



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

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WO52-72 Rm 4324; 240-402-8213

To: File for 125562/0

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240-402-8236

Subject: Final Product Review Memo, Original BLA
Product: Anthrax Immune Globulin Intravenous (Human)
Submission Date: July 25, 2014
Manufacturer: Cangene Corporation (Emergent Biosolutions)

Summary and Recommendations:

This memo covers manufacturing information, drug substance and drug product characterization information submitted in support of Anthrax Immune Globulin Intravenous (Human; AIGIV). Manufacturing of AIGIV 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, product characterization, 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.

Introduction

Anthrax Immune Globulin Intravenous (Human; AIGIV) is a purified polyclonal preparation of IgG containing antibodies directed against *Bacillus anthracis*. AIGIV binds protective antigen (PA) and other potential antigens in anthrax vaccine (BioThrax). AIGIV is a passive immunizing agent intended to

neutralize the pathogenic effects of anthrax toxin in adults and children with toxemia associated with inhalational anthrax, alone or in combination with antibacterial agents.

AlGIV is prepared at Cangene Corporation's Winnipeg, Manitoba, Canada facility, using manufacturing steps and equipment identical to those in the currently licensed process for WinRho SDF Liquid, HepaGam B, and VIGIV. The starting material is source plasma from selected healthy donors immunized with BioThrax, who have elevated titers of Bacillus anthracis directed antibodies. Plasma units are tested by (b) (4) (serological evaluation) and (b) (4)

(nucleic acid testing of (b) (4) and plasma pools). Initial plasma (b) (4)

Ig purification begins with anion exchange chromatography, followed by nanofiltration, (b) (4), and solvent/ detergent treatment steps.

processing step, final formulation, and 0.2 micron filtration are completed to prepare the bulk drug substance. No reprocessing steps are approved. (b) (4)

(b) (4)

Materials

Materials used in manufacture of AlGIV are purchased from approved suppliers, and all are from non-animal sources except for human plasma starting material, (b) (4) and maltose which is manufactured using (b) (4). Raw material testing, performed by the Applicant's QC department, utilizes compendial monographs, ACS and/or in house methods for qualification. Source plasma used for AlGIV manufacture is collected at FDA licensed plasma collection facilities in the US. Plasma is collected from eligible donors who have received a minimum of 3 doses of anthrax vaccine (AVA, BioThrax). Source plasma is screened for viral markers at licensed facilities using approved test kits, according to 21 CFR 610.40 and industry standard.

Adventitious Agents Safety Evaluation

Control of bacterial and fungal growth across the manufacturing process is monitored by total bacterial count and endotoxin testing, and sterility testing on finished product. The Applicant reports no sterility failures for AlGIV lots to date.

Control of transmissible spongiform encephalopathy (TSE) / prions is achieved at several levels, including donor selection/ exclusion according to FDA approved procedures; implementation of a supplier qualification management program; exclusion of animal-derived components originating from

high-risk countries; supplier audit for raw material quality; validated cleaning systems including caustic cleaning materials; (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4) risk

assessment indicate that the TSE risk, if any, is extremely low.

Control of viral agents across the manufacturing process is achieved through viral testing (b) (4) mini-pool, manufacturing plasma pool), and by dedicated manufacturing steps (20N filtration, solvent/detergent (b) (4) designed to remove and inactivate viruses. Additional viral removal may occur through the anion exchange chromatography step in AIGIV manufacturing. The Applicant provides historic studies L.100.00.001, Pv.HYP.04.002, Pv.HYP.04.006, Pv.HYP.04.008, L.100.00.004, 858893, 856021, and Pv.HYP.03.001, which validated down-scale models of 20N filtration, solvent/detergent, and anion exchange chromatography steps, and tested removal / inactivation of spiked model viruses. These studies have been previously reviewed by CBER and approved.

Process Validation

Production of AIG drug substance has been carried out at (b) (4) plasma pool scales. (b) (4)

(b) (4)
(b) (4) Critical process parameters are similar to those identified for WinRho SDF, and are listed below in Table 1 below. Critical quality attributes during AIG manufacture are listed in Table 2. Numerous changes in analytical testing that occurred between 2004 to present are listed as footnotes.

Table 1: Critical Process Parameters, AIG Manufacture



(b) (4)

Conformance Lots

The Sponsor has generated (b) (4) AIG drug substance lots. Of these, (b) (4) were used to generate (b) (4) AIGIV drug product lots. All of these lots were manufactured under IND 11982 between 2004 and 2011. In 2007, Cangene was permitted to ship AIGIV to the Strategic National Stockpile (SNS) after submission of supporting data to FDA documenting product quality and process consistency. In 2009 FDA further agreed that AIGIV product met requirements for pre-Emergency Use Authorization. Because all AIG and AIGIV batches were manufactured with the intent to enter into the SNS, there was no conformance batch campaign designated to support the BLA. Instead, the Sponsor submits study PV0288, which documents a retrospective validation of manufacturing process consistency across all (b) (4) drug substance lots and (b) (4) drug product lots. Retrospective validation of an aspect of manufacturing is usually reserved for licensed products. To support retrospective validation, the Sponsor notes that AIGIV has already met requirements for pre-EUA designation, allowing the product to be distributed and administered under defined circumstances. The Sponsor also notes that AIGIV was manufactured using a validated hyperimmune process, using approved manufacturing batch records with specified critical process parameters, qualified raw materials, and validated assays for testing of product safety, identity, purity and potency.

Manufacturing process changes that were implemented over the years that AIG and AIGIV drug substance and drug product batches were produced could complicate the assessment of process consistency. Changes in key operational parameters (KOP) established by the Sponsor along with the dates of implementation are listed below.

- 1) (b) (4)
[Redacted]
- 2) (b) (4)
[Redacted]
- 3) (b) (4)
[Redacted]

4) (b) (4) [Redacted]

5) (b) (4) [Redacted]

6) (b) (4) [Redacted]

Changes in In-Process Testing, listed below, were implemented over the years that AIGIV drug product batches were produced.

1) (b) (4) [Redacted]

2) [Redacted]

3) (b) (4) [Redacted]

4) (b) (4) [Redacted]

Changes in Critical Quality Attributes and their Measurement, listed below, were implemented over the years that AIGIV drug product batches were produced.

1) (b) (4) [Redacted]

2) [Redacted]

3) (b) (4) [Redacted]

4) (b) (4) [Redacted]

5) Change in potency reporting from U/ml to U/vial. Potency specification per vial was implemented in Q3 2005

AIGIV Batches Used In Vivo

Study	Filled Lot Numbers	Associated Drug	Manufacturing Scale(L)
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		Substance	
Rabbit safety study (GLP)	2440501	(b) (4)	(b) (4)
Non-clinical efficacy	10602912 (2490602) 11007147 (11006949)	(b) (4) (b) (4) (b) (4)	(b) (4) (b) (4) (b) (4)
Clinical safety	24906011 (2490601) 10804812 (2490501) 10804816 (10804572)	(b) (4) (b) (4) (b) (4)	(b) (4) (b) (4) (b) (4)

Deviations, Reprocessing

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

Batch Record Review

Three completed batch records were reviewed, corresponding to the most recently manufactured AIG drug substance lots, (b) (4). The batch records were complete, signed, and the processes matched the manufacturing details presented in the BLA text. Plasma processing, chromatography, S/D and filtration procedures were all well documented without major errors or deviations, suggesting the process is well controlled. However the analytical section had missing detail. All three batch records are reported in modules:

Plasma module: Electronic inventory of all materials, the lot number and expiry date, and how much was used is presented. There are about 10 errors listed as “late entries” after data lock in this section across the three batch records, and one entry that was reported as “wrong room” and removed from

the list. Next a work order is attached listing the requested plasma samples amounting to approximately (b) (4). A worksheet is completed for tabulating total potency and other characteristics, and a series of completed inventory sheets is presented verifying the correct plasma samples were pulled from the intended racks/ trays and scanned into the electronic inventory. QC of equipment cleaning and initial steps (e.g. plasma thawing and pooling) are contained in this module.

Plasma treatment module: Documents additions to plasma including (b) (4)

There are a number of transcription errors, usually incorrect documentation of the time of addition, which are corrected and signed.

Column chromatography module: (b) (4)

These sections contain a few date / time transcription errors and some late entries here after data lock.

20N filtration module: Documents preparation of the filtration equipment, skid and receiving tank. A few date and time transcription errors.

(b) (4) module: (b) (4) for (b) (4)

Minimal transcription errors.

Solvent / detergent module: (b) (4)

Minimal documentation errors noted.

(b) (4) module: (b) (4)

Minimal documentation errors noted.

Formulation and 0.2u filtration module: Preparation of the formulation buffer, documentation of filters used and their entry into electronic inventory, prefilter flushing and filtration of the product are documented in this section. Minimal documentation errors.

Recovery module: This section contains an initial assessment of potency measured by TNA and (b) (4) in samples at each manufacturing stage. Minimal transcription errors.

In process sampling matrix module: A listing of all testing performed on various samples collected across the manufacturing process. Minimal transcription errors.

In-process analytical report: Transcription errors were more frequent here – assay number, reagent lot numbers, date and time, and results were crossed out and written again with supervisor concurrence. Large portions of bacterial endotoxin assay reports were blacked out. Smaller portions of (b) (4) report details and (importantly) conclusions were also blacked out. In follow up communications, the Sponsor did provide unredacted versions for these analytical sections. Any time an individual sample or control had failed,

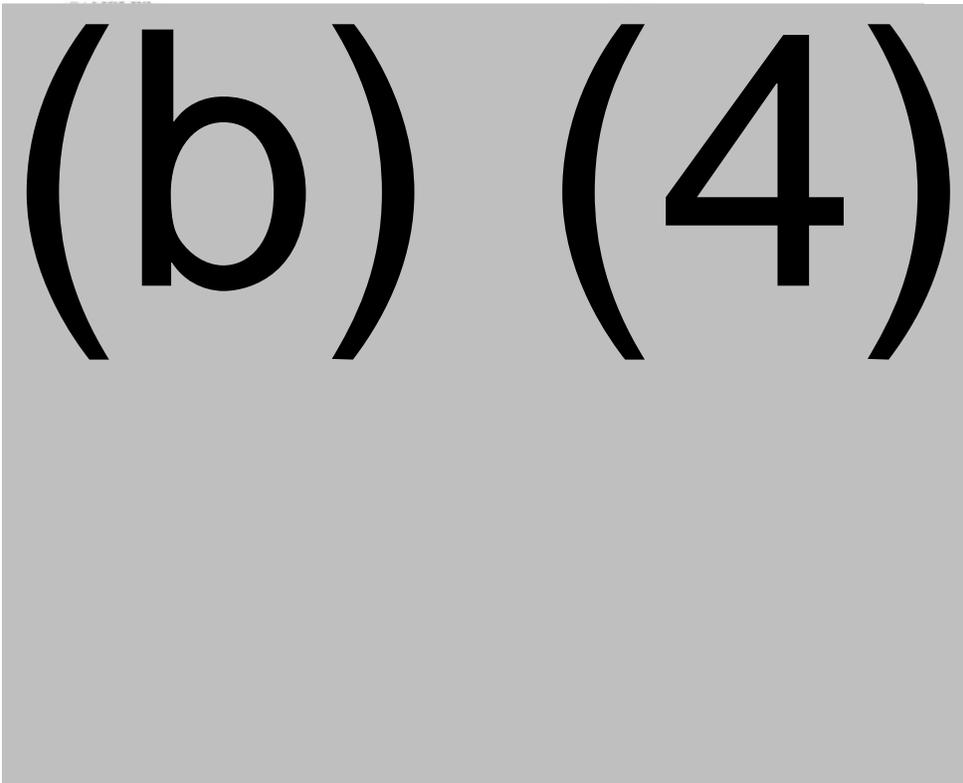
the Sponsor had redacted all reference to the sample, even though the recording of the data and concurrences were appropriate. For lot (b) (4), two TNA assay (b) (4) failures apparently due to no reference standard added to the (b) (4)

Inspected Lot

(b) (4) contained (b) (4) vials of Anthrax IGIV in 50 ml vials. The lot was subject to 100% inspection, and 50 vials were rejected. Of the 50 rejected vials, 47 were designated as containing foreign particulate, identified as arising from product (1), foreign material (13) or stopper material (33). Two of the remaining rejected vials had mold imperfections associated with the stopper, and one had color variation that was associated with the stopper. The percentage of rejected vials (b) (4) was within acceptance criteria (b) (4). Evidence of proper disposal of rejected lots was provided.

Product Characterization

The Sponsor compares licensed hyperimmune products WinRho and HepaGam B with AIVIG using (b) (4).



antigen was analyzed by (b) (4), and was found similar across non-clinical and clinical lots of AIGIV and the single lot of AIGIV prepared from plasma of source donors who received IM vaccination.