisory Committee recommendations from the February 12-13, 2013 BPAC meeting.

3. Adverse events characteristic of the pharmacological class

The main safety concerns with heterologous immune globulins are anaphylactic and anaphylactoid reactions, delayed allergic reactions (serum sickness) and febrile responses to immune complexes formed from animal antibodies. These reactions were listed in the package inserts of previously licensed Botulism Antitoxin Bivalent Type A and B (2 & 3).
The sponsor cited Black and Gunn's review of the 268 individuals who received equine botulism antitoxins between 1967 and 1977 (4). This analysis showed that 24 (9.0%) had non-fatal hypersensitivity reactions, including 5.3% acute and 3.7% delayed. The overall reaction rates did not differ with age, sex or with the botulism antitoxin type BAT AB (BAT AB package insert) or BAT ABE (BAT ABE package insert). However serum sickness occurred significantly ($p<0.02$) more frequently in individuals receiving more than 40mL of botulism antitoxin, compared to those who received 40mL or less.

4. Pharmacovigilance plan review

a. Toxicity database

No toxicology studies were conducted for BAT or any of its components. The sponsor noted that the safety of equine derived immune globulins was well documented following their use in clinical practice. For details on animals studies, please refer to pharmacology review.

b. Safety database

The clinical safety database in support of the BAT Clinical Development Program submitted by the sponsor as part of the BLA consists of 56 healthy subjects participating in two clinical studies (BT-001 and BT-002 stage B) and 148 patients with suspected or confirmed botulism who were treated with BAT under a CDC-sponsored Expanded Access Program (BB-IND 6750, BB-IND 13615) from 15 January 2008 through 31 December 2011.

i. Clinical trials

Participation in trials BT-001 and BT-002 was limited to healthy adults 18-55 years of age. Both studies excluded individuals with any known or documented allergies to horse, to blood products derived from human or equine source and allergy to latex, asthma, history of substance abuse, smokers, pregnancy or lactation, HIV, HBV or HCV positive individuals, individuals with significant blood loss or blood/plasma donation within the 56 days prior to dosing and individuals with demonstrated potential for allergic reaction to 4-(hydroxyl-3-nitro-phenyl) acetyl (NP)-08 based on positive horse dander (E3) IgE test or positive NP-018 skin sensitivity test prior to dosing. Additional criteria were added in study BT-002 aimed at excluding individuals with conditions that would impact nerve conduction such as individuals previously injected with Botox, documented botulism infection/intoxication, food or seasonal allergies requiring treatment with immunosuppressive drugs, individual with positive result for botulism antitoxin skin

sensitivity test, previously documented or currently suspected motor neuron disease, peripheral neuropathy, lumbosacral radiculopathy, diabetes, coagulopathies, and vasculites.
In the combined protocols BT-001 and BT-002, two subjects (3.6%) received less than one dose IV in less than 1 hour, 34 subjects (60.7%) received one single adult dose IV over 1.5 to 2.5 hours and 20 subjects received one single dose IV in about 2.5 hours.
During either trial, no subject experienced anaphylactic reactions however 2 subjects experienced mild allergic reactions, possibly or probably related to BAT, leading to infusion termination in both cases. No cases of serum sickness or deaths were reported. Overall BAT was well tolerated by participating subjects.

Clinical trial BT-001 (n=40) was designed to assess the safety and PK of BAT following IV administration in a total of 40 health adults 18 to 55 years of age. Half of the subjects (n=20) received one vial of BAT and the other half (n=20) 2 vials of BAT diluted 1:10 in saline. One subject received about 30% of the BAT dose because of moderate allergic reaction, possibly related to the study treatment (see below for detail). The infusion was terminated after 52 minutes.
There were no reports of death and no reports of cases of serum sickness in either trial.

- Allergic reactions: No subject experience anaphylactic reaction. One subject experienced a mild allergic reaction at the time of BAT infusion which included skin disorder (subcutaneous bumps) and urticaria, mild and moderate headache, mild pain (body ache), mild and moderate pyrexia and mild pharyngolaryngeal pain. This subject did not react to either horse dander IgE test or the skin sensitivity test during screening. Human anti-e-BAT NP-108 antibody testing before and after dosing was also negative. The subject's infusion was terminated after 52 minutes (approximately 30% of the dose).
- Adverse events (AEs) occurring in 10% of the subjects or more included headache (n=5 or 13% of subjects) and somnolence (n=4 or 10% of subjects). Headache was graded as mild (n=5) and moderate (n=2) and possibly or probably attributed to the study medication. All instances of somnolence were classified as mild and assessed as unlikely related to the study medication.
- AEs occurring in less than 10% of the subjects and assessed as possibly or probably related to the study medication included: dysphagia, flatulence, nausea, throat irritation, feeling cold, pain, pyrexia, swelling, musculo-skeletal stiffness, pharyngolaryngeal pain, hyperhidrosis, pruritus, pruritus generalized, skin disorder and urticaria. These AEs were mild or moderate in severity.

Clinical trial BT-002 (n=26) was designed as a two-stage (A and B) pharmacodynamic study modeling human efficacy. Stage A evaluated the Extensor Digitalis Brevis (EDB) muscle paralysis model in healthy adult subjects using a licensed equine-derived botulism antitoxin for serotype A and B (Botulism Antitoxin Bivalent (Equine) Types A and B, Adventis Pasteur). In Stage B of the study, the EDB model was used to evaluate the effectiveness of BAT in neutralizing BoNT serotype A-G in healthy adult subjects. In this study, sixteen subjects were given one single infusion of BAT diluted 1:10 in saline and ten subjects received an equivalent volume of placebo (0.9% saline). One subject did not receive the entire BAT dose because of a moderate allergic reaction. Most reported AEs were considered mild or moderate.

- Allergic reactions: No subject experienced anaphylactic reaction. One subject experienced a moderate allergic reaction at the time of BAT infusion. This subject developed urticaria within 5 minutes following the start of the administration of the study drug. The subject also experienced chest discomfort, elevated body temperature and elevated fibrinogen levels. This subject's infusion was terminated after 5 minutes (about 1.5% of the dose). This subject did not react to either horse dander IgE test or the skin sensitivity test during screening. Human anti-e-BAT NP-108 antibody testing before and after dosing was also negative.
- The most frequently reported AEs in subjects receiving a single IV dose of BAT in Stage B of BT-002 were: tonsillar hypertrophy (n=4 or 25% of subjects), contusions (n=4 or 25% of subjects), skin lacerations (n=3 or 19% of subjects), lymphadenopathy (n=3 or 19% of subjects), pain in extremity, rhabdomyolysis, headache and somnolence (n=2 or 13% of subjects). All cases of lacerations and/or contusions were the results of an active life style and determined to be unrelated to the study drug. Similarly cases of tonsillar hypertrophy and/or lymphadenopathy were associated with concurrent illness and also determined to be unrelated to the study drug.

- Seven AEs were considered severe and included generalized pain (n=1), viral infection (n=1), skin laceration (n=3), upper respiratory tract infection (n=1) and tonsillar disorder (n=1). None of these were considered related to the study drug.
- Among the ten subjects who received a placebo, 2 subjects reported lymphadenopathy, 2 subjects reported aphthous stomatitis, 2 subjects reported viral upper respiratory infection and 2 subjects reported somnolence. Other AEs occurred in 1 patient (<10% of the placebo group). All AEs in the placebo group were considered mild.

ii. CDC-sponsored Expanded Access Program (BB-IND 6750, BB-IND 13615)

Of the 148 patients treated with BAT, 121 (81.8%) were between 18-64 years of age, 7 (4.7%) were less than 18 years of age and, 20 (13.5%) were geriatric patients (≥ 65 years of age). The majority of patients were males (70.9%). Among the 148 patients who received BAT for a suspected or confirmed diagnosis of botulism under protocols BB-IND 6750 and 13615, 93.2% received only one adult dose of BAT. Three adult patients were exposed to a second dose of the product. One patient received two infant doses (10% of the adult dose) and one patient received two pediatric doses and five patients received one pediatric dose (pediatric and infant doses were calculated using the "Salisbury Rule"). Of the pediatric patients dosed with BAT, only one patient's infusion was stopped early due to the onset of hemodynamic instability. The administration of the second BAT dose varied from 7 days to one month. The "Salisbury rule" defines children dose as follows: children who weight less than 30kg should receive their weight (in kg) times 2 percentage of the adult dose and children who weight more than 30kg should receive their weight (in kg) plus 30 percentage of the adult dose. The majority of patients treated with BAT had a final diagnosis of botulism as reported by the physician (97/146; 65.5%). Table 1 shows the patient diagnosis at discharge.

Table 1: Patient diagnosis at discharge

Final diagnosis (as reported by the physician)	Overall (n=148)
Botulism	97 (65.5%)
Guillain-Barre Syndrome	14 (9.5%)
Myasthenia gravis	5 (3.4%)
Tick paralysis	1 (0.7%)
Other	21 (14.2%)
Missing	10 (6.8%)

Adverse reactions: Safety information was available for 146 of the 148 patients treated with BAT through the CDC-sponsor Expanded Access Program, between 15 January 2008 and 31 December 2011. In 128 patients the product was well tolerated. AEs were reported in 18 patients. These included agitation, asystole, bradycardia, bronchospasm, chest pressure, chills, diaphoresis, "jittery", pyrexia, mild hypertension, mild serum sickness, nausea, rash, severe anxiety, slight facial erythema, edema, tachycardia, urinary retention and vomiting. The most common AEs were pyrexia (reported in 8 patients or 11%), chills (n=3 or 2 %), rash (n=3 or 2%), nausea (n=2 or 1%) and edema (n=2 or 1%). Five patients appeared to have experienced symptoms potentially related to hypersensitivity (limited information). No patient experienced anaphylaxis.

Deaths: Six deaths were reported in patients after treatment with BAT under the CDC Expanded Access Program (BB-IND 6750) between January 15, 2008 and December 31, 2011. These deaths were determined to be due to the progression of botulism toxicity and co-morbidity complications and unrelated to BAT treatment. Table 2 is a summary of the deaths presented in the pharmacovigilance plan.

Table 2 Summary of the deaths of CDC patients treated with BAT

Age/Sex	*Date of death*	*Diagnosis*	*Other AEs related to BAT*	*Cause of death*
64yr/M	*-(b)(6)-*	*Final diagnosis botulism*	*Mild diaphoresis during BAT infusion resolving within a few hours, later experienced*	*Died of unknown cause 52 days after BAT administration. Death*

Age/Sex	*Date of death*	*Diagnosis*	*Other AEs related to BAT*	*Cause of death*
			mild serum sickness with myalgia, arthralgia and dark urine 12 days after BAT. administration	*assessed as unrelated to BAT and not directly linked to botulism*
82yr/F	*-(b)(6)-*	*Final diagnosis not botulism*	*None reported*	*Died of respiratory failure and pneumonia 3 days after BAT administration. The patient had tolerated BAT well but showed no improvement with regard to her encephalopathy. Death was assessed as unrelated to BAT*
77yr/M	*-(b)(6)-*	*Final diagnosis botulism*	*None reported*	*Died of unknown causes 94 days after BAT administration. Death was assessed as unrelated to BAT.*
88yr/F	*-(b)(6)-*	*Final diagnosis not botulism Guillain-Barre Syndrome*	*None reported*	*Died of Miller-Fisher variant of Guillain-Barre syndrome 7 days after administration of BAT. Death assessed as unrelated to BAT.*
64yr/M	*-(b)(6)-*	*Final diagnosis Botulism*	*None reported*	*Died 45 days after BAT administration. Cause of death was respiratory failure and metastatic cancer. Death was assessed as unrelated to BAT*
27yr/M	*-(b)(6)-*	*Final diagnosis Botulism*	*None reported due to BAT. The patient experienced respiratory and cardiac arrest resulting in pulseless status for 25 minutes before circulation was restored and was neurologically devastated.,*	*Died 27 hrs after BAT administration. Respiratory and cardiac arrest due to hypoxia from a mucus plug during tracheostomy change. Death was assessed as unrelated to BAT.*

Other serious AEs:

Bradycardia/cardiac arrest: A ten year old Hispanic male from Mexico was diagnosed with food-borne botulism due to home-canned peppers. The patient botulism's symptoms began on October 13, 2010 and included vomiting, muscles weakness and diplopia. The next day he developed decreased skin reflexes and required intubation due to breathing difficulties. The patient received an incomplete pediatric dose of BAT under the CDC-sponsored Expanded Access Program (BB-IND-6750). The BAT infusion started on October 16, 2010 at 8:45 am. The patient experienced bradycardia at 10:15am which lasted about 2 minutes until asystole occurred. The administration of BAT was suspended and chest compression and IV epinephrine were administered. The patient recovered. The BAT infusion resumed at 10:20am. At 10:50am the patient abruptly experienced a second episode of bradycardia which lasted about 3 minutes. Infusion of BAT was suspended and IV epinephrine was administered. The patient's hemodynamic status returned to normal. The infusion of BAT was discontinued entirely. The patient had received about 70% of the intended pediatric dose of BAT. The patient was successfully stabilized on the day of the event and did not experience any other reactions or complications. The event of hemodynamic instability including

two episodes of severe bradycardia with one progressing to cardiac arrest after receiving an incomplete pediatric dose of BAT administration was assessed as serious, unexpected and possibly related to BAT but the possibility that it may be related to botulism neurotoxin could not be rule out. The patient recovered from the event.

Rebound toxicity: A 72 year old female complained of nausea, vomiting, abdominal pain, constipation, shortness of breath, weakness, and fatigue on July 31, 2009. She presented with bilateral extraocular palsy, bilateral ptosis, dilated pupils, bilateral facial paralysis, bilateral palatal weakness and impaired gag reflex. She was diagnosed with botulism, hospitalized and placed on a ventilator in ICU on August 2, 2009. She was treated with licensed BAT AB and BAT E on August 5, 2009 which she tolerated well but her symptoms continued to progress. A serum sample confirmed the type F botulism on August 12, 2009. BAT was administered on August 13, 2009 and the patient started having physical therapy near the end of the infusion. The patient did not experience any adverse events at 6 days post-infusion. On August 19, 2009, the patient had substantial recovery of upper and lower extremity muscle strength, and underwent weaning trials from the mechanical ventilator.
The patient experienced what appeared to be a recurrence of botulism symptoms after BAT treatment. She experienced proximal and distal upper and lower extremity weakness, trouble breathing and return to mechanical ventilator, partial ptosis and bilateral facial paralysis. The patient was also constipated. In the morning of August 26, she was slightly weaker and had bilateral ptosis. Her symptoms indicated a recurrence of botulism symptoms from intestinal colonization of *Clostridia* with ongoing production of toxin. The patient was treated with metronidazole and vancomycin for 2 weeks. The patient symptoms improved and she was transferred to a rehabilitation unit. As of October 15, 2009, the patient was 'back to normal". This case was described in the journal of Clinical Infectious Disease (5).

Serum sickness: A 64 year old male patient experienced mild serum sickness after receiving BAT under the CDC-sponsored Expanded Access Program (BB-IND-6750). The patient's onset of symptoms occurred on April 27, 2009 with neurologic symptoms onset 3 days later. His clinical presentation included nausea, vomiting, blurred vision, diplopia, dizziness, slurred speech, thick tongue, change in sound of voice, hoarseness, dysphagia, weakness, fatigue and cough. He was alert and oriented, had bilateral extraocular palsy, bilateral ptosis, dilated pupils, and pupils reactive but sluggish. He was admitted to the ICU and placed on a ventilator in May 2, 2009. Initial serum sample tested for botulism toxin was indeterminate. The patient showed some improvement of neurologic symptoms starting on May 9, 2009. On May 14, 2009, a serum specimen collected on May 4, 2009, was found to be preliminary positive for type F botulism. One vial of BAT was administered. After the infusion, the patient experienced mild diaphoresis that resolved within a few hours. The patient also had mild serum sickness with myalgia, arthralgia and dark urine (hematuria) 12 days after administration of BAT. The patient did not experience any rash. The serum sickness was determined to be mild. The patient was discharged from the hospital and transferred to a rehabilitation center on May 27, 2009. Upon discharge, the patient had residual weakness, including proximal extremity weakness, diminished deep tendon reflexes and bilateral cranial nerves deficits. During the course of the rehabilitation, the patient was treated for methicillin-resistant *Staphylococcus Aureus* tracheobronchitis, recurrent hematuria, neuropathic pain in the lower extremities, and deep thrombosis prophylaxis. Later in his hospitalization, the patient was tolerating tracheostomy plugging during the daytime and later on at night. Results of oximetry performed on July 5 indicated no absolute contraindication to decannulation. The patient opted for proceeding with decannulation instead of maintaining his tracheostomy tube for another month or two. On ---(b)(6)----, he was found unresponsive in his room. Code blue was called. Code was unsuccessful and the patient was pronounced dead on ----(b)(6)-----. The patient died of unknown causes while recovering from botulism and the cause of death was assessed as not related to BAT and not directly caused by botulism.

c. New safety concern

No death and no serious AEs were reported from clinical trials BT-001 and BT-002. The six deaths reported in patients treated with BAT under the CDC-sponsored Expanded Access Program were determined to be due to the progression of botulism toxicity and co-morbidity complications and unrelated to BAT treatment. The sponsor noted that no **new** safety concern have been identified following

administration of one dose of one or two vials in healthy subjects and when administered to patients with suspected or confirmed botulism.

Reviewer's comments:

Bradycardia: One case of bradycardia lasting about 2 minutes before progressing to asystole has been observed in a 10 year old boy with confirmed food-borne botulism. The reaction occurred within 1.5 hours from the start of the infusion of BAT and the infusion was temporarily stopped. When the patient was stabilized, infusion was resumed. The patient subsequently experienced a second episode of bradycardia within 30 minutes of the restart of the infusion that lasted 3 minutes. The infusion was permanently discontinued and the patient's hemodynamic status returned to normal. This adverse event was assessed as serious, unexpected and possibly related to BAT by the CDC and by the sponsor. Other than possible botulism neurotoxin activity, no alternative etiology was reported. Literature reports of bradycardia in association with anaphylaxis exist, and thus anaphylaxis remains in the differential diagnosis from a clinical standpoint (5). However, this OBE/DE reviewer determined that this case does not meet epidemiologic criteria for classification as anaphylaxis after application of the internationally accepted Brighton Collaboration criteria (which are designed to assess diagnostic certainty from case reports) (6). For all levels of diagnostic certainty, anaphylaxis is a clinical syndrome characterized by

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involving multiple (≥2) organ systems

For this patient, the 2 first criteria are fulfilled but not the 3rd as there is no description of more than one system involvement (cardiovascular).

This reviewer considers this adverse event a positive rechallenge indicative of a causal relationship with the resulting adverse event of hemodynamic instability. In the context of the limited human safety database, this spontaneous report represents a safety signal.

d. Important identified safety issue: Allergic reactions

The manufacturing process of BAT is believed to lessen the risk of allergenic reactions compared to previously licensed botulism antitoxins. Yet, the main safety concerns for BAT remain similar to those observed with previously licensed equine derived botulism antitoxins and other equine derived immune globulins. These reactions include anaphylactic reactions, thermal reactions (chilly sensation, dyspnea and rapid rise in body temperature within 20-60 minutes after injection of serum or antitoxin), serum sickness and hypersensitivity reactions. No anaphylactic reactions were observed in either clinical trials BT-001 or BT-002. However symptoms of allergic reactions were reported in both trials and in the CDC Expanded Access Program.

In study BT-001 one subject experienced a mild allergic reaction at the time of BAT infusion which included skin disorder (subcutaneous bumps) and urticaria, mild and moderate headache, mild pain (body ache), mild and moderate pyrexia and mild pharyngolaryngeal pain. The subject's infusion was terminated after 52 minutes (approximately 30% of the dose). In study BT-002 one subject also experienced a moderate allergic reaction at the time of BAT infusion. This subject developed urticaria within 5 minutes following the start of the administration of BAT, followed by chest discomfort, elevated body temperature and elevated fibrinogen levels. This subject's infusion was terminated after 5 minutes (about 1.5% of the dose). Neither of these two subjects reacted to either horse dander IgE test or the skin sensitivity test during screening. Human anti-e-BAT NP-108 antibody testing before and after dosing was also negative in both subjects.

In the CDC Expanded Access Program, one patient experienced mild serum sickness following BAT exposure (frequency 0.7%). In addition, reported events of rash, edema and bronchospasm in 5 patients (3.4% of patients who received BAT in the CDC Expanded Access Program) were suggestive of hypersensitivity reactions. By comparison, risk of urticaria (hives), serum sickness or other hypersensitivity reactions occurred in 9% of recipients of older antitoxins preparations.

In addition, with regard to the serious episodes of bradycardia described above, anaphylaxis remains a differential diagnosis. From her review of the safety database submitted to the BLA, this reviewer concludes that despite its novel manufacturing process, BAT like previously licensed botulism antitoxin remains associated with the risk of potentially life-threatening allergic reactions.

e. Important potential safety issue

Blood glucose false positive: BAT contains 10% maltose that may confer a potential risk of falsely elevated blood glucose readings when using a non-glucose specific point of care test systems such as glucose dehydrogenase pyrroloquinolinequinone (GDP_PQQ) base-tests. These systems cannot distinguish maltose from glucose. A false positive glucose test may result in inappropriate treatment with insulin (iatrogenic hypoglycemia) or in masked hypoglycemia, both potentially life threatening. No cases of false glucose readings were observed in clinical trials or in the CDC Expanded Access Program and no evaluation of such a risk could be carried out. Such a risk has been documented in an FDA review of reported adverse events following the administration of FDA-licensed maltose-containing immune globulin products (7 & 8). These events were linked to the used of GDH-PQQ glucose testing systems. Falsely-elevated blood glucose readings constitute an important safety issue (7). However the sponsor noted that the risk of falsely elevated blood glucose is unlikely due to the volume of BAT administered and the relatively small total amount of maltose in BAT (<50mL of fluid contains less than 5 grams of maltose) compared to high dose of immune globulin products, such as IVIG, containing maltose (500mL of fluid contains at least 50 grams of maltose).

Interaction with live attenuated viral vaccines: In a review of the published literature, the sponsor noted that there is a potential risk of interaction between live attenuated virus vaccines such as measles mumps, rubella or varicella leading to reduced efficacy of the vaccine. The reduced efficacy is attributed to a reduced virus replication and a decreased response in the immune response. Should this occur, a patient who received BAT would not be protected against the disease targeted by the vaccine.

f. Important missing information

For ethical reasons, the safety and efficacy evaluation of BAT as a new treatment option for botulism could not be carried out using human clinical trials. Participation in studies BT-001 and BT-002 was limited to health adult subjects with the exclusion of individuals with severe food or seasonal allergies. Individuals with hypersensitivity to horse and equine derived products were excluded in both studies. In addition individuals with medical history that would impact nerve conduction study were also excluded in BT-002.

No infants or children were included in study BT-001 or BT-002. Infants less than 1 year old with intestinal BoNT colonization are generally treated with IV human botulism immune globulin BabyBIG or BIG-IV. BIG-IV is effective against BoNT serotype A and B. BAT is used only in rare cases where the patient is infected with BoNT other than serotype A or B. Similarly no geriatric subjects were included in either study BT-001 or BT-002. However, both children and geriatric individuals were administered BAT under the CDC Expanded Access Program.

The safety of BAT was not evaluated in pregnant women or immunocompromised individuals. To date there is no evidence suggesting that the risk of developing hypersensitivity reactions following the treatment with BAT is greater in these populations.

g. High risk populations

Participation in studies BT-001 and BT-002 was limited to healthy adult subjects with the exclusion of individuals with severe food or seasonal allergies. Individuals with hypersensitivity to horse and equine derived products were excluded in both studies. The sponsor noted that the limited clinical safety database did not allowed for assessment of specific risk factors or risk groups contributing to the onset of hypersensitivity reactions following the treatment with BAT. However, since BAT is manufactured from pooled equine plasma, the potential risk of developing hypersensitivity reactions following exposure to BAT may be greater in patients with a known history of hypersensitivity of horse or equine blood products.

No infants were included in study BT-001 or BT-002. Infants less than 1 year old with intestinal BoNT colonization are generally treated with IV human botulism immune globulin BabyBIG or BIG-IV. BIG-IV is effective against BoNT serotype A and B. BAT is used only in rare cases where the patient is infected with BoNT other than serotype A or B.

h. Potential for overdose, transmission of infectious agents and off-label use

Overdose: The sponsor's recommended dose for pediatric patients is expressed as a percentage of the adult dose based on the patient's weight in Kg using the "Salisbury Rule" (see 4. b. ii for details). The recommended dose for infant is 10% of the adult dose (based on volume in vial) regardless of body weight. Miscalculation can lead to overdose. The sponsor noted that no instance of overdose with BAT was reported in the clinical trials or the CDC Expanded Access Program and therefore the evaluation of adverse events resulting from an overdose was not possible.
Transmission of infectious agents: The sponsor noted that the manufacturing process of the product includes various steps such as the use of solvent/detergent (S/D) to inactivate known lipid-enveloped viruses and the use of ------(b)(4)------ nanofilter to reduce the levels of viral particles that may be present in the pooled plasma from horses. However the sponsor also noted that these measures cannot completely exclude the possibility of transmission of some unknown, emerging or other pathogens.
Off-label use: The sponsor does not anticipate off label use.

i. Sponsor proposed action and timeline

The sponsor proposes to carry out routine passive post-marketing surveillance including monitoring of spontaneous reports of adverse events (AEs/ADRs) associated with the use of BAT and conducting periodic signal detection to identify changes in reporting frequencies of new and potential risk associated with the use of BAT. The sponsor intends to assess the expectedness, the seriousness and the causality of the events. Following this assessment, the sponsor proposes to report to the FDA all spontaneous serious and unexpected AEs including death, and serious and unexpected related events from clinical trials as 15 days reports. In addition the sponsor will consider special requirements for expedited submissions for cases of no drug effect, overdose, medication error, blood borne infections and other request from the FDA regarding non-serious AEs subjected to enhanced surveillance. The sponsor proposes to submit PSUR according to the ICH E2C (R1), E2C addendum and to follow the requirements of local regulatory agencies such as including a list of non-expedited reports in the addendum of the PSUR sent to the FDA.

In addition, to comply with the FDA "Animal Rule" regulatory pathway for approval (21 CFR 601.90), the sponsor proposes to conduct a phase IV study to evaluate the efficacy and the safety of BAT. Due to the small number of individuals exposed to botulism toxin yearly in the US and worldwide, the sponsor states that such study would not be feasible in ordinary condition and therefore, the study protocol (BT-003) will be implemented in the event of a mass exposure to botulism toxin (intentional/bioterrorism scenario) if a sample of at least 100 patients can be achieved. The objective of the study will be to evaluate the safety and efficacy to BAT in the treatment of patients with suspected or confirmed botulism. The sponsor proposes that in the event of a major botulism exposure Cangene will contact the CDC to obtain contact information for health care providers involved in the care of botulism patients treated or untreated with BAT. All eligible patients diagnosed with suspected or confirmed botulism, regardless of treatment with BAT will be eligible for enrollment into the study. This will allow inclusion of BAT untreated patients, if any, in the study as a comparison group. Data will be collected retrospectively and/or prospectively from the medical records of patients with confirmed or suspected botulism after their informed consent is obtained. The primary endpoints will relate to the efficacy of BAT and will be selected based on the type of exposure scenario and the availability of supportive therapy standard of care (SOC). The sponsor noted that it is possible that the SOC including mechanical ventilation may be limited in case of a large exposure scenario. In combination of SOC, the objective of the treatment is to reduce the severity and the duration of the illness, given that SOC alone can be sufficient to prevent death in patients with botulism. Mortality rates will be secondary end points. In the absence of SOC, the objective of the treatment with BAT is to prevent mortality as well as to reduce the severity and the duration of the illness. In this case the mortality rate will be the primary end point and the maximum severity of the illness will be the

secondary endpoint. Primary and secondary endpoints will be determined depending on the situation at time of implementation. Secondary endpoints include, in days, duration of hospitalization, duration of hospitalization in ICU, duration of mechanical ventilation, time to sustained clinical improvement. The safety endpoints will be related adverse events. Incidence of adverse events will be tabulated for patients treated with BAT. The sponsor proposes to stratify the enrolled patients according to the time from exposure to BAT administration (early treatment (≤2 days from symptoms onset) vs. late treatment (>2days from symptoms onset) vs. no treatment with BAT. Of note, the sponsor adds that BAT is stockpiled by the CDC for emergency use in the Strategic National Stockpile (SNS) and that depending on the emergency situation BAT may not be available to all patients. The data collected will be similar to the data collected in the CDC Expanded Access Program IND (IND 6750). With regard to the collection of the data, the sponsor plans to request from the CDC contact information of health care providers treating botulism patients. The sponsor will then contact the HCPs to discuss the study protocol and potential participation in the study.

5. CBER safety review

At the time of this report, CBER's clinical review also noted that the episodes of bradycardia in the 10 year old boy treated with BAT through the CDC Expanded Access Program constitutes a new safety concern and concur with OBE/DE's proposal for a PMR to better define BAT's safey profile. (See clinical reviewer's memo).

6. Medical literature review

No new safety concern identified in literature review.

7. Advisory committee meetings

Because this product is the first CBER product to be reviewed under the "Animal rule", the results of the BLA application review were presented prior to final licensure decision at the BPAC on February 12-13, 2013. The BPAC members agreed that the data presented was adequate to support licensure of BAT. The committee voiced concerns about the limited safety database in particular in view of the bradycadia episodes in a child and stressed the importance of collecting detailed post-marketing safety data in order to characterize serious adverse reactions to BAT both in children and in adults.

8. Integrated risk assessment

Botulism neurotoxins are extremely potent and lethal. The main therapy relies on intensive care unit support with mechanical ventilation if needed and administration of equine antitoxin. Timely administration of antitoxin may arrest the progression of paralysis and decrease the duration of the illness. Previously licensed botulism antitoxins are no longer available and BAT will come as their replacement for the treatment of botulism caused by any of the 7 toxin serotypes (A, B, C, D, E, F, and G).

The clinical safety database in support of the BAT Clinical Development Program submitted by the sponsor as part of the BLA consists of 56 healthy subjects participating in two clinical studies (BT-001 and BT-002 stage B) and 148 patients with suspected or confirmed botulism who were treated with BAT under a CDC-sponsored Expanded Access Program (BB-IND 6750, BB-IND 13615) from 15 January 2008 through 31 December 2011.

Clinical studies safety data:

- Overall BAT was well tolerated by participating subjects in two pre-licensure clinical trials (n=56).
- No death or serious adverse events were reported in either BAT clinical trials BT-001 or BT-002.
- Two subjects experienced mild hypersensitivity reaction leading to infusion termination in both cases.

CDC Expanded Access Program safety data:

- Safety information was available for 146 of the 148 patients treated with BAT.

- Six deaths were reported in patients after treatment with BAT. All deaths were assessed as unrelated to BAT and due to the progression of botulism toxicity and co-morbidity complications.
- BAT was well tolerated in the majority of the patients (128/148= 86.5%).
- The most common AEs were pyrexia, (reported in 8 patients or 11%), chills (n=3 or 2 %), rash (n=3 or 2%), nausea (n=2 or 1%) and edema (n=2 or 1%). Five patients appeared to have experienced symptoms potentially related to hypersensitivity.
- No patient experienced anaphylaxis.
- The recurrence of bradycardic episodes was observed in a 10 year old boy with confirmed food-borne botulism. The first episode led to asystole and suspension of infusion. The second episode occurred when BAT infusion resumed. The infusion was then permanently discontinued and the patient recovered from the event.

The data presented by the sponsor suggests that the safety profile of BAT is similar to previously licensed equine derived botulism antitoxins with one exception: two consecutive serious and unexplained episodes of bradycardia. Previously identified safety concerns include allergic reactions, including anaphylaxis, thermal reaction and serum sickness.

Potential important safety concerns included possible interference with blood glucose level readings using non-glucose specific point-of-care test system leading to life-threatening iatrogenic or masked hypoglycemia. This risk is linked to the fact that BAT contains maltose and that non-glucose specific test kits cannot differentiate maltose from glucose. In addition, potential interaction with live attenuated viral vaccines may lead to a decreased vaccine efficacy. A six month delay following treatment with BAT is recommended for the receipt of an attenuated viral vaccine.

Because bradycardia has been reported in the literature in association with anaphylaxis, anaphylaxis remains in the differential diagnosis for the bradycardia episodes following BAT administration. However, OBE/DE considers the recurrence of bradycardia episodes a positive rechallenge with the resulting adverse event of hemodynamic instability. OBE considers this event as serious, ***unexpected,*** and possibly related to BAT, and therefore represents a new safety concern. Regardless of the exact physiopathology of the bradycadia episodes, given its seriousness and the limited safety database accumulated pre-licensure, rigorous investigation is needed post-licensure to further evaluate the safety profile of BAT. The investigation should start soon after licensure because the product will be used by sporadic cases, rather than waiting until a mass exposure occurs which triggers a required study under Animal Rule.

OBE/DE therefore recommends a registry study that will enable active data collection for all BAT recipients who provide informed consent and facilitate collection of information that will make additional cases (if they occur) easier to assess and classify. This registry should be in place no later than six months from the date of licensure and remain active for a minimum of 3 years post-licensure in order to include a minimum of 100 individuals treated with BAT of which at least 10 individuals should be children age 18 or under. The registry should be conducted as.a post-marketing requirement (PMR) under section 901 of FDAAA 2007 Title IX, independent of that required under the “Animal Rule,” and the purpose will be “To identify an unexpected serious risk when available data indicates the potential for a serious risk.”, or “To assess a known serious risk related to the use of the drug involved” because anaphylaxis (a known risk) remains a differential diagnosis.

Because the CDC will be distributing the product, this registry requires that the sponsor collaborates with the CDC to obtain contact information of health care practitioners (HCPs) requesting BAT. FDA will engage with CDC to ensure that CDC recognizes that transmission of contact information to the sponsor upon release of product is an interagency public health priority and that CDC will not need to fund the PMR registry.

9. Recommendations

Based on the review of the pre-licensure safety data and the sponsor’s proposed pharmacovigilance plan, OBE/DE recommends the following actions for post-licensure safety surveillance activities:

1) Adverse event reporting: All serious adverse events, labeled and unlabeled, and all non-serious events related to hypersensitivity/allergic reactions, bradycardia, hemodynamic instability, serum sickness, rebound toxicity febrile reactions, should be submitted as 15-day alert reports under 21 CFR 600.80(c)(1)(i). Adverse events that are not reported as 15-day alert reports should be submitted as periodic reports under 21 CFR 600.80(c)(2)(i).

2) A registry study should be conducted as a post-marketing requirement (PMR) under section 901 of FDAAA 2007 Title IX, independent of that required under the "Animal Rule"

A protocol detailing the data to be collected for the registry should be submitted to the FDA no later than 60 days from the date of licensure. The final study report should be submitted to FDA/CBER nine months after the last subject is entered into the registry.

a) The sponsor should establish and maintain a registry that will enable active data collection for all BAT recipients that provide informed consent.

b) This registry should be in place no later than six months from the date of licensure and remain active for a minimum of 3 years post-licensure in order to include a minimum of 100 individuals treated with BAT of which at least 10 individuals should be children age 18 or under.

c) Because the CDC will be distributing the product, this registry requires that the sponsor collaborates with the CDC to obtain contact information of health care practitioners (HCPs) requesting BAT. The sponsor would be responsible for actively following up with the provider and for collecting safety information on patients treated with BAT.

d) Data collection elements should be described in the registry protocol, be similar to that of the CDC Expanded Access Program and at minimum include patient's demographics, time of exposure to botulism toxin, time of treatment(s) with BAT, BAT dosage, standard of care treatment, concomitant medications, pre-BAT treatment with anti-allergy medications, past medical history (if any) in particular neurological diseases or allergy to equine derived products or horse, all adverse events following BAT administration and outcomes.

e) Particular attention should be given to the following adverse events: hypersensitivity/allergic reactions, hemodynamic instability, serum sickness, rebound toxicity, febrile reactions, overdose, medication error, blood borne infections, no drug effect and any serious expected or unexpected adverse reactions including death.

f) Patient follow up should be continued for at least 30 days after the last BAT administration.

3) Review of safety data collected as part of the Animal Rule Requirement

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VSB/DE/OBE/CBER

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