Nonclinical Pharmacology/Toxicology 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: Final Memo, Nonclinical Pharmacology/Toxicology

Executive Summary
There were no dedicated toxicity studies performed to support this BLA. A toxicological assessment of the excipients and impurities present in the proposed product does not reveal any potential toxicity issues at dose proposed. In conclusion, there are no toxicology issues that would prevent this preparation from being approved.

Introduction
Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G), Equine (herein referred to as BAT) contains as an active ingredient equine F(ab')2/Fab fragments in a liquid formulation. The 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 infant dose (< 1 year) for BAT is 10% of the adult dose and the pediatric dose (1-16 years) is adjusted based on body weight. 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 substance (modified from submission)

Test Parameter	**Acceptance Criteria**
Identity	Sample bands consistent to internal control standard a
Purity and Identity	-------(b)(4)---------- ----------

Test Parameter	Acceptance Criteria
F(ab′)2 + F(ab′)2 related fragments + Fab	-(b)(4)-
Fab + F(ab′)2 related fragments	-(b)(4)-
F(ab′)2	-(b)(4)-
-(b)(4)-	-(b)(4)-
-(b)(4)-	-(b)(4)-
-------(b)(4)--------	-(b)(4)-
Pepsin	-----(b)(4)------
Tri-n-Butyl Phosphate (TnBP) b	---(b)(4)---
Triton X-100 (TX-100) b	---(b)(4)---
Bacterial Endotoxins	------(b)(4)-----
Total Bacteria	-------(b)(4)-------
Potency-Serotype c	Report results
Total Protein	-----(b)(4)-----

-(b)(4)-	-(b)(4)-
Maltose	---(b)(4)---
Polysorbate 80	------(b)(4)------

a Internal Control Standard (ICS) is a previously released lot of BAT NP-018 which met all release criteria.
b Concentrated product, pre-formulation.
c Performed at Battelle Biomedical Research Center, West Jefferson, OH, USA.

Toxicology, Main Findings

There were no dedicated toxicity studies performed to support this BLA. The pharmacokinetic/pharmacodynamic 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 calculate safety factors for 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 BAT. 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	0.08 (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 BAT 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)**

Reference Nonclinical Dose	Reference	Safety Margin (SM)	Multiples of Human Safe Dose
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). In response to FDA request and based on manufacturing experience, the manufacturer revised the acceptance criterion downwards from -------(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.	250,000	410 (SM/10x6x10)*
Single dose IP LD50 in rats (251 mg/kg bw)	Menzer, 1990	799,000	130 (SM /100x10x6)**
Single dose oral NOAEL in rats (325 mg/kg bw)	Healy et al., 1995	1,035,000	1,720 (SM/10x10x6) #

Reference Nonclinical Dose	Reference	Safety Margin (SM)	Multiples of Safe Dose
Repeat dose oral NOAEL in rats (100 mg/kg bw)	Healy et al., 1995	318,000	530 (SM/10x10x6)#
Developmental toxicity oral NOAEL in rats (125 mg/kg bw)	Noda et al., 1994	398,000	660 (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 BAT Drug Substance manufacturing process. The manufacturer decreased the acceptance criterion from -----(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)	Multiples of Safe Dose
Single dose IP LD50 in rats (100 mg/kg bw)	Final Report on the Safety Assessment of Octoxynols, 2004	31,800	5.3 (SM/100x10x6)**
Repeat dose oral NOAEL in rats (1,000 mg/kg bw)	Smyth and Calandra, 1969	636,940	1060 (SM/10x10x6)#
Reproductive/developmental oral NOAEL in rats (70 mg/kg bw)	Leung and Ballatyne, 1999	44,580	74 (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

All the batches produced so far contain --(b)(4)-- TnBP and --(b)(4)-- TX-100. As such, this reviewer recommended the acceptance criteria for these impurities be revised downward to reflect the process and included as release specifications.

In their response dated 1/18/2013, the sponsor agreed. The criteria for TnBP and Triton-X 100 were revised downwards to -(b)(4)- and -(b)(4)- respectively and included in the release specification table for drug substance. This response was considered acceptable.

Note 2

This reviewer recommended that sponsor consider setting an acceptance criterion for ---(b)(4)---, given its use during manufacturing process.

The sponsor provided the following calculations to justify not setting a specification.

----------(b)(4)----------. Based on this information, Cangene believes that a specification for ---(b)(4)-- is not warranted.

This reviewer accepts this rationale – the amount of --(b)(4)-- in BAT it is not likely to pose a toxicity risk to patients.