Information Request Letter, November 20, 2012 - BAT

Our Reference: STN 125462/0

Cangene Corporation
Attention: Mr. Terry Kraynyk
November 20, 2012
Sent by email

Dear Mr. Kryanyk:

We are reviewing your biologics license application for Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) (Equine) submitted on September 20, 2012 for Treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin (BoNT) serotypes A, B, C, D, E, F or G. We have the following request for information:

Clinical

2. Please provide an xpt data file for all concomitant medications for IND-6750.
3. The draft label in the highlights and section 2.4 suggest that corticosteroids and antihistamines be considered prior to dosing. However:
    a. The clinical studies do not mention such pretreatment.
        i. Please indicate whether patients in BT-001, BT-002A/B, or the CDC study IND 6750 received pretreatment.
            1. If yes, please provide any data and discuss the impact on pretreatment on the safety and efficacy of the product.
            2. If no, please explain why pretreatment is recommended on the label when it was not used in any of the tria
    b. There is some evidence in the literature (see references) that the anticholinergic side effects of some antihistamines might be relatively contraindicated in other diseases of the neuromuscular junction, such as myasthenia gravis. Please discuss the potential impact of antihistamines on safety and efficacy of the product in the setting of symptomatic botulism, particularly the possibility that the antihistamines could make advanced paralytic botulism worse.
4. The administration dilution stated is 1 vial diluted 1:10 in saline for both the 10 to 22 mL fill volumes. Despite the fact that these have nominally the same amount of active ingredient, the end volumes and times for administration will vary by more than two fold. Please justify these instructions and provide data from the clinical trials regarding administration times, clinical acceptability and tolerability relevant to volume and time, provider preference, and other convenience factors.

5. In table 5, the first patient listed who died suffered an adverse reaction and died 52 days after administration. However, the death is listed as unrelated to H-BAT and not caused by botulism itself. Please provide more detailed information about the clinical course, the cause of death, and why the death could not be plausibly related to the study product.

CMC

1. Please provide a table for all eBAT lots currently in the SNS to include:
    a. Lot number
    b. Date of manufacture
    c. Potency for each serotype
    d. F(ab')2 and Fab content
    e. Fill volume

2. Please provide a copy of the release specifications applicable to lots of eBAT currently in the SNS.
3. Please provide a schedule to indicate when additional blending operations for new eBAT lots will occur.
4. Please indicate the status of the horse herd to indicate the number of horses currently in the program, current titers, and plasma collection schedules.

Pharmacokinetics

1. Your estimated NP-018 clearance from population PK analysis for serotype A is 14.75 mL/hr/kg (Table 6.2.3). This value does not match with the observed human clearance (4.2 mL/hr/kg). Please explain this discrepancy. We would like to emphasize that the clearance values obtained from POPPK analysis for guinea pig and monkey are close to the observed clearance values.
2. From your logistic regression model parameters (Table 7.2.3) the projected survival probability of 0.80 at AUC 0.137 U*hr/mL does not match with our calculation. Please provide your calculation to demonstrate that the projected survival probability of 0.80 is indeed at AUC 0.137 U*hr/mL.
3. Please provide 3 separate Figures (only for serotype A) of the fit of the model (POPPK analysis) for predicted vs observed concentration in each of the three species. The figures should be on a linear scale and should include a line of identity and a linear regression line.
4. Your calculation of the human margin of efficiency (MOE) is based on an animal reference survival probability of 0.8. Please provide a rational why a survival probability of 0.8 was chosen as cut-off value. We are concerned that this critical value is too low and one should consider a value higher than 0.9.
5. The therapeutic efficacy animal studies in Rhesus Macaques (No. FY10-066) and in Guinea Pigs (No. 1180-G005630) have not been included in your exposure-response and risk analysis. We consider these 2 studies relevant for approval. Please explain why the study results were not included in your risk analysis and human predictions.

Pharmacovigilance

1. In Section 2.5, Cangene stated that "The phase IV study protocol will be implemented only in the event of mass exposure in which a sample size of at least 100 patients can be achieved. An example of such a scenario would be the intentional/bioterrorist exposure of a large group." Please explain how it will be decided when the mass exposure scenario occurs and the study will be implemented.
2. In Annex III, BT-003 *Study Population* stated that the study population will include "Patients with a confirmed or suspected diagnosis of botulism as a result of a broad exposure scenario." Please clarify if the study population can potentially include any individual to whom H-BAT may be indicated or contraindicated.
3. In Annex III, BT-003 *Number of Trial Sites* stated that "trial sites will be selected based on location of eligible patients and site willingness to participate in the study." Please clarify if the study participants are anticipated to be recruited from specific sites, or any site or location.
4. In Annex III, BT-003 *Sample Size* stated that the study will recruit "a minimum of 100 eligible patients".

    a. Please explain how the sample size of a minimum of 100 patients was determined.
    b. Please clarify how many H-BAT treated and how many H-BAT non-treated patients will be recruited.
    c. Please clarify if the proposed sample size is sufficient for subgroup analyses.
6. In Annex III, BT-003 *Protocol Design* stated that "In the event of a major botulism exposure, Cangene will contact the CDC to obtain contact information for health care providers treating botulism patients, including those who requested eBAT NP-018 from the SNS."
    a. Please clarify if Cangene will obtain contact information of healthcare providers from CDC for all patients treated or non-treated with H-BAT.
    b. Please clarify if CDC is the only source of information for outreaching healthcare providers.
    c. Please clarify if there are alternative approaches to recruit patients.
7. In Annex III, BT-003 *Protocol Design* stated that "Relevant data will be collected (retrospectively and/or prospectively, as applicable) from patient's medical records and recorded on the case report forms."
    a. Please clarify in what circumstances prospective data collection will be performed.
    b. Please clarify how long the patient will be followed up for prospective data collection, if applicable.
    c. Please clarify if copies of case report forms or data collection forms will be provided to CBER.
8. In Annex III, BT-003 *Assessments* listed "Adverse events related to eBAT NP-018" as one of the clinical outcomes. Please clarify what "Adverse events related to eBAT NP-018" means and how those adverse events will be defined and assessed.
9. In Annex III, BT-003 *Assessments* listed "Treatment and supportive data" that will be collected. Please clarify if information on treatment other than H-BAT (e.g., botulism immune globulin) will be collected and considered in analysis.
10. Please provide an analysis plan for the safety data.

11. Please provide a time line for study implementation and submission of study reports, interim analyses and final study report, in the event that a broad exposure scenario occurs.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your response to this information request as an amendment to this file by December 4, 2012 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If you have any questions, please contact me at (301) 827-6174.
Sincerely,

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