Midcycle Toxicology Review Memo - BAT

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

To: BLA STN 125462/0

Cross Reference: BB-IND-12052

From: Evi Struble, Ph.D.

Through: Dorothy E. Scott, M.D.

CC: Robert Fisher, PhD

Applicant: Cangene Corporation

Product: Botulism Antitoxin Heptavalent, Equine

Subject: Midcycle Memo, Nonclinical Pharmacology/Toxicology

Letter ready recommendations
1. All the batches produced so far contain -(b)(4)- TnBP and -(b)(4)- TX-100. As such, the acceptance criteria for this impurity should be revised downward to reflect the process. These acceptance criteria should be included in the release specifications table.

2. There is no acceptance criterion set for ----(b)(4)---, although the final product likely contains appreciable amounts, given that ---(b)(4)--- buffer is used for elution in chromatographic steps and ------(b)(4)----- is added during formulation. A specification for ---(b)(4)--- should be added.

Introduction
Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G), Equine (herein referred to as eBAT) contains as an active ingredient equine F(ab')2/Fab fragments in a liquid

formulation.
The intended indication is for the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin (BoNT) serotypes A, B, C, D, E, F or G via intravenous infusion after dilution 1:10 in normal saline at a proposed dose of **one vial** per adult patient at a rate of 0.5-2 mL/min. The dose and rate of infusion for infants and pediatric patients will be adjusted.
The vial size (20 or 50 milliliters) and fill volume (approximately 10 to 22 milliliters) vary between product lots. The release specifications are shown in table 1.
Table 1
Release Specifications, Drug product

Purity and Identity	**----------(b)(4)----------**
F(ab′)2 + F(ab′)2 related fragments + Fab	-(b)(4)-
F(ab′)2	-(b)(4)-
Fab + F(ab′)2 related fragments	-(b)(4)-
Impurities – Product Related	
-(b)(4)-	-(b)(4)-
-(b)(4)-	-(b)(4)-
------(b)(4)------	-(b)(4)-
Impurities – Process Related	
---------(b)(4)----------	[--(b)(4)--]
Total Protein	30-70 mg/mL
-(b)(4)-	-(b)(4)-
---(b)(4)---	-(b)(4)-
Maltose	---(b)(4)---
Polysorbate 80	-------(b)(4)------
General Safety	Meets 21 CFR 610.11 requirements

Toxicology, Main Findings
There were no dedicated toxicity studies performed to support this BLA. The pharmacokinetic studies performed in animals do not reveal toxicity concerns for the preparation. However, these studies were not intended to assess possible toxicity concerns with the preparation, as the doses used in animals are not high enough to determine a safe human dose. This is acceptable because of the following reasons.
1) Other products that contain equine antibody as the active ingredient have been approved by the FDA including two that contain proteolytically digested antibody: Anascorp (Rare Disease Therapeutics Inc.), and Botulism Antitoxin Bivalent (Equine) Types A and B (Sanofi Pasteur Ltd/Aventis). To date this reviewer is not aware of safety concerns with these preparations.
2) A toxicological assessment of the formulation and impurity profile of the proposed product does not reveal any potential toxicity issues, even at a dose two times the dose proposed.

In conclusion, there are no toxicology issues that would prevent this preparation from being approved.

Review and Analysis

Excipients
Maltose
This compound is used as excipient in the formulation at a final concentration not to exceed -(b)(4)-. Thus, a patient receiving one 22 mL vial would receive ----(b)(4)---- ------ maltose. The sponsor performed a toxicological assessment using this potential exposure, the calculated safety margins are shown in table 2. The safety margins in rats do not support the use of maltose at these levels, whereas those in rabbits do. The rabbit may be a better model of human response due to comparable activity of enzyme maltase.
This is further supported with existing data from clinical use of maltose formulated marketed products, including IGIV products such asOctagam (Octapharma) at levels similar to eBAT. As such, this reviewer considers the amount of maltose in the preparation safe.

Table 2: Non-clinical Reference Dose for Maltose and the Calculated Safety Margins

Reference Nonclinical Dose	**Reference**	**Safety Margin (SM)**	**Multiples of Human Safe Dose**
Single dose IV LD50 in rats (17.3 g/kg bw)	Kotera et al., 1972a	455	None (SM/100x10x6)*
Repeat dose IV NOAEL in rabbits for a month (10 g/kg bw)	Kotera et al., 1972b	263	8.7 (SM/10x3)#
Repeat dose IV NOAEL in rabbits for 6 months (2.5 g/kg bw)	Kotera et al., 1972d (14)	65	2 (SM/10x3)#
Developmental IV NOAEL in mice and rabbits (10 g/kg bw)	Maruoka et al., 1972, 1973, 1978	260	8.7 (SM/10x3)#

Multiples of Safe Dose were derived by dividing the safety margins (SM) with uncertainty factors. The factors applied were:
* - 100 for converting LD50 to NOAEL, 10 for individual differences, 6 for conversion from rats to human dose
# - 10 for individual differences, 3 for conversion from rabbit to human dose

Polysorbate 80 (PS-80, Tween)
PS80 is used as an excipient in eBAT at levels not to exceed ---(b)(4)--. Thus, a patient receiving one 22 mL vial would receive ----------(b)(4)---------- PS-80.

Table 3: Non-clinical Reference Dose for PS-80 and the Calculated Safety Margins

Reference Nonclinical Dose	**Reference**	**Safety Margin (SM)**	**Multiples of Human Safe Dose**
Single dose IV LD50 in rats (1.79 g/kg bw)	Journal of the American College of Toxicology, 1984	14,200	2.3 (SM/100x10x6)*
Single dose IV LD50 in mice (5.8 g/kg bw)	Hopper et al., 1949	46,000	3.8 (SM/100x10x12)**
Repeat dose (juvenile toxicity) IV NOAEL in neonatal rabbits for 6-7 days (400 mg/kg bw)	Rivera et al., 1990	3,175	106 (SM/10x3)#
Repeat dose IV NOAEL in rabbits up to 40 days (2,000 mg/kg bw)	Payne and Duff, 1951	15,800	527 (SM/10x3)#
Developmental IV NOAEL in rabbits (62.5 mg/kg bw)	Hilbish et al., 1997	490	16 (SM/10x3)#

Multiples of Safe Dose were derived by dividing the safety margins (SM) with uncertainty factors. The factors applied were:
* - 100 for converting LD50 to NOAEL, 10 for individual differences, 6 for conversion from rats to human dose
** - 100 for converting LD50 to NOAEL, 10 for individual differences, 12 for conversion from rats to human dose
# - 10 for individual differences, 3 for conversion from rabbit to human dose

Impurities
Tri-n-Butyl Phosphate (TnBP)
This compound is used as part of solvent/detergent treatment (in combination with Triton X-100, see below). The manufacturer has set an in-process acceptance criterion of -(b)(4)-. Thus, a patient receiving one vial of 22 mL, would potentially receive up to -(b)(4)- TnBP or, for a 70 kg individual, -(b)(4)- BW. Using this potential exposure, the calculated safety margins (i.e. the ratio between the nonclinical reference dose and the expected exposure) are shown in table 4. From these, this reviewer estimated a safe dose from these safety margins by applying appropriate uncertainty factors.

Table 4: Non-clinical Reference Dose for TnBP and the Calculated Safety Margins

Reference Nonclinical Dose	**Reference**	**Safety Margin (SM)**	**Multiples of Safe Dose**
Single dose IV LOAEL in rats (80 mg/kg bw)	Vandekar, 1957 The 80 mg/kg bw dose elicited incoordination and mild anesthesia within one hour and pronounced weakness after four hours.	25,000	41 (SM/10x6x10)*
Single dose IP LD50 in rats (251 mg/kg bw)	Menzer, 1990	79,900	13 (SM /100x10x6)**
Single dose oral NOAEL in rats (325 mg/kg bw)	Healy et al., 1995 (10)	103,500	172 (SM/10x10x6) #
Repeat dose oral NOAEL in rats (100 mg/kg bw)	Healy et al., 1995 (10)	31,800	53 (SM/10x10x6)#
Developmental toxicity oral NOAEL in rats (125 mg/kg bw)	Noda et al., 1994 (52)	39,800	66 (SM/10x10x6)#

Multiples of Safe Dose were derived by dividing the safety margins (SM) with uncertainty factors. The factors applied were:
* - 10 for individual differences, 6 for conversion from rats to human dose, 10 for the toxicity observed in rats
** - 100 for converting LD50 to NOAEL, 10 for individual differences, 6 for conversion from rats to human dose
# - 10 for individual differences, 10 for different administration route, 6 for conversion from rats to human dose

Triton X-100
Triton X-100 (TX-100) is considered a potential process related impurity as it is a detergent employed in the viral SD inactivation step of the eBAT Drug Substance manufacturing process. The manufacturer has set an in-process acceptance criterion of -(b)(4)-. Thus, a patient receiving one vial of 22 mL, would potentially receive up to -(b)(4)- TX-100 or, for a 70 kg individual, -(b)(4)- BW. Using this potential exposure, the calculated safety margins are shown in table 5.

Table 5: Non-clinical Reference Dose for TX-100 and the Calculated Safety Margins

Reference Nonclinical Dose	Reference	Safety Margin (SM)	
Single dose IP LD50 in rats (100 mg/kg bw)	Final Report on the Safety Assessment of Octoxynols, 2004	15,900	2.65 (SM/100x10x6)**
Repeat dose oral NOAEL in rats (1,000 mg/kg bw)	Smyth and Calandra, 1969	318,470	530 (SM/10x10x6)#
Reproductive/developmental oral NOAEL in rats (70 mg/kg bw)	Leung and Ballatyne, 1999	22,290	37 (SM/10x10x6)#

The safety margins were derived from the ratio divided by conversion factors/uncertainty levels. The factors applied were:
* - 10 for individual differences, 6 for conversion from rats to human dose, 10 for the toxicity observed in rats
** - 100 for converting LD50 to NOAEL, 10 for individual differences, 6 for conversion from rats to human dose
# - 10 for individual differences, 10 for different administration route, 6 for conversion from rats to human dose

Note 1
Based on discussions within the committee, it is likely that, if approved, eBAT will be administered at a higher dose, i.e. up to 2 vials may be used. The safety margins of excipients and impurities are such that this higher dose is supported.

Note 2
All the batches produced so far contain -(b)(4)- TnBP and -(b)(4)- TX-100. As such, this reviewer recommends the acceptance criteria for this impurity be revised downward to reflect the process.

Note 3
The release specifications for the drug product are shown in Table 1. Although not reflected in the table, TnBP and Triton X-100 levels are measured as part of in-process control (----------(b)(4)----------) and acceptance criteria have been set. It is suggested that these acceptance criteria be included in the release specifications table.

Note 4
There are no acceptance criteria for --(b)(4)--, although the final product likely contains appreciable amounts, given that ----(b)(4)--- buffer is used for elution and -----(b)(4)------ is added during formulation. This reviewer suggests adding a ---(b)(4)-- specification at release.