DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Administration

Food and Drug

1401 Rockville Pike
Rockville, MD 20852-1448

Our Reference: STN 125462/0

Cangene Corporation
Attention: Mr. Terry Kraynyk
December 21, 2012
Sent by email

Dear Mr. Kraynyk:

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 the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin (BoNT) serotypes A, B, C, D, E, F or G. We determined that the following information is necessary to continue our review:

Animal efficacy studies:

1. Please clarify what form of purified botulism neurotoxin complex was used for the animal challenge studies, e.g. 300, 500, or 900 kDa complex.

2. For each study please provide a timeline of the in-life portion of the study annotated to indicate what (if any) protocol amendments were made to the study protocol in relation to the toxin challenge date and treatment date.

3. Please indicate the reason guinea pigs 614, 616, 623, 3763, 3727, 3707, 3759, 3738, 3749, and 3775 were euthanized during the in-life portion of study 1180. They did not appear to meet any of the predefined euthanasia criteria indicated in the study protocol, e.g. 25% or greater weight loss in conjunction with any concurrent severe signs of intoxication, two consecutive observations of paralysis, or a determination that the animal was moribund.

4. Please indicate if any individuals were unblinded to group treatment assignments prior to locking of the clinical observation data and general unblinding for study 1180.

5. With regards to study 1180, please provide:
    a. A list of animals replaced prior to intoxication and the reason for the replacement, grouped according to serotype, and;

    b. A list of animals replaced after intoxication and the reason for the replacement, grouped according to serotype, and a line listing of clinical signs observed in those animals after intoxication.

6. Please supply a detailed listing of all deviations which occurred in studies FY09-114 and FY10-066. Please include in the listing a description of the deviation, date(s) of occurrence, summary of the investigation, any CAPAs, and any relevant document numbers.

Clinical:

7. Protocol deviation:

   A protocol deviation occurred in BT-002A where the unblinded pharmacy assistant who prepared the infusions also administered both the test drug (Aventis Pasteur botulism antitoxin bivalent (equine) types A and B) and placebo, and adjusted infusion rates for these infusions based on prior experience in administering IV infusions. This was a violation of "To maintain the blinding in this study, only a research pharmacist (or a designate not involved in study drug administration) will know in which arm of the study subjects are enrolled" written on page 25 of the protocol. Even though BT-002A did not study NP-018, it did study the prior licensed product to which NP-018 (Cangene botulism antitoxin heptavalent (equine) types A-G) was compared, "thereby introducing bias into the study" as stated in the report. Please explain how this happened given the prohibition on such an occurrence. Please also analyze the infusion rates chosen by the pharmacy assistant vs. products that the pharmacy assistant administered to quantify the effect of his administration on results in each arm. Finally, please analyze the possible bias that this introduced into the trial, including differential infusion rates, and how this bias impacted on the ultimate outcome. It is important to be sure that the conclusions drawn are not compromised by the bias potentially introduced into the study.

8. Multiple doses:

   The report for IND BB-6750 indicates that five subjects were given multiple doses of NP-018. The protocol allows this per "Repeat dosing may be indicated for patients with recurrent botulism symptoms on an individual basis with consultation with the CDC botulism duty officer by calling the CDC Emergency Operations Center (770-488-7100). If a second dose of NP-018 H-BAT is determined as being clinically appropriate, the patient's treating physician will contact CDC and a second vial of NP-018 H-BAT may be released if necessary." However, the reasons and rationale for multiple dosing were not provided in the report. Please provide a table for the five subjects including 1) the clinical situation and reasons for request of the second dose, 2) the rationale for granting the second dose, 3) detailed ultimate outcome, and 4) discussion of the effectiveness of the second dose. This information could be important in developing the language in the final label.

9. Tonsillar hypertrophy:

In BT-002B which studied NP-018 vs. placebo, both tonsillar hypertrophy and lymphadenopathy occurred in the NP-018 group at a rate higher than occurred in the earlier sequential BT-002A treatment arm (Aventis Pasteur antitoxin types A and B). In part because the rate of lymphadenopathy in BT-002B was similar between treatment (NP-018) and placebo, both the lymphadenopathy and tonsillar hypertrophy were deemed due to intercurrent viral illness. However, though the data support the assertion that the lymphadenopathy could be secondary to viral infection, the four-fold differential rates in tonsillar hypertrophy between the NP-018 and placebo arms are not directly explained by that data. Please parse out tonsillar hypertrophy separately and explain the increased incidence of this adverse incident over placebo and over the licensed product in BT-002A. This explanation is requested because it is possible that tonsillar hypertrophy is an adverse event specific to NP-018.

10. Time course of adverse events in subject -(b)(6)-
    a. Hematuria was reported in subject -(b)(6)- after administration of NP-018 and both before and after transfer to the rehabilitation hospital. However, it is not clear if those events were the same longitudinal event or different adverse events. Please provide complete information about the hematuria in this subject including time course, quality, severity, and diagnostic considerations, and conclusions including discussion of whether the recurring hematuria events were one or several event(s). Please also provide a table of BUN, creatinine, and (if available) creatinine clearance values at all known points. This information is important to help determine the contribution of the serum sickness to the ultimate demise of the subject.

    b. Neuropathic pain was described in subject -(b)(6)- after transfer to the rehabilitation hospital. Please describe whether this was present before transfer. Please also describe the known or proposed etiology of this neuropathic pain.

11. Causes of other deaths in IND 6750
    a. On page 222 of the IND 6750 study report for subject BOT IDNUM 10049, it is stated that the "cause of death is unknown" and concluded that the death "was unrelated to HBAT administration." However, it is not clear how that conclusion was reached, since initial tolerance of NP-018 and death 94 days after administration by itself is not sufficient evidence to reach that firm conclusion. Please provide further available information from the course of the subject or other information to justify the conclusion that NP-018 did not contribute to the demise of the subject.

    b. On page 222 of the IND 6750 study report for subject BOT IDNUM 10066, it is stated that the subject died of "Miller Fisher variant of Guillain-Barré syndrome" seven days after administration of NP-018.

Though she might have died with that disease, it is not clear exactly how or why she died. Please provide further available information from the course of the subject or other information to explain why she died and justify a conclusion that NP-018 did not contribute to the demise of the subject.

12. Distribution of moderate and severe adverse events in BT-002B

Table 14 Adverse Event Frequencies by Treatment, Severity and Relationship to eBAT NP-018 in Clinical Trial BT-002 Stage B

		eBAT NP-018 1 Vial	Placebo
		Events (%)	Events (%)
Frequency		50	31
Severity	Mild	35 (70%)	31 (100%)
	Moderate	8 (16%)	0 (0%)
	Severe	7 (14%)	0 (0%)
Relationship	Related	4 (8%)	0 (0%)
	Unrelated	46 (92%)	31 (100%)
Not Serious		50 (100%)	31 (100%)

You conclude in the summary of BT-002B that "no notable differences in the number of AEs […] were reported between the treatment and placebo arms." However, you report a difference in the distribution of moderate and severe adverse events between the treatment and placebo arms (15 vs. 0 in aggregate) in BT-002B. Even though all but four of the events were classified as unrelated and the events are scattered as to their classification, this difference between 15 and zero still represents a highly statistically significant difference ($p < 0.001$ per our statistician) between the two arms. Please offer an explanation as to the difference in distribution of moderate and severe adverse events between treatment and placebo arms in BT-002B.

CMC/process validation:

13. Please confirm which process scales you intend to license.

14. Please submit a table indicating which adjuvant was used to produce the anti-sera for each monovalent bulk.

15. 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.

16. 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.

17. Please explain what procedure is in place if the alert limit is reached for each in-process specification?

18. Please describe the maltose endotoxin deviation and what increased testing is being done.

19. Please provide clearer pictures of figures in report L.194.05.060, (e.g. Figure 3).

20. Please describe the containers in which the plasma is aliquoted and shipped back to Cangene. Please provide this shipping validation.

21. 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.

22. 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.

23. 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.

24. What is the process in place if you experience -(b)(4)- membrane fouling?

25. Please set the equilibrated column hold times for each column.

26. 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)-.

27. Please set a maximum time of pepsin digestion.

28. Please explain the origin of the precipitate in the --(b)(4)-- step.

29. Please provide a validation for the -(b)(4)- hold time of the Drug Substance Hold prior to aliquoting.

30. Please direct us to the eCTD document section where we may find the following validation reports: PV_5025, PV_5028, PV 5029.

31. Has a leachables and particle shedding study been performed with product on the ----------(b)(4)---------- sterile filter?

32. 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".

CMC/Adventitious agents

33. Table 2 and Table 6 in "3.2.A.2 Adventitious Agents Safety Evaluation" indicate a reduction factor of -(b)(4)- log for BVDV, however your viral reduction table in the prescribing information does not include this data. Moreover, PV-194-04-002 does not include validation of S/D inactivation of BVDV. Please clarify whether S/D inactivation of BVDV was validated, and if so, please submit the validation report.

34. Please provide a description and a list of specifications for the -----(b)(4)----- filter.

35. Please clarify the geometry of your ----(b)(4)---- virus filtration system. Are -(b)(4)- filters fed by -(b)(4)- pressure tank?

36. ----(b)(4)---- has calculated reduction factors for Ad2 and EMCV using a -(b)(4)----------, while the PV.194.04.004 process validation report and the viral clearance table in your package insert apparently used approximately half this volume. Please explain the discrepancy.

37. Table 1 in ----(b)(4)---- report AB00AV.022271.BSV specifies a volume of -------(b)(4)----------, while your viral load calculations are based on -------(b)(4)------ volume samples. Likewise, the volumes listed in table 6-8 for PPV, WNV, and XMuLV clearance do not appear to reflect those in the applicable ----(b)(4)---- reports. Please explain the discrepancies in how Cangene and ------(b)(4)----- have calculated log reduction factors.

38. Please provide a table summarizing your viral filtration validation studies as follows: ----------(b)(4)----------. For each of the table entries, please provide a copy of the original source documentation (e.g. lab notebook page/pages).

Nonclinical Pharmacology/Toxicology:

39. 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.

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

Pharmacovigilance:

41. With regards to your pharmacovigilance plan, routine surveillance should:

    a. Be enhanced such that all serious reports (both labeled and unlabeled) would be reported as 15 day reports. In addition specific non-serious reports related to hypersensitivity/allergic reaction, serum sickness, febrile reactions and bradycardia should also be reported as 15-day reports.

    b. Include ongoing communications with CDC to collect contact information of H-BAT requestors in order to conduct a more pro-active follow up of treated patients.

    c. If possible, include patients that received BAT under IND 6750. These patients should be encouraged to participate in the post-marketing study once that study has been initiated.

42. Please provide a schedule for implementing your phase 4 study, taking into consideration that it should begin as soon as possible after licensure. The study should include all patients treated (including those treated outside a mass exposure scenario).

43. Please provide an analysis plan for a mass exposure scenario where the number of patients is greater than 100, the time to exposure is less certain, and the patient population includes exposed and nonexposed individuals treated at various times. For a discussion of the variables that might be involved in such a study, please refer to Arnon, S. S., et al. (2001). Botulinum Toxin as a Biological Weapon Medical and Public Health Management. JAMA: The Journal of the American Medical Association, 285(8), 1059–1070. doi:10.1001/jama.285.8.1059.

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 January 18, 2013 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 we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

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

Sincerely,

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