

Mid-Cycle Meeting Summary

Application type and number: BLA 125562/0
Product name: Anthrax Immune Globulin Intravenous (Human)
Proposed Indication: Treatment of adult and pediatric patients with toxemia associated with inhalational anthrax.
Applicant: Cangene Corporation
Meeting date & time: November 6, 2014, 2 p.m. to 3:30 p.m.
Committee Chair: Robert Fisher, PhD
RPM: LT Thomas J. Maruna, USPHS, MSc, MLS(ASCP)^{CM}

Attendees	Dicipline/Representation
Robert Fisher	Chair/CMC (Natural History and Primate Studies)
Karen Campbell	DBSQC (Lot Release Protocol and Testing plan)
Howard Chazin	Deputy Director/CBER/OBRR/DHCR
Nicolette Devore	CBER/OD
Mahmood Farshid	Deputy Director/CBER/OBRR/DHRR
Basil Golding	Director/CBER/OBRR/DHRR
Anthony Hawkins	BIMO (Nonclinical)
Patricia Holobaugh	Chief/CBER/OCBQ/DIS/BIMO
Jiang (Jessica) Hu	Statistical Review - Primary
Cheryl Hulme	DBSQC
Cynthia Kelley	CBER/OD
Michael Kennedy	CMC
Colonious King	BIMO (Clinical)
Iftexhar Mahmood	Clinical Pharmacology
Thomas J. Maruna	Regulatory Management - OBRR
Randa Melhem	CMC/Facilities
David Menschik	Epidemiology/Pharmacovigilence
Ginette Michaud	Deputy Director/CBER/OBRR
Paul D. Mintz	Director/CBER/OBRR/DHCR
Miriam Ngundi	Consult reviewer for TNA Assay
Leland (Ross) Pierce	Clinical
Alpita Popat	Promotional Labeling
Jennifer Reed	CMC
Renee Rees	Statistical Review - Alternate
Josephine Resnick	DBSQC (Testing Plan)
Lisa Stockbridge	Chief/CBER/OCBQ/DCM/APLB
Evi Struble	Nonclinical Toxicology
Amanda Trayer	Regulatory Management - OCBQ
Yonggang Wang	CMC (Stability and Assay Validation)
Claire Wernly	CMC (Bioburden, Sterility and Endotoxin)
Pei Zhang	CMC (Viral Safety Evaluation)
Boguang Zhen	Chief/CBER/OBE/DB/TEB

Discussion Summary:

Cangene Corporation, operating as Emergent Biosolutions, submitted to the FDA for review an original Biologics License Application (BLA), STN 125562/0. This BLA arrived to the Agency on July 25, 2014. The product was granted Orphan status on July 29, 2008 for “treatment of toxemia associated with inhalational anthrax.” Cangene received Fast Track designation for this product on December 21, 2006; FDA indicated during the pre-BLA meeting (CRMTS 9270) on March 18, 2014 that this product would qualify for priority review, which was granted by DHCR management at the First Committee Meeting on August 13, 2014. The cross-reference to Investigational New Drug (IND) application is IND 11982. Cangene is requesting review of proposed proprietary name Anthrasil. The proposed indication at the time of BLA submission is: “Treatment of adult and pediatric patients with toxemia associated inhalational anthrax.”

No substantive issues have been identified that would preclude approval of this application or impact the review timeline have been identified at this time. A summary of individual discipline reviews is as follows:

Chemistry Manufacturing and Controls:

No substantive issues with regard to the natural history studies or the nonhuman primate efficacy studies have been identified at this time.

Manufacturing of Anthrax Immune Globulin Intravenous uses manufacturing steps, equipment, and formulation that are identical to those used for the licensed hyperimmune products WinRho SDF, HepaGam B, and VIGIV. Data collected in support of WinRho SDF, HepaGam B, and VIGIV suggest that the manufacturing process can yield IGIV product with an acceptable safety profile. Original source plasma for AIGIV is obtained from donors vaccinated against B. anthracis antigens. The different plasma source is not expected to adversely impact the safety profile. The manufacturing details, process validation, and batch records provided here all suggest that AIGIV manufacture in its current iteration is generally well controlled. Biochemical analysis data shows AIGIV product characteristics (e.g. purity, Ig subclass distribution) are similar to those of other hyperimmune products. There are no problematic issues identified from the product review perspective that would preclude approval. Some details are missing from biochemical analysis of submitted lots (b) (4) which will require follow-up.

No major issues for product viral safety have been identified. IR for clarification of viral validation may be needed. The available stability data appears to support applicant proposed drug substance shelf-life of (b) (4) and drug product shelf-life of 72 months. (b) (4) validation and data were not provided, and will be requested.

CBER finds the method suitability test for the (b) (4) Assay (STM 500114) (QCM_MS_0021_rep_v1) to be incomplete. CBER does not agree that the method passes the suitability test as per (b) (4) as the sponsor only provided data for indicator microorganisms and sample controls grown under one condition. To date, the applicant only provided data for the determination of (b) (4) and did not include data for the determination of (b) (4) Additional data is

requested to complete the review and to confirm that the method passes the suitability test as per (b) (4)

In the validation of the toxin neutralization assays for product release (potency and stability) and PK studies (rabbit, NHP and human), data analysis for assay precision was done on un-transformed data. After discussions with statisticians on the committee, an IR will be send requesting that the applicant re-analyze the data for the validations using a log-transformed scale.

Areas not reviewed to date:

1. 3.2.S.4.3 - Validation of analytical procedures
2. 3.2.S.4.4 - Batch Analysis not finished (still blacked out)
3. 3.2.A.2 - Adventitious Agents Safety Evaluation
4. 3.2.S2.2 - Description of Manufacturing process controls
5. Attachments for study reports on viral validation at manufacturing steps of Anion Exchange chromatography, 20N filtration, and SD treatment (description of results in details)
6. Review of IR responses received on October 17, 2014

Action Pending:

1. Applicant should provide data that has been blacked out / redacted from the batch records of submitted lots (b) (4)

Outstanding information requests:

1. 11/5/14 – requested clarification of (b) (4) potency assay, validation reports for tests of (b) (4)
2. 10/31/14 – requested confirmation that the method passes the suitability test as per (b) (4)

Pending information requests:

1. Will request (b) (4) Protocol and Data.
2. IR for clarification of viral validation may be needed.
3. IR requesting the applicant re-analyze the data for the validations using a log-transformed scale.

Pharmacology/Toxicology:

At this point in the review process, there are no toxicology issues that would prevent this application from being approved.

Areas not reviewed to date:

1. Safety of Excipients

Action Pending:

None

Outstanding information requests:

None

Pending information requests:

None

Clinical:

The safety in healthy volunteers of single doses of AIGIV in fixed doses up to 840 U TNA appears adequate from review of RCT AX-001 in relation to the potential benefits in the treatment of adults with inhalational anthrax.

The safety of AIGIV has not been studied in the pediatric population. Given the serious and life-threatening nature of inhalational anthrax, it may be reasonable to extrapolate the safety profile of other licensed Cangene hyperimmune immunoglobulin products in pediatric subjects to pediatric patients who would receive AIGIV for inhalational anthrax. Review of pediatric safety data for those other products submitted in amendment 07 is ongoing.

Review of three cases of inhalational anthrax, one of GI anthrax, and 15 of injectional anthrax all treated with single 420 U doses of AIGIV for severe systemic illness is consistent with the possibility that the product, in combination with appropriate antimicrobial therapy, might confer benefit in inhalation anthrax in some patients (as well as in severe systemic anthrax from other routes of exposure). However, in the absence of a fully satisfactory historical control group, in terms of size and availability of a full characterization of the comparability of historical controls to patients treated on a compassionate use basis with AIGIV, the very limited available experience in patients with inhalational anthrax (or other systemic anthrax disease) is insufficient as a basis for concluding substantial evidence of efficacy or safety in the target population. Thus, primary reliance on the animal model of inhalational anthrax efficacy models and PK scaling from animals humans to provide substantial evidence of extrapolated efficacy appears appropriate.

Review of the compassionate use of the product in human cases of severe systemic anthrax suggests the need for studying administration of additional dose(s) of AIGIV in selected patients and consideration of inclusion of a discussion of optional additional dosing for selected patients on a case-by-case basis in the draft package insert. It is recommended that the applicant incorporate plans to study the use of additional dose(s) of the product in selected patients in both sporadic and broad exposure event components of the PMR study.

The clinical reviewer agrees with the clinical pharmacology reviewer that the single fixed 420 U TNA dosing regimen might not be adequate/optimal for morbidly obese patients. I agree with the clinical pharmacology reviewer's request for PK data to be obtained as a PMC to evaluate dosing in morbidly obese subjects with BMI >35.

The clinical reviewer agrees with the applicant's inclusion of a boxed warning regarding the risks of serious and potentially fatal hypoglycemia that could result from using glucose non-specific glucose meters/strips to measure blood glucose following administration of this maltose-

containing product. The glucose data measured using various methods from RCT AX-001 confirm that the maltose content of the proposed dose of the product is sufficient to produce clinically significant false elevations in point-of-care device glucose determinations using glucose non-specific methodology.

The submitted PMC field study contingency protocol is limited to a “broad [anthrax] exposure event scenario,” and does not provide for capture, analysis, and sharing with FDA data from ongoing sporadic cases of inhalational or systemic anthrax. The submitted PMC protocol is limited to the U.S. and does not include provision for blood and/or body fluid sampling for lethal factor levels, which could add to an understanding of the role and efficacy of the product, as well as contribute to a better understanding of dose selection in the target population. A draft information request has been prepared to address these deficiencies/features in a full protocol to be submitted well before the Action Due Date.

The sponsor needs to revise the first paragraph of the INDICATIONS AND USAGE sections of the PI to read as follows:

ANTHRASIL is an Anthrax Immune Globulin Intravenous (Human) indicated for the treatment of toxemia associated with inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs.

In addition, it is recommended to include a limitation statement in the INDICATIONS AND USAGE sections of the PI to the effect that an independent contribution to efficacy (survival) of ANTHRASIL above and beyond that conferred by appropriate antibiotic therapy was unable to be demonstrated in animal efficacy trials. Although the efficacy of ANTHRASIL monotherapy was demonstrated animal efficacy models of inhalational anthrax, ANTHRASIL needs to be administered in combination with appropriate antibiotic therapy as the product is not known to have bactericidal activity against anthrax bacteria which otherwise would continue to grow and produce anthrax toxins.

The above issues should not impact approval unless the sponsor were to be uncooperative in revising the draft package insert per FDA requests.

Areas not reviewed to date:

1. 5.3.5.2 Patient Experience Report & associated datasets
2. 1.14.1.2 Package Insert
3. Amendment 7 regarding pediatric safety data for other hyperimmune products licensed by Cangene

Action Pending:

None

Outstanding information requests:

None

Pending information requests:

None

Clinical Pharmacology:

Re-analysis of population PK is needed to assure that projected dose in human is reasonably accurate. Furthermore, the allometric scaling method for pediatric dosing projection requires modification and re-analysis. Package insert also requires modification.

Areas not reviewed to date:

1. Modeling and simulation for human dose projection is not complete.

Action Pending:

None

Outstanding information requests:

1. Re-analysis of population PK and adult and pediatric dose projection has been requested.

Pending information requests:

None

Epidemiology:

At this point in the review process, there are no epidemiology issues that would prevent this application from being approved.

Areas not reviewed to date:

None

Action Pending:

None

Outstanding information requests:

None

Pending information requests:

None

Bioresearch Monitoring (BIMO):

No BIMO findings or substantive issues to report at this time

Areas not reviewed to date:

Nonclinical. Receipt and review of one inspection report covering the following four non-clinical Good Laboratory Practice (GLP) study protocols (inspection ended on 10/10/2014):

1. *Pharmacokinetic Evaluation of Anthrax Immune Globulin (AIG), NP-015 in Cynomolgus Macaques Following Single Intravenous Infusion* (Protocol (b) (4) 695-G005780)

2. *Determination of Pharmacokinetics of Anthrax Immune Globulin (AIG), NP-015 in Rabbits* (Protocol (b) (4) 694-G005681)
3. *Determination of Dose Range Efficacy of Anthrax Immune Globulin (AIG), NP-015 in Cynomolgus Monkeys Exposed to Inhalation Anthrax: GLP Study* (Protocol (b) (4) 828-G005780)
4. *Therapeutic Efficacy of Anthrax Immune Globulin Intravenous (AIGIV), NP-015 in Rabbit Model of Inhalation Anthrax: GLP Study* (Protocol (b) (4) 1207-100005104)

Clinical. Review of one inspection report covering the following clinical study protocol (AX-001). (Inspection ended on 10/02/2014):

1. *Safety and Pharmacokinetics of Anthrax Immune Globulin Intravenous (Human), NP-015, in Healthy Volunteers*

Action Pending:

None

Outstanding information requests:

None

Pending information requests:

None

Division of Manufacturing and Product Quality (DMPQ):

Review of all sections, in the original submission, under DMPQ purview have been completed, including facilities and room classifications, utilities, equipment, cleaning, sterilization and depyrogenation, container closure, aseptic manufacturing, containment, line clearance, environmental monitoring, filling, visual inspection, packaging and shipping. The responses to October 13, 2014 IR were received on November 3, 2014 (amendment 125562/0/9) and have **NOT** been completely reviewed. An inspection waiver memo was drafted to waive the pre-license inspection, as the manufacturing operations for this product are similar to other US licensed hyperimmune products, and the facility was inspected in July 2014 by Team Bio, and the inspection will be classified as VAI (Voluntary Action Indicated).

No outstanding information requests at this point. Cangene submitted responses to September 4, 2014 IR in amendment 125562/0/2, received September 16, 2014. Cangene submitted the responses to the October 13, 2014 IR in amendment 125562/0/9, received November 3, 2014, which are currently under review. Additional information may be requested after review of the information provided in the November 3, 2014 submitted response.

Areas not reviewed to date:

Responses to October 13, 2014 IR (amendment 125562/0/9)

Action Pending:

None

Outstanding information requests:

None

Pending information requests:

None

Division of Biological Standards and Quality Control (DBSQC):

The Lot Release protocol template is consistent with other similar approved products from the same manufacturer, and listed specifications are consistent with those specified in the BLA. Minor changes and formatting edits may be requested.

Areas not reviewed to date:

1. Lot Release Protocol Template has been partially reviewed – no major issues. Still awaiting comments/edits from PRB and other DBSQC reviewers.
2. Product testing plan development – a testing plan is currently being drafted

Action Pending:

None

Outstanding information requests:

1. An IR for minor edits to LRP has yet to be submitted to applicant.

Pending information requests:

None

Biostatistics:

Two animal models were introduced by the sponsor. One of the animal studies failed the primary efficacy endpoints after a fail of increase in the sample size in the 2nd stage; this study was based upon a 2-stage adaptive design and it was concluded (with input from the Agency) after stage 1 that it would not be possible to reach statistical significance by proceeding to stage 2 .

Areas not reviewed to date:

1. Verification of secondary efficacy endpoints of study 1182, 1207.
2. Verification of AE statistics in study AX-001 in detail.

Action Pending:

None

Outstanding information requests:

None

Pending information requests:
None

MID-CYCLE CHECK LIST

Major target and milestone dates:

<u>Meeting type</u>	<u>Date</u>
Mid-Cycle communication with the Applicant	November 14, 2014, 10:30 – 11 AM
Internal Late-Cycle Meeting	December 4, 2014, 3:30 – 5 PM
Promotional labeling review (APLB)	December 25, 2014
Late-Cycle Meeting with the Applicant	January 8, 2015, 1 – 2:30 PM
Labeling Meeting	January 22, 2015, 2 – 3 PM
PMC Study Target	February 23, 2015
Action Due Date	March 25, 2015
Post-Action Debrief Meeting	TBD

All discipline reviewers are on schedule with the primary review of the BLA. Target date to complete primary reviews is January 2, 2015. However, pending responses to outstanding information requests, and information from BIMO protocol reviews, target dates may be impacted for completion of discipline reviews.

The dates for the Internal and External Late-Cycle Meetings stated above may be revised depending on Review Committee and other invitee's schedules.

The RPM will work with the Clinical reviewer and Committee Chair to schedule an initial Labeling meeting.

The application will not be presented at the Blood Products Advisory Committee (BPAC). The Committee Chair and Clinical Reviewers are preparing the BPAC waiver memo.

National Drug Code (NDC) assignments to product/packaging are presently pending and will be completed by the RPM, if applicable. Because this may be an approval under Animal Rule, NDC review may not be necessary; the RPM will investigate.

The CBER Substance Registration System (SRS) name has been requested and is pending.

The Unique Ingredient Identifier (UNII) Code has been requested and is pending.

END