CMC Final Review - BAT

Memorandum

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

To: File for STN 125462

From: Robert W. Fisher, DH, OBRR, HFM-345

Through: Michael Kennedy, Team Leader LPD, DH, OBRR, HFM-345

CC: Nannette Cagungun, RPM, RPMB, DBA, OBRR, HFM-380

Applicant: Cangene Corporation

Product: Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G)-(Equine)

Subject: CMC final review, STN 125462/0 adventitious agents safety evaluation

Recommendation:

Approval with the following postmarketing commitment related to hepacivirus screening:

Cangene commits to developing a qualified ----(b)(4)--- test for detection and quantification of canine hepacivirus and GBV-like viruses in equine plasma. This test will be used to quantitate canine hepacivirus and GBV-like viruses in retention samples from plasma used to manufacture lots of BAT currently maintained in the Strategic National Stockpile. The results of this testing will be used to develop a risk assessment based on the validated BAT manufacturing viral clearance process and to establish an upper limit for screened plasma units and manufacturing pools for canine hepacivirus and GBV-like viruses. The ----(b)(4)---- test validation, retention sample results, and risk assessment will be submitted as a Prior Approval Supplement by 22 September 2013.

Executive Summary:

Cangene Corporation (Cangene) has submitted a Biologics License Application for Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G)-Equine with an indication for the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotypes A, B, C, D, E, F, or G. The application includes vaccination information for the horse herd, an overview of plasma testing procedures, and validation reports for viral clearance at two steps in the manufacturing process. An ongoing issue relates to the potential presence of hepacivirus nucleic acid sequences in plasma from the donor horse herd. ----------(b)(4)----------. This issue is being mitigated by requesting a postmarketing commitment to determine the levels of this adventitious agent in the plasma and manufacturing pools via a validated or qualified assay, and using the data to conduct a risk assessment based on the demonstrated viral clearance of the manufacturing process. In the event of a large-scale, national emergency involving botulinum neurotoxins the -------(b)(4)------ lots could be either released through usual lot release procedures due to the altered risk-benefit situation or used under an existing Emergency Use Authorization.

Submission Review Summary:

1. STN 125462/0 is an eCTD format original Biologics License Application (BLA) for Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G)-(Equine), (BAT) submitted by Cangene Corporation.
   a. This submission was received at DCC on 20 September 2012 and a chair assigned on 21 September 2012.
   b. The Action Due Date is 22 March 2013.
2. BAT is a polyclonal antibody preparation manufactured from hyperimmune horse plasma. The manufacturing procedure includes a solvent/detergent (S/D) viral inactivation step and a nanofiltration based virus removal step. Performance of

these procedures was demonstrated using a ---(b)(4)--- approach; please refer to the CMC adventitious agents safety evaluation midcycle memo for STN 125462/0 dated 11 December 2012. Please note that viral clearances in the midcycle memo were based on -----(b)(4)----- clearance calculations, which have been corrected. This issue is discussed in section 3.c.i, below. The viral clearance table in the package insert has been updated based on the corrected calculations.

3. The midcycle review identified several items requiring clarification.
   a. The donor horse herd is the property of the United States Government. Cangene is responsible for the vaccination program and issues immunization orders to Auburn University, who carries out the vaccination procedures and maintains the horse herd. Quality agreements are in place between Cangene and Auburn University, BARDA, and the SNS.
   b. Two tables in the 3.2.A.2 Adventitious Agents Safety Evaluation indicated S/D log reduction factors for bovine viral diarrhea virus (BVDV). Validation for S/D inactivation of BVDV could not be located in the BLA, nor was there an entry for S/D inactivation of BVDV in the viral reduction table in the prescribing information.

i. Cangene was requested to clarify whether S/D inactivation of BVDV had been validated, and if so, to provide data to support the validation

ii. Cangene replied that S/D inactivation of BVDV was not validated and the tables in the original 3.2.A.2 Adventitious Agents Safety Evaluation were in error.

iii. A corrected version of 3.2.A.2 Adventitious Agents Safety Evaluation was submitted in amendment 125462/0.8.

   c. Cangene did not provide an adequate description or specifications for the ----------(b)(4)---------- filter used for viral filtration.

i. Cangene provided detailed specifications for the -(b)(4)- filters in amendment 125462/0.6.

ii. --(b)(4)-- does not provide a nominal pore size for this filter, However, the manufacturer does list a log reduction factor of -----(b)(4)------ ----------.

   d. Cangene was asked to clarify the geometry of the ---(b)(4)-- virus filtration system.

i. A description was provided in amendment 125462/0.6. The -----(b)(4)----- described in Cangene's validation reports consist of --------(b)(4)-------- ----------. This explains the consistency in the starting titers for the ----------(b)(4)---------- ----------.

e. Differences were noted between the reduction factors calculated by Cangene and by ----(b)(4)-----, primarily in the -----(b)(4)--- samples.

i. Cangene was asked to explain the discrepancies, especially in the volumes used to calculate the viral load of the samples.

ii. Cangene responded in amendment 125462/0.6 that ----(b)(4)---- utilized --(b)(4)------------------------------ ------------- -- ------------------------------------- -- ------------- --- -- -- --- ---.

1. Cangene also identified errors in PV.194.04.004. Some errors were a result of transcription between the ----(b)(4)--- reports and the Cangene document. Other errors included instances where ----(b)(4)--- did not adjust volumes to account for samples taken during filtration.

iii. In order to correct for these errors, Cangene was requested to provide a table summarizing all viral filtration studies, including references to the original data. This table (and its accompanying references) was used to recalculate the LRF for each virus and compare against the values provided by Cangene in the prescribing information table. Cangene also annotated the table to identify differences between their calculations and those performed by ----(b)(4)----. Please refer to Table 1.

1. Recalculated values for XMuLV, BVDV, Ad2, and EMC agree with the table in the prescribing information.

2. A range was provided for PPV clearance, based on -(b)(4)- filtration runs that varied pressure and protein concentration. It would be more appropriate to report the least robust result (average LRF of 4.5 logs).

3. WNV clearance was overstated in the table due to an incorrect calculation. The correct average LRF for the -(b)(4)- runs should be reported as -------------------------(b)(4)---------------------------.

f. Each plasma unit is tested for West Nile Virus (WNV) using a ---------(b)(4)----------------; however the validation report was not provided in the original submission.

i. Cangene was requested to provide a validation report or a cross-reference to a master file supporting use of the WNV -(b)(4)-.

ii. In amendment 125462_0.4 Cangene supplied a copy of the study protocol and study summary report for study 194.0 to support use of the WNV -(b)(4)- test for detecting WNV sequences in equine plasma.

1. Study 194 was performed in 2005 to demonstrate non-interference from the equine serum matrix on the sensitivity of the -(b)(4)-WNV --------(b)(4)------ assay. -(b)(4)---------- ---------- WNV reference control WNV -(b)(4)-. The assays used a ----------(b)(4)----------

2. Of the -(b)(4)- performed, one assay did not yield a valid test result. The remaining -(b)(4)- tests all scored positive for the presence of WNV.

3. The study conclusion was that equine plasma did not affect the analytical sensitivity of the -(b)(4)- WNV ----------(b)(4)------- assay.

g. Equine plasma is also tested for adventitious agents using the procedures outlined in 9 CFR 113. The ----(b)(4)---- study reports supporting the validation of these procedures were referenced by Cangene but were not included with the original BLA submission.

i. Cangene was requested to provide ----(b)(4)---- reports for the three 9 CFR 113 validation studies performed: AB32EU.034090.BSV, AB32EZ.034090.BSV, and AB47CR.034090.BSV.

ii. These reports were submitted in amendment 125462_0.4 as appendices in Method Validation Report VAL_MV_150_rep_v1 and included the protocol, protocol amendments, and final report for each study.

iii. In each study, viral stocks of BVDV, equine herpesvirus (EHV), bovine parainfluenza virus (PI3), equine arteritis virus (EAV), Sindbis virus (SINV), or reovirus type 3 (REO3) were diluted into samples of a plasma pool.

----------(b)(4)----------

[redacted]

[redacted] (b)(4) [redacted]

[redacted] (b)(4) [redacted]

[redacted]

[redacted]

[redacted] (b)(4) [redacted]

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----------(b)(4)---------- --
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----------(b)(4)----------

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iv. Cangene indicates that the sensitivity of the 9 CFR testing is at least --(b)(4)-- for bovine viral diarrhea virus, equine herpesvirus, bovine parainfluenza virus, equine arteritis virus, Sindbis virus, and reovirus type 3. This conclusion is based on the results from the three studies described above. The test procedure in 9 CFR 113 has been modified -----(b)(4)----------
. This change ----------(b)(4)---------- ----
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4. On 13 December 2012, the Agency was notified of a potential issue with the horse herd used as a plasma source for Cangene's BAT product.
   a. Cangene informed us that they had received information from Dr. Charlie Rice (Rockefeller University) that plasma from 20 of the 150+ horses in the Auburn donor herd had tested positive in a ----(b)(4)-- assay for hepaciviruses. 5 horses were positive for canine hepacivirus, 17 horses were positive for GBV-like virus, and 3 were positive for both.

i. This testing was performed utilizing a nonvalidated ----(b)(4)---- test in a research environment as part of an academic collaboration. Dr. Rice was investigating the incidence of a newly identified hepacivirus in horses.

ii. ----------(b)(4)---------- ---
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iii. --------(b)(4)------- (again, with a nonvalidated assay) was performed on a subset (four) of the samples, and detected < 4.7 logs of RNA genome copies/mL in two samples, 6.2 genome copies/mL in one sample, and 6.8 genome copies/mL in the remaining sample.

b. Hepaciviruses are in the Flaviviridae family, and are in the same genus as hepatitis C virus (*1*). Canine hepacivirus (more recently known as nonprimate hepacivirus) was identified in 2011 as a respiratory illness in dogs (*2*, *3*), however follow-up studies suggest that infection is much more prevalent in horses where it is asymptomatic and potentially chronic (*4*, *5*). Known GBV-like viruses are divided into three groups: GBV-A, GBV-B, and GBV-C. GBV-A is restricted to new world primates and is not pathogenic. GBV-B viruses are also restricted to new world primates. They cause acute hepatitis in tamarins but not chimpanzees or humans. GBV-C can infect chimpanzees and humans, but is not associated with viral hepatitis and is fairly common in volunteer blood donors(*6*, *7*). It does not cause a chronic infection and there are no clinical sequeale related to the acute infection in either humans or chimpanzees.

i. Neither canine hepacivirus nor any of the three known GBV-like viruses have been demonstrated to cause illness in humans.

ii. The GBV-like virus in the horse herd has not been positively identified as either GBV-A, GBV-B, or GBV-C.

iii. The transmission mode, incidence, and natural host of these viruses are unknown. One study identified nucleic acid and serological evidence of infection in horses in New York State. Interestingly, horses from Lake Immunogenics (Ontario, New York) were transferred to the Auburn facility in 2010 however these horses have been maintained as a separate herd. Horses from both herds have tested positive for the viruses at similar rates.

iv. Hepaciviruses are enveloped RNA viruses in the ~40 nm range and virus titers would be expected to be effectively decreased by the validated viral clearance steps in the BAT manufacturing process. This includes S/D treatment of the plasma and nanofiltration, and viral clearance using these procedures was demonstrated using two Flaviviruses (BVDV and WNV).

c. Cangene has isolated the affected horses, ----------(b)(4)----------, is performing lookback, and all BAT lots manufactured from potentially affected plasma have been ----(b)(4)---. This includes all SNS lots except one (fill lot 20604011); approximately -(b)(4)- vials of this non-affected lot are available for distribution.
d. Since there is limited evidence of transmission of these viruses to humans, and the Cangene manufacturing process has a validated, robust viral clearance capacity, the risk assessment favors use of the potentially affected BAT lots if necessary to respond to a national emergency involving botulinum neurotoxin.

e. Cangene will be requested to agree to a postmarketing commitment to address the hepacivirus issue. The requested PMC is as follows:

Cangene commits to developing a qualified ----(b)(4)---- test for detection and quantification of canine hepacivirus and GBV-like viruses in equine plasma. This test will be used to quantitate canine hepacivirus and GBV-like viruses in retention samples from plasma used to manufacture lots of BAT currently maintained in the Strategic National Stockpile. The results of this testing will be used to develop a risk assessment based on the validated BAT manufacturing viral clearance process and to establish an upper limit for screened plasma units and manufacturing pools for canine hepacivirus and GBV-like viruses. The ----(b)(4)--- test validation, retention sample results, and risk assessment will be submitted as a Prior Approval Supplement by 22 September 2013.

----------(b)(4)----------

[--(b)(4)--]

Table 2. Final label claims for viral inactivation and clearance.

	Enveloped					**Non-enveloped**		
Genome	RNA	RNA	RNA	DNA	RNA	DNA	RNA	RNA
Virus	XmuLV	WNV	BVDV	PRV	PI3	Ad2	EMC	Porcine Parvovirus
Family	Retro	Flavi	Flavi	Herpes	Paramyxo	Adeno	Picorna	Parvo
Size (nm)	80-110	40-70	50-70	150-200	100-200	70-90	25-30	18-24
Nanofiltration (log_{10})	≥ 2.7	≥ 2.1	≥ 4.5			≥ 4.7	≥ 4.5	4.5
S/D (log_{10})	≥ 4.3	≥ 5.1		≥ 5.1	≥ 5.5			
Total Reduction (log_{10})	≥ 7.0	≥ 7.2	≥ 4.5	≥ 5.1	≥ 5.5	≥ 4.7	≥ 4.5	4.5

XmuLV: Xenotropic Murine Leukemia Virus; specific model for equine infectious anemia, and a model for lipid-enveloped RNA viruses of similar size, such as vesicular stomatitis virus (Rhabdo family).

WNV: West Nile Virus; relevant virus, and specific model for lipid-enveloped RNA viruses, including the arboviruses, which contains both Flavividae and Togaviridae and includes equine encephalitis viruses (Toga family) and equine viral arteritis (Arteri

	Enveloped	Non-enveloped
family, formerly a Toga virus). BVDV: Bovine Viral Diarrhea Virus; relevant virus, and specific model for lipid-enveloped RNA viruses, including the arboviruses, which contains both Flavividae and Togaviridae and includes equine encephalitis viruses (Toga family) and equine viral arteritis (Arteri family, formerly a Toga virus). PRV: Pseudorabies Virus; specific model for equine herpes viruses and non-specific model for lipid-enveloped viruses. PI3: Parainfluenza III Virus; model for lipid enveloped RNA viruses, and viruses of the similar family, orthomyxo, which includes equine influenza virus. Ad2: Adenovirus; specific model for equine adenovirus. EMC: Encephalomyocarditis Virus; specific model for equine parvovirus and adeno-associated virus, non-specific model for small lipid and non-lipid enveloped viruses.		

References:

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3. A. Kapoor *et al.*, Characterization of a canine homolog of hepatitis C virus, *Proc Natl Acad Sci USA* **108**, 11608–11613 (2011).

4. S. Lyons *et al.*, Nonprimate Hepaciviruses in Domestic Horses, United Kingdom, *Emerg Infect Dis* **18**, 1976–1982 (2012).

5. P. D. Burbelo *et al.*, Serology-Enabled Discovery of Genetically Diverse Hepaciviruses in a New Host, *J Virol* **86**, 6171–6178 (2012).

6. M. J. Alter *et al.*, Acute Non-A–E Hepatitis in the United States and the Role of Hepatitis G Virus Infection, *N Engl J Med* **336**, 741–746 (1997).

7. H. J. Alter *et al.*, The Incidence of Transfusion-Associated Hepatitis G Virus Infection and Its Relation to Liver Disease, *N Engl J Med* **336**, 747–754 (1997).