Committee Filing Memorandum - BAT

To: File for STN 125462
From: Robert W. Fisher, Chair of the Review Committee, 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: Committee Filing Memorandum: Original BLA

Recommendation:
The review committee recommends filing.

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. No licensed products are currently available to treat botulism in adults, and Cangene has requested priority review and approval under 21 CFR 601 (subpart H) regulations ("Animal Rule"). The review committee has evaluated the data submitted and concluded unanimously that the submission is suitable for filing and further review.

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 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. The review committee is as follows:
    a. Bioresearch monitoring: Christine J. Drabick
    b. Biostatistics: Xiang (Judy) Li
    c. Committee Chair, Chemistry, Manufacturing, and Controls (animal [guinea pig] efficacy and characterization studies, and viral validation): Robert W. Fisher
    d. Clinical: Irwin Feuerstein
    e. Chemistry, Manufacturing, and Controls (animal [primate] efficacy and characterization studies): Michael Kennedy
    f. Chemistry, Manufacturing, and Controls (assay validation, stability): Douglas Frazier
    g. Chemistry, Manufacturing, and Controls (facilities): Anthony F. Lorenzo

h. Chemistry, Manufacturing, and Controls (process validation): Malgorzata Norton
i. Clinical Pharmacology: Iftekhar Mahmood
j. Epidemiology: Marthe Bryant
k. Labeling: Alpita Popat
l. Pharmacology/Toxicology: Evi Struble
m. Product Release: Erica L. Giordano
n. Regulatory Project Manager: Nannette Cagungun
o. Testing plan: Karen Campbell

3. Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G)-Equine (abbreviated HBAT) is a liquid formulation F(ab')2 product manufactured from hyperimmune equine plasma. It is stabilized with 10% maltose and 0.03% polysorbate 80 and is intended for intravenous administration.
4. Cangene is requesting 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.
    a. Cangene has submitted this BLA for approval under the 21 CFR 601 (subpart H) regulations. These regulations allow licensure of biological products based on animal efficacy data when human efficacy studies are not feasible or ethical.
        1. Cangene's intention to utilize the 21 CFR 601 (subpart H) regulations for licensure has been the subject of numerous communications with the Agency since the related IND (BB-IND 12052) was filed in 2004.
        2. Well controlled clinical trials in humans would be complicated by a small number of naturally occurring cases. These cases occur over a large geographical area in an unpredictable pattern and are diverse in terms of exposure route. Exposure to botulinum neurotoxins is usually via contaminated food or due to wound colonization with *Clostridium* spp., although inhalational exposures have been described in the literature in humans and aerosol exposure cannot be ruled out in terms of battlefield or terrorism events.
        3. Use of a placebo control in a human clinical trial involving naturally occurring botulism would likely be considered unethical.
        4. It would be unethical to expose healthy individuals to a lethal challenge of botulism neurotoxin, regardless of the exposure route.
    b. Cangene was granted orphan drug designation for this product on 29 June 2011.
    c. Cangene has submitted draft labeling, a description of the manufacturing process (including batch records), process and assay validations, a pharmacovigilence plan, viral clearance studies, facility information, pharmacokinetic/pharmacodynamic data, a safety study in normal human volunteers, and data from characterization and efficacy studies in guinea pigs and nonhuman primates.
5. Cangene's request for priority review is being evaluated by the clinical reviewer.
6. Discussions with DBSQC and PRB regarding the testing plan and lot release protocols have been initiated.

7. In accordance with CBER policy described in SOPP 8404 version 3, effective 27 August 2007 and 21 CFR 601.2 the submission was subjected to initial review to determine if major deficiencies were present.
    b. A filing meeting was scheduled for 01 November 2012 by the Regulatory Project Manager.
    c. The committee was polled via email on 23 October 2012 whether the submission was appropriate for filing.
    d. There was unanimous consent among the committee members that this BLA should be accepted for filing. Emails documenting their responses were posted to the Electronic Document Room for STN 125462/0.