Summary Basis for Regulatory Action

Date: 25 March 2015

From: Robert W. Fisher, Ph.D., Chair of the Review Committee

BLA/ STN#: 125562

Applicant Name: Cangene Corporation

Date of Submission: 25 July 2014

PDUFA Goal Date: 25 March 2015

Proprietary Name/ Established Name: ANTHRASIL/Anthrax Immune Globulin Intravenous (Human)

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

Recommended Action: Approval

Signatory Authorities Action:

Jay S. Epstein, MD
Director, Office of Blood Research and Review
Offices Signatory Authority:

X I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

Mary Malarkey
Director, Office of Compliance and Biologics Quality
Offices Signatory Authority:

X I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

Disciplines and specific documentation used in developing the SBRA	
Advisory Committee Materials	N/A
Bioresearch Monitoring Review	Anthony Hawkins-15 December 2014, Colonious King-24 November 2014
Clinical Review	L. Ross Pierce-13 January 2015
Clinical Pharmacology Review	Iftekhar Mahmood-18 December 2014
CMC Review	Robert Fisher-21 March 2015, Michael Kennedy-25 February 2015, Miriam Ngundi-18 December 2014, Jennifer Reed, Yonggang Wang-12 January 2015, Claire Wernly-08 December 2014, Pei Zhang-09 January 2015
Facilities and Inspection Waiver	Randa Melhem-05 November 2014 (waiver), 31 December 2014 (facilities)
Labeling Review	Alpita Popat-26 January 2015
Lot Release Protocol and Testing Plan	Karen Campbell, Josephine Resnick-08 January 2015
Pharmacology/Toxicology Review	Evi Struble-07 August 2014
Pharmacovigilance/Epidemiology Review	David Menschik-16 December 2014
Proprietary Name Review	Alpita Popat-21 October 2014
Regulatory Project Manager	Thomas Maruna, Tracy Tilghman, Iliana Valencia
Statistical Review	Jiang Hu-03 January 2015

1. Introduction

Anthrax Immune Globulin Intravenous (Human); (AIGIV, proprietary name ANTHRASIL) is a purified polyclonal preparation of immunoglobulin containing antibodies directed against *Bacillus anthracis*, mainly directed against Protective Antigen (PA). AIGIV is prepared from the plasma of human donors previously vaccinated with Anthrax Vaccine Adsorbed (Biothrax; Emergent Biosolutions, Inc.). AIGIV acts against anthrax toxin and is not known to have direct antibacterial activity, so it is to be administered in combination with appropriate antimicrobial therapy. The labeled potency is >60 units per vial. One unit is defined by comparison against an in-house reference standard calibrated against the Centers for Disease Control and Prevention Reference Serum standard in a toxin neutralization assay (TNA) such that 1 unit is equivalent to the anti-PA neutralizing activity of 1 mg of the standard.

AIGIV is indicated for the treatment of inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs.

AIGIV is supplied in clear (b) (4) glass vials (50 mL) with (b) (4) bromobutyl rubber stoppers (20 mm), aluminum seals, and plastic flip-top caps. Each vial contains >60 units per vial, and the target fill volume is calculated based on a target TNA potency of (b) (4) per vial. The drug product is a clear or slightly opalescent colorless liquid essentially free of foreign particles and is formulated with 10% maltose and 0.03% polysorbate 80. The protein concentration of AIGIV is 40-70 mg/mL.

An investigational new drug application (BB-IND 11982) for AIGIV was received by the FDA from Cangene on 12 October 2004 with a requested indication "for the treatment of inhalational anthrax." Fast track designation was granted for the product on 21 December 2006, and orphan drug status was granted for "treatment of toxemia associated with inhalational anthrax" on 29 July 2008; the orphan drug status indication is being updated to match that approved under this BLA. The Strategic National Stockpile (SNS) began acquiring lots of AIGIV in March 2006, and there are currently (b) (4) lots in the inventory. A preEUA from the Centers for Disease Control and Prevention for use of AIGIV in the event of a declared emergency was acknowledged on 10 August 2010.

Because it is unethical to deliberately expose humans to anthrax and not feasible, due to the low incidence of disease, to evaluate a therapeutic product against inhalational anthrax in humans, FDA is relying on data from animal efficacy models of inhalational anthrax in rabbit and nonhuman primates to provide substantial evidence of efficacy of AIGIV. Cangene provided evidence to support their choice of animal models under 21 CFR 601 Subpart H "Animal Rule" regulations as outlined in *Guidance for Industry: Animal Models-Essential Elements to Address Efficacy Under the Animal Rule*. Dose ranging and anthrax natural history studies were performed in New Zealand White rabbits and in cynomolgus macaques

exposed to aerosols of *B. anthracis* Ames spores with a target dose of 200 LD_{50} (i.e 200 times the dose of spores that will kill half of the exposed animals). These studies helped define the treatment trigger for that challenge model: the clinical sign, signs, or biological indicator(s) that provide consistent evidence of infection with the challenge agent. The pharmacokinetics of AIGIV administered at various dose levels and AIGIV dose ranging studies following anthrax challenge were evaluated in both species. Finally, randomized, placebo-controlled studies were performed in rabbits and nonhuman primates to evaluate the efficacy of AIGIV in a treatment scenario with or without levofloxacin (in rabbits) or ciprofloxacin (in nonhuman primates), both broad spectrum antibiotics. These studies demonstrated that AIGIV was reasonably likely to provide clinical benefit in humans with inhalational anthrax disease.

As required under 21 CFR 601 Subpart H, the safety of AIGIV was evaluated in healthy human adults (i.e. healthy volunteers not infected with anthrax). Both safety and pharmacokinetics were examined in a single two-part randomized, double-blind phase 1 trial in healthy human volunteers, AX-001. The first part of the trial evaluated a total of 54 subjects (28 males and 26 females ranging in age from 19 to 55 years of age) who were randomized in cohorts of 18 to one of three doses of AIGIV (210 units, 420 units and 840 units) and 18 subjects (11 males and 7 females ranging in age from 20 to 52 years of age) who were randomized in cohorts of 6 to receive saline placebo. The second part of this trial, which did not have a placebo control, involved randomization of 20 subjects (9 males and 11 females ranging in age from 19 to 55 years of age) to either of two AIGIV product lots not studied in the first part of the trial. There were a total of three American Indians or Alaska Natives, seven Asians, 13 Blacks/African Americans, and 69 Whites enrolled in AX-001 including 3 Hispanics/Latinos enrolled in the safety and PK trial. Limited safety data were also evaluated from 19 sporadic human cases of systemic anthrax, including 3 inhalational anthrax cases in males aged 34 to 61 years of age, in which AIGIV was administered with antibiotics.

Review Challenges

There was uncertainty regarding the optimal effective initial dose. The 420 unit dose was based upon an extrapolation of neutralizing titers associated with protection of animals in vaccine studies. A rabbit study of survival in bacteremic and toxemic animals treated with AIGIV plus levofloxacin, compared to animals treated with IGIV plus levofloxacin, was conducted at a single dose of AIGIV (i.e. the human equivalent of 420 units). In additional multi-dose studies, a trend (not statistically significant) toward increasing efficacy with increasing dose exposure was observed in both the rabbit and nonhuman primate models. A dose-response model predicted improved survival with increasing exposure both to AIGIV alone and AIGIV in combination with antibiotics. Because some patients with inhalational anthrax come to medical attention at the fulminant stage of disease, and because the dose scaling from animal efficacy studies to humans used mean clearance values, which do not take into account individual variation in clearance and exposure to the product, FDA determined

that physicians need the flexibility to prescribe a higher initial AIGIV dose (840 units), depending on the condition of the patient.

A related issue was the need to consider repeat dosing for selected patients. Data on anti-PA levels in some injectional anthrax patients with substantial hemorrhage and repeated therapeutic thoracentesis/abdominal paracentesis demonstrated that up to 90% of the peak anti-PA antibody levels were eliminated from the blood within 24 hours following AIGIV dosing. FDA determined that such patients with large blood/fluid losses following an initial dose of AIGIV were candidates for repeat dosing.

Safety and efficacy data were not determined for special populations, including pediatrics, elderly and obese patients. Although the product is indicated for both adult and pediatric patients with anthrax, pediatric studies were not performed with AIGIV, and the animal models providing data on efficacy were biased for the adult population. To address the issue of pediatric dosing, Cangene was asked to submit and summarize pediatric safety data for their other hyperimmune immunoglobulin products that are manufactured similarly for other indications, and were considered supportive of the safety of AIGIV in pediatric patients. FDA has requested that Cangene incorporates PK testing in the postmarketing requirement (PMR) field trial and in sporadic systemic anthrax patients receiving AIGIV which may include special populations such as pediatrics, elderly, and obsese patients.

2. Background

Anthrax is a severe disease produced by the gram-positive spore-forming bacterial rod *B. anthracis*. Anthrax manifests based upon the route of exposure: cutaneous, inhalational, and gastrointestinal (GI) anthrax; more recently a form of anthrax has been described in drug users who inject spore-contaminated heroin (injectional anthrax). Sporadic human infection occurs from direct contact with infected animals or by inhalation of spores from contaminated animal-associated materials (typically hides or wool), however anthrax has a history of being developed as a biological weapon due to several favorable characteristics: stability of aerosolized *B. anthracis* spores, the inherent efficacy of the *B. anthracis* spore to be retained in the lung once inhaled due to its ~ 1µm aerodynamic diameter, and the high case fatality rate of inhalational anthrax (45% in the 2001 U.S. anthrax attack in patients who received antibiotic and supportive therapy[1,2]). *B. anthracis* spores can also be produced and concentrated to a high level as demonstrated by the approximately 10^{12} spores/g content of the material found in an anthrax contaminated letter that was mailed in the 2001 terrorism event[3]. The human ID_{50}, or the dose of inhaled spores that will cause infection in 50% of the susceptible population, is estimated to be $1.1x10^4$ spores[4].

Inhalational anthrax is triggered when *B. anthracis* spores are inhaled and deposited in the lung. The spores are phagocytized by alveolar macrophages that traffic to regional lymph

nodes. The spores germinate within phagosomes of the infected macrophages, and the vegetative bacteria secrete several proteins including Lethal Factor (LF), Edema Factor (EF) and PA[5]. During anthrax infection, PA binds to one of two cellular receptors (tumor endothelial marker 8 or capillary morphogenesis gene 2) on host cells. A furin cleavage event activates PA and triggers the formation of a PA heptamer that can bind LF or EF; PA complexed with EF or LF forms edema toxin (ET) and lethal toxin (LT), respectively. These complexes undergo endocytosis and the internalized ET and LT interfere with critical cellular pathways[6]. ET is an adenylyl cyclase, which increases intracellular cAMP levels, and triggers influx of interstitial fluid, resulting in edema. LT inactivates mitogen-activated protein kinase kinases and interferes with the host immune response by triggering apoptosis of macrophages. The bacteria disseminate widely, continue replicating, and contribute to hemorrhagic mediastinitis, septicemia, meningitis, and eventually death. The concentration of circulating PA correlates with the extent of bacteremia in the blood of experimentally infected animals[7] and is a useful marker of infection. The incubation period following aerosol exposure of *B. anthracis* spores ranges from one to 43 days, and the disease follows a biphasic clinical course. The initial symptoms are often nonspecific. Malaise, fever, diaphoresis, cough, chest discomfort, nausea, and vomiting were common in patients following the 2001 attack, and these patients sought care after a median of 3.5 days after symptom onset[8]. In the absence of treatment, and sometimes despite treatment, the disease becomes fulminant and progresses rapidly; this state is characterized by hypotension, dyspnea, cyanosis, respiratory failure (often resulting from massive pleural effusions), and shock; this fulminant stage may be preceded by a period of apparent improvement in constitutional symptoms. Pleural effusion is common and may require aggressive drainage to maintain lung function as well as to remove a large potential toxin reservoir[9,10]. Anthrax meningitis can complicate inhalational and other forms of systemic anthrax and has an extremely high mortality rate despite aggressive therapy.

Wild-type strains of anthrax are sensitive in vitro to antibiotics from a wide range of pharmacologic classes but are resistant to some cephalosporins. Antibiotics approved for post-exposure prophylaxis and for reducing the progression of inhalational anthrax in humans include doxycycline, ciprofloxacin, and levofloxacin. The only product currently approved in the U.S. as an adjunct to antibiotic therapy in the treatment of inhalational/systemic anthrax is a PA-binding monoclonal antibody product, raxibacumab. As detailed in section 11 below, raxibacumab was approved by the Center for Drug Evaluation and Research (CDER) using animal models identical to those used to determine the efficacy of AIGIV.

Because it is not ethical or feasible to conduct placebo-controlled clinical trials in humans with inhalational anthrax, AIGIV was developed under the Animal Rule (21 CFR 601 Subpart H, Approval of Biologic Products when Human Efficacy Studies are Not Ethical or Feasible). The therapeutic benefit of AIGIV is based on efficacy studies demonstrating a survival benefit in animal models of inhalational anthrax infection. As required under the 21 CFR 601 Subpart H regulations, the safety of AIGIV has been assessed in healthy adults. Data were also

available from a limited number of patients with anthrax who were treated with AIGIV and antibiotics under expanded access use (see Clinical Section 6 and Safety Section 7).

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

AIGIV is a purified polyclonal preparation of IgG containing antibodies directed against *Bacillus anthracis*. AIGIV binds PA and may also recognize other potential antigens present in the anthrax vaccine (BioThrax). It is used as a passive immunizing agent intended to neutralize anthrax toxins in adults and children with inhalational anthrax, and is to be administered in combination with appropriate antibacterial drugs.

Manufacturing

AIGIV is prepared at Cangene Corporation's Winnipeg, Manitoba, Canada facility, using manufacturing steps and equipment identical to those in the currently licensed process for manufacture of other hyperimmune immune globulins 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 *B. anthracis*-directed antibodies. Plasma units are tested for blood borne pathogens by (b) (4) (nucleic acid testing of (b) (4) plasma pools). Initial plasma processing includes (b) (4) Immune globulin (Ig) purification begins with anion exchange chromatography, followed by nanofiltration, (b) (4), and solvent/ detergent (S/D) treatment steps. (b) (4) No routine reprocessing steps are approved, (b) (4) .

Cangene has requested a (b) (4) storage of the bulk drug substance when held at (b) (4). The stability of the drug substance was found acceptable, with a caveat. The study submitted to support the (b) (4) hold time did not use a representative sample, (b) (4) . Real-time and accelerated studies on drug product in final container support a dating period of 72 months when stored at ≤ -15 °C.

In 2010 an increase in same-day thromboembolic events was linked to several lots of an IGIV product manufactured under a modified process. This increase was attributable to high levels of procoagulant Factor XIa, which co-purified along with the desired immunoglobulin proteins. Some IGIV processes in particular are affected by the copurification phenomenon.

(b) (4)

Adventitious Agent Control

Control of bacterial and fungal growth across the manufacturing process is maintained by total bacterial count and endotoxin testing, and sterility testing on the finished product. No sterility failures for AIGIV lots have been reported.

(b) (4)

Control of viral agents across the manufacturing process is achieved through virus screening of plasma (b) (4) , mini-pool, and manufacturing plasma pool), and through dedicated steps in the manufacturing process (20nm filtration andsolvent/detergent incubation) designed to remove and inactivate viruses. Additional viral clearance may occur through the anion exchange chromatography step in AIGIV manufacturing. No specific studies were performed for the AIGIV submission; Cangene's hyperimmune manufacturing platform had been previously validated using scaled-down models of 20nm filtration, solvent/detergent (b) (4) , and anion exchange chromatography steps, including removal/inactivation of model virus spikes. The capacity of the manufacturing process for reducing viral contamination is outlined in the table below.

Virus reduction values (Log_{10}) validated for Cangene's human hyperimmune manufacturing process.

Enveloped	**Enveloped**			**Non-Enveloped**			
Genome	**RNA**		**DNA**	**RNA**		**DNA**	
Virus	**HIV-1**	**BVDV**	**PRV**	**HAV**	**EMC**	**MMV**	**PPV**
Family	Retrovirus	Flavivirus	Herpes virus	Picornavirus		Parvovirus	
Size (nm)	80–100	50–70	120–200	25–30	30	20–25	18–24
Anion Exchange Chromatography (partitioning)	Not evaluated			2.3	n.e.	3.4	n.e.
20N Filtration (size exclusion)	≥4.7	≥3.5	≥5.6	n.e.	4.8	n.e.	4.1
Solvent/Detergent (inactivation)	≥4.7	≥7.3	≥5.5	Not evaluated			
Total Reduction (log_{10})	**≥9.4**	**≥10.8**	**≥11.1**	**2.3**	**4.8**	**3.4**	**4.1**

Abbreviations:

BVDV = Bovine viral diarrhea virus; model virus for hepatitis C virus (HCV) and West Nile virus (WNV)

DNA = Deoxyribonucleic Acid

EMC = Encephalomyocarditis virus; model for HAV and for small non-enveloped viruses in general

HIV-1 = Human immunodeficiency virus-1; relevant virus for HIV-1 and model for HIV-2

HAV = Human hepatitis A virus; relevant virus for HAV and model for small non-enveloped viruses in general

MMV = Murine minute virus; model for human B19 parvovirus and for small non-enveloped viruses in general

n.e. = Not evaluated

PPV = Porcine parvovirus; model for human B19 parvovirus and for small non-enveloped viruses in general

PRV = Pseudorabies virus; model for large enveloped DNA viruses, including herpes

RNA = Ribonucleic Acid

b) CBER Lot Release

Cangene has an adequate history of compliance for the production of hyperimmune products and the product will therefore be released exclusively by protocol review.

As was the case with the other Cangene product (Botulism Antitoxin; BAT) acquired for the SNS, AIGIV specifications will evolve over time while the manufacturing process is maturing and the product is being stockpiled in the SNS. The testing plan includes release specifications for lots already produced, and new lots will conform to the most recent lot release specifications and lot release protocol template.

c) Facilities Review/Inspection

The facilities involved in the manufacture of Anthrax Immune Globulin Intravenous (Human) are listed in the table below. The activities performed and the inspectional history are noted in the following table, and are further described in the paragraphs that follow.

Table: Manufacturing facilities for Anthrax Immune Globulin Intravenous (Human)

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification/ Results
Drug Substance *Drug Product* *Release Testing* Cangene Corporation 155 Innovation Drive Winnipeg, MB Canada R3T 5Y3	3003153579	244844056	Waived November 2014 memo	Team Biologics June 2012 VAI Team Biologics July 2014 VAI

Team Biologics performed CGMP inspections of the Cangene Manitoba facility from June 12-21, 2012 and July 9-18, 2014. All 483 issues were resolved and the inspections were classified as voluntary action indicated (VAI).

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product does not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Toxicology

There were no dedicated toxicology studies performed to support this BLA. Cangene submitted two Good Laboratory Practice (GLP) toxicity studies performed with an IGIV product manufactured with a similar process and containing the same excipients as AIGIV. The first study was an acute single dose toxicity study of immune globulin intravenous (NP-021) in rats performed by (b) (4) A No Observed Adverse Event Level (NOAEL) of 5000 mg/kg was demonstrated under the conditions of this study. The second study, in rabbits, was to determine the local tolerance of immune globulin intravenous (NP-021), delivered via intravenous, intra-arterial, perivascular, subcutaneous, and intramuscular routes. There were no test article-related clinical findings, effects on body weight, or macroscopic observations. Erythema and edema were slight to very slight, and there was no difference noted between the test article and saline controls in macro- or microscopic evaluations of the injection sites. Although IGIV products (including AIGIV) carry the risk of triggering thrombotic adverse events, no evidence of thrombosis was noted in the GLP toxicity studies.

Exposure calculations assumed a maximum adult dose of 840 units (14 vials) and a maximum pediatric exposure of 4 vials in a 10 kg subject. Exposure to excipients in AIGIV was comparable or lower than excipient exposure from other approved IGIV products: the lowest safety margins are 4 and 4.5 exposure in pediatric patients to protein and maltose, respectively. Maximum protein exposure is 630 mg/kg in a 70 kg adult and 1260 mg/kg in a 10 kg pediatric subject compared to a NOAEL of 5000 mg/kg in a single dose IV study in rats. Maltose exposure is 1.1 g/kg in a 70 kg adult or 2.2 g/kg in a 10 kg pediatric subject compared to a 10 g/kg NOAEL demonstrated in a repeated dose IV study in rabbits. Polysorbate 80 exposure is 3.6 g/kg in a 70 kg adult and 7.2 g/kg in a 10 kg pediatric subject compared to a NOAEL of 62.5 mg/kg in a rabbit developmental study.

Manufacturing related impurities (Tri-n-butyl phosphate and Triton X-100) correspond to (b) (4) ug/kg and (b) (4) ug/kg in a 70 kg adult at the 840U AIGIV dose level, respectively. The lowest observed adverse effect level for tri-n-butyl phosphate is 80 mg/kg in a single dose IV study in rats, and the intravenous LD_{50} for triton X-100 is 1200 mg/kg in rats.

In summary, the excipient and impurity levels in AIGIV are comparable to those found in other approved Immune Globulin Intravenous (Human) (IGIV) products, and provide an acceptable margin of safety for both adult and pediatric patients.

5. Clinical Pharmacology

The description of animal pharmacokinetics (PK) is included in the clinical pharmacology section because the approval of AIGIV is based on the "Animal Rule" and it was considered appropriate to provide animal PK along with human PK for clarity and better understanding of interspecies PK.

Pharmacokinetics in Unaffected (Non-Anthrax Challenged) Species

Pharmacokinetic (PK) studies of AIGIV were conducted in rabbits, cynomolgus macaques, and humans. Serum anti-protective antigen (anti-PA) levels were determined using a validated anti-PA (b) (4) and a validated Toxin Neutralization Assay (TNA). The PK parameters reported in this summary are based on the TNA analytical method since it measures neutralizing antibodies as opposed to the anti-PA (b) (4). PK parameters of AIGIV were calculated by non-compartmental analysis.

New Zealand White rabbits (*Oryctolagus cuniculus*) received intravenous infusion of AIGIV at the doses of 5, 10, 15, 30 and 40 U/kg body weight. Blood samples for PK study were drawn before infusion (day -7) and at 1, 8, 24, 48 hours, and days 3, 5, 8, 11, 14, 21, and 28. At the 40 U/kg dose of AIGIV, rabbits did not survive due to toxicity of the dose (attributed to volume overload) hence, no PK could be assessed in rabbits at this dose.

Cynomolgus macaques (*Macaca fascicularis*) received intravenous infusion of AIGIV at the doses of 5 and 30 U/kg body weight. Blood samples were collected on day -7 or day -8 (prior to infusion), day 0 (1 h and 12 h post-infusion), and days 1, 3, 5, 7, 14, 21, 28, 35, 45 and 56.

To determine the PK of AIGIV in humans, a dose-ranging study was designed to assess the PK (and safety) of three doses of AIGIV (210 U, 420 U and 840 U) after intravenous administration to healthy volunteers. This study was double-blinded, randomized and placebo controlled. A total of 72 healthy adult male and female subjects aged 19-55 were recruited in three cohorts of 24. Subjects were randomized to receive a 210 U (cohort 1), 420 U (cohort 2) or 840 U (cohort 3) dose of AIGIV (N = 18/dosing group) or an equal volume of saline placebo (N = 6/dosing group). Blood samples were drawn from the subjects in cohorts 1 - 3 at the following times after drug administration: 1, 3, and 8 hours and days 1, 3, 5, 7, 9, 11, 14, 21, 28, 42, 56 and 84 or at early withdrawal. A comparison of PK parameters among rabbits, cynomolgus macaques, and humans is presented in the table, below.

Interspecies comparison of AIGIV PK parameters (determined using the toxin neutralization assay) among healthy study subjects of each species

PK Parameter	Rabbit			Cynomolgus Macaque		Human		
	5 U/kg	15 U/kg	30 U/kg	5 U/kg	30 U/kg	210 U	420 U	840 U
C_{max} (mU/mL)	111 ±9	420 ±15	559 ±29	101 ±10	532 ±14	82.3 ±13.7	152.9 ±22.4	311.8 ±18.2
$t_{1/2}$ (days)	4.61 ±0.58	4.56 ±0.38	4.43 ±0.49	9.8[a]	6.71 ±1.02	24.3 ±33.3	28.3 ±19.9	28.0 ±25.2
Cl (mL/day/kg)	11.5 ±0.7	9.46 ±0.41	13.2 ±0.9	6.55[a]	12.5 ±1.2	2.34[b]	2.33[b]	2.48[b]
V_d (mL/kg)	75.6 ±9.9	55.2 ±2.70	80.2 ±5.9	92.6[a]	112.0 ±12.0	76.8[b]	93.9[b]	95.4[b]
$AUC_{0\text{-inf}}$ (day*mU/mL)	475 ±32	1710 ±80	2450 ±180	752[a]	2437 ±200	1239.4 ±26.5	2507.5 ±16.4	4624.2 ±28.5

Values for rabbits and NHPs are means ±SEM (standard error of the mean); values for humans are means ±SD (standard deviation).

[a] Data represent a single animal.

[b] Cl and V_d were calculated per kg body weight for human subjects using the following average weights: 210 U – 74.4 kg; 420 U – 72.8 kg; 840 U – 75.9 kg

The clearance (CL) of AIGIV in healthy rabbits (9.46 to 13.2. mL/day/kg) and healthy cynomolgus macaques (12.5 mL/day/kg at the 30 U/kg dose), was at least 4-5 fold faster (based on per kg basis) than in healthy humans (2.33 to 2.48 mL/day/kg). The volume of distribution was relatively similar in all species when normalized for body weight. The half-

life of AIGIV in humans is four to five times longer than in rabbits and cynomolgus macaques primarily due to slower clearance of AIGIV in humans. Gender had no impact on the PK of AIGIV.

Summary of pharmacokinetics in healthy human subjects

Based on TNA activity the PK of AIGIV is linear over the dose range of 210 U to 840 U. The half-life ranged from 24 to 28 days and the clearance ranged from 170 to 189 mL/day over the dose range of 210 to 840 U. The pharmacokinetic parameters of a single influsion of AIGIV are presented in the table below. There was no impact of gender on the PK of AIGIV analyzed with either the TNA.

Pharmacokinetic parameters of AIGIV in humans (TNA data)

PK Parameters	Dose Levels		
	210 U TNA	**420 U TNA**	**840 U TNA**
AUC_{inf} (mUxd/mL)	1239 (27)	2507 (16)	4624 (29)
Half-life (days)	24.3 (33.3)	28.3 (19.9)	28.0 (25.2)
Clearance (mL/day)	174 (24)	170 (18)	189 (30)
V_d (mL)*	5715 (11)	6837 (20)	7238 (19)

*Volume of distribution; numbers in parenthesis are %CV

Pharmacokinetics in Anthrax Challenged Models

The pharmacokinetics of AIGIV were also evaluated in both anthrax-infected rabbits and in anthrax-infected nonhuman primates.

Rabbits

The PK profile of AIGIV in anthrax exposed rabbits was determined at a single AIGIV dose of 15 U/kg. Rabbits were exposed to a target dose of 200 LD_{50} anthrax spores via aerosol route. In this study, 34 rabbits out of 110 were excluded from the PK analysis because they did not survive to Day 7 post-exposure. The $AUC_{(0-7)}$ and $AUC_{(0-14)}$ were different in the group of rabbits with aerosolized anthrax spores than the group of rabbits who were not exposed to spores. PK parameters (with the exception of AUC and CL) could not be assessed in this study. The clearance of AIGIV was more than 2-fold higher in the rabbits exposed to anthrax than in those rabbits who were not. The clearance of AIGIV in normal healthy rabbits based on $AUC_{(0-7)}$ and $AUC_{(0-14)}$ was 12.6 and 9.7 mL/day/kg, respectively. The clearance of AIGIV in

the exposed rabbits, based on $AUC_{(0-7)}$ and $AUC_{(0-14)}$ was 26.3 and 23.1 mL/day/kg, respectively.

Nonhuman Primates (NHP)

The pharmacokinetic profile of AIGIV in anthrax exposed NHPs was determined at AIGIV doses of 7.5, 15, or 30 U/kg. NHP were exposed to a target dose of 200 LD_{50} anthrax spores via the aerosol route. Due to the nature of the study (exposure to aerosol spores), animals died prior to their scheduled termination time. For the assessment of AUC (both AUC_{0-7} and AUC_{0-14}), all animals that survived to 7 or 14 days post-infusion were included in the analysis. The clearance of AIGIV was not different in the group of NHP exposed to aerosolized anthrax spores compared to the group of NHP who were not exposed. The clearance of AIGIV in normal healthy non-exposed NHPs based on $AUC_{(0-7)}$ and $AUC_{(0-14)}$ was 18.5 and 13.9 mL/day/kg (30 U/kg), respectively. The clearance of AIGIV in the exposed NHPs, based on $AUC_{(0-7)}$ and $AUC_{(0-14)}$ was 21 and 13 mL/day/kg, respectively.

In anthrax exposed animals, the PK assessment was difficult due to deaths in the animals. There were 16/50 rabbits used for calculating AUC, while data from all 50 (50/50) was available for determining clearance. In the NHP, data from 9/48 animals was used to calculate AUC while data from 14/48 was used to calculate clearance. The $AUC_{(0\text{-}7\ days)}$ and $AUC_{(0\text{-}14\ days)}$ was estimated for animals who survived until days 7 and 14. The clearance of AIGIV in anthrax exposed rabbits based on $AUC_{(0\text{-}7\ days)}$ and $AUC_{(0\text{-}14\ days)}$ was at least 2-fold higher than in the healthy rabbits. On the other hand, no difference in the CL of AIGIV was found between healthy and anthrax exposed NHPs. Cangene noted that in the NHP study the concentration of anti-PA antibody by TNA continued to rise after administration of the single dose of AIGIV, suggesting that the assay was measuring both endogenously produced as well as exogenously administered antibody. This explanation appears reasonable since the assay used (TNA) measures toxin neutralization activity regardless of source (AIGIV or endogenous immune response to anthrax infection), and would explain why the observed clearance in exposed NHP was not increased in comparison to healthy NHP as had been the case in the rabbit study.

Pharmacodynamics of AIGIV in Human Anthrax Cases

Three adult inhalational anthrax patients, concomitantly treated with antibiotics and a single dose of 420 units of AIGIV, exhibited increases in serum and pleural anti-PA levels; these levels remained at >50% of the peak anti-PA levels over the next five days, probably reflecting rising antibody production by the patients at the same time that the exogenously-administered antibody was being cleared. Mean peak anti-PA blood levels among the three treated inhalational anthrax cases following AIGIV administration were 25% lower than the C_{max} observed for the 420 U AIGIV dose cohort in the healthy volunteer randomized clinical trial AX-001. This, coupled with the fact that patients with systemic anthrax are expected to be

hypermetabolic/catabolic and may have third space or pleural effusions that may shift fluid compartments or provide additional toxin reservoirs, suggests that the pharmacokinetics of AIGIV in patients with inhalational anthrax may be altered compared to that observed in healthy volunteers. This mirrored the situation in rabbits, where the clearance of anti-PA antibody following AIGIV administration to animals exposed to anthrax was more than twice that of healthy animals. As noted earlier, in cynomolgus macaques, observed clearance in healthy and anthrax-exposed animals was similar, but Cangene considered this comparison unreliable due to the possibility of endogenous antibody synthesis in exposed animals and other limitations of the experiment. In the three inhalational anthrax patients, serum and pleural levels of LF declined after initiation of antibiotics and further decreased over the period of five days following administration; however, plasma and pleural LF levels remained detectable when measured 2 to 5 days following AIGIV administration. In some injectional anthrax cases, complicated by substantial hemorrhage and pleural and/or peritoneal fluid losses from thoracentesis and/or paracentesis, serum anti-PA antibody levels fell as much as approximately 90% from their post-AIGIV peak levels by 24 hours following AIGIV administration.

Pharmacokinetics in Special Populations

It was noted during the clinical pharmacology review that PK data for AIGIV are lacking for pediatric patients. Pediatric PK data will be obtained using sparse sampling during the postmarketing requirement (PMR) field trial and use of AIGIV in any future sporadic systemic anthrax cases that might involve pediatric patients. Additionally, FDA has requested PK data for anti-PA and LF following AIGIV administration in patients with inhalational anthrax during the postmarketing requirement field study and in future sporadic cases of systemic anthrax infection. These data will be analyzed by age, body mass index (BMI), and body weight to provide information on efficacy of AIGIV in special populations.

Modeling and Simulation of AIGIV to Support Dosing in Pediatrics

The applicant proposed dosing of AIGIV in children (neonates to adolescents) based on allometric scaling. The applicant used a single exponent of 0.75 across all age groups, which is an incorrect approach because a single exponent does not describe the PK parameters across all age groups. A fixed exponent 0.75 on CL may substantially overestimate the CL of a drug in children <5 years of age, especially in neonates and infants. In the analysis, the applicant did not take into account the possibility that the clearance of AIGIV in exposed humans may be higher compared to clearance in unexposed healthy subjects.

Application of age dependent exponents (1.2 for ≤ 3 months, 1.0 from >3 months to 2 years, 0.9 from >2 to 5 years, and 0.75 for >5 years of age) and the use of a projected AIGIV clearance value of 14 mL/hr in anthrax-exposed adults resulted in the similar projection of

AIGIV pediatric dose as a fixed exponent of 0.75 across all age groups. This similarity in pediatric dosing by two methods is by chance. Clearance of AIGIV increased with age hence, the projected dose of AIGIV also increased with age.

6. Clinical/ Statistical/Data to Support Efficacy

a) Nonclinical Efficacy Studies

Rabbit Studies

Three rabbit studies were conducted by Cangene in order to support the efficacy of AIGIV for the treatment of inhalational anthrax under the Animal Rule. These studies were performed at (b) (4) under Good Laboratory Practices (GLP) using New Zealand White Rabbits (*Oryctolagus cuniculus*). The pivotal efficacy study (b) (4) 1207-100005104) consisted of 110 rabbits (55 male, 55 female) challenged with *B. anthracis* Ames spores via aerosol exposure (average challenge dose = 194 ± 33LD_{50}). After the occurrence of a temperature spike and a positive test for circulating PA, 100 of the randomized animals were treated with either AIGIV (50 animals, 15 U/kg) or normal Immune Globulin Intravenous (Human) (IGIV) as control (50 animals). The remaining 10 challenged rabbits were used as untreated Ames spore aerosol challenged controls. All rabbits except for 2 IGIV control animals were later confirmed to be bacteremic prior to treatment. Of the AIGIV treated animals, 26% survived as compared to 2% in the IGIV controls (and 0% in the untreated but spore exposed rabbits), with an average time to death of 148.5 hours post-challenge for non-survivors in the AIGIV treatment group as compared to 75.8 hours for the IGIV controls. Both the increase in survival and time to death for the AIGIV treatment group were statistically significant.

An earlier dose ranging study (677-G005681) treated 6 groups of Ames spore aerosol challenged rabbits (14 animals/group, average dose of 265 ± 37 LD_{50}) with AIGIV dosed at either, 7.5 U/kg, 15 U/kg, or 30 U/kg, and treated at either 20 or 30 hours post-challenge. Additionally, two post-challenge IVIG treatment control groups (20 hour and 30 hour) and an untreated Ames spore aerosol challenged control group were included in the study. While the 20 hour post-challenge groups treated with AIGIV showed good dose responses to the drug, none of the animals in these groups were bacteremic or PA positive, so these data are only relevant to post-exposure prophylaxis (not the indication sought for this BLA). The 30 hour post-challenge AIGIV treatment groups did have a number of bacteremic and PA positive animals at the time of treatment, and forty-three to fifty-seven percent of animals treated at 30 hours post-challenge also exhibited a febrile response. If only animals positive for PA and bacteremia are taken into consideration, the 7.5 U/kg treatment group had 2 of 10 survive (20% survival), the 15 U/kg treatment group had 2 of 8 (25% survival), and the 30 U/kg group had 4 of 12 (30% survival). Twenty-five (25%, 2/8), thirty-three (33%, 2/6), and six percent (6%, 1/7) of febrile animals survived when treated with 7.5 U/kg, 15 U/kg, or 30 U/kg AIGIV

at 30 hours, respectively. No animals in the IGIV control groups or the untreated group survived, so the survival numbers comparing AIGIV treatment groups to the IGIV or no treatment groups are statistically significant, however the results between the 30 hour AIGIV dosing groups are not.

The third study (1182-G005681) assessed levofloxacin and either AIGIV or IGIV therapy, used in combination. Treatment was initiated 96 hours post-challenge (average of 238 LD_{50}) and involved a large number of animals (n=336) because of the narrow antibiotic therapeutic window in this model. Sixty-four animals who survived to 96 hours were treated with both levofloxacin and either AIGIV at 15 U/kg (n=31) or IGIV (n=33). All animals were bacteremic and PA positive at the time of treatment; body temperature was not monitored for this study. Animals infused with AIGIV exhibited a 58% (18/31) survival rate compared to a survival rate of 39% (13/33) in animals who were treated with IGIV. This increase in survival following treatment with AIGIV in addition to levofloxacin was not statistically significant compared to IGIV given in addition to levofloxacin.

Nonhuman Primate Studies

Two studies were performed in NHPs (cynomolgus macaques; *Macaca fascicularis*, Vietnamese origin) to demonstrate the efficacy of AIGIV. Both studies were performed at (b) (4) and used *B. anthracis* Ames as the challenge agent with a target dose of 200 LD_{50} spores. One LD_{50} corresponds to approximately $6.3x10^4$ spores in the cynomolgus macaque.

Study (b) (4) 987-G005780 was a randomized, non-GLP study to evaluate AIGIV efficacy in NHPs when administered in combination with antibiotic therapy after an anthrax aerosol challenge. One group (Group 1) of 12 NHPs (6 males, 6 females) and three groups (Groups 2-4) of 20 NHPs (10 male, 10 female) were exposed to an anthrax challenge dose averaging 366 ± 115 LD_{50} and a mass median aerodynamic diameter of ~ 1.3 µm. Group 1 animals (n=12) were untreated, and Group 2-4 animals (n=20 each group) received oral ciprofloxacin twice daily for 5 days starting at 64 hours post-challenge. Ciprofloxacin treatment involved a loading dose of 32 mg/kg followed by maintenance doses of 16 mg/kg. In addition, Group 2-4 animals received IGIV placebo (Group 2), 15 U/kg AIGIV (Group 3), or 30 U/kg AIGIV (Group 4) in conjunction with the ciprofloxacin loading dose. As was the case with study (b) (4) 828-G005780, survival at 28 days was evaluated in NHPs with confirmed anthrax infection. Not all animals survived to the 64 hour timepoint to receive antibiotic treatment; the cause of death for 4 animals could not be positively attributed to anthrax. Overall 93% of the NHPs were positive for PA, including all of Group 1 and all of Group 3. Including only animals bacteremic prior to treatment, survival in the control group (Group 1) was 8% (1/12). The lone survivor in this group had a single positive result for bacteremia at day 4 and did develop toxemia 30 hours post-challenge, which resolved by day 10 suggesting some level of pre-existing immunity.Survival in the IGIV + ciprofloxacin arm (Group 2) was 75% (9/12).

The 15 U/kg AIGIV + ciprofloxacin group (Group 3) and 30 U/kg AIGIV + ciprofloxacin group (Group 4) exhibited 83% (10/12) and 79% (11/14) survival, respectively. Survival in all antibiotic treatment groups (Groups 2-4) was statistically significant compared to the untreated arm (Group 1), but there was no significant difference between Groups 2-4. Toxemia (as measured by PA levels) was decreased in Groups 3 and 4 compared to Groups 1 and 2.

Study(b) (4) 828-G005780 was a randomized, placebo-controlled GLP study consisting of 4 groups of 16 NHPs (8 males, 8 females) each exposed to *B. anthracis* Ames spores. The average aerosol exposure was 154 ± 40 LD_{50} and the mass median aerodynamic diameter was ~ 1 µm, consistent with the size distribution for deposition of spores into the lower respiratory tract. Upon evidence of toxemia as defined by PA concentrations ≥1.5 ng/mL in serum, the animals were treated with placebo (IGIV) or AIGIV at 7.5 U/kg, 15 U/kg, or 30 U/kg. The primary endpoint was survival at 28 days post-challenge. Three animals were excluded from analysis; one NHP in the control group excised its telemetry implant and was euthanized for humane reasons, while two animals in the 30 U/kg group were dosed prior to reaching the treatment trigger of ≥1.5 ng/mL PA. Including only animals that were both PA (+) and bacteremic prior to treatment, 0% (0/11) survived in the IGIV group. Survival in the 7.5 U/kg, 15 U/kg, and 30 U/kg groups was 36% (4/11), 43% (6/14), and 70% (7/10), respectively. Compared to the IGIV placebo and adjusted for multiple comparisons, the increase in survival was statistically significant for all three doses. The trend toward increasing efficacy with dose was not statistically significant. Toxemia recurrence was observed in the 7.5 U/kg and 15 U/kg groups (8/15 and 2/15, respectively), and the animals in which this occurred invariably died.

Summary of Animal Efficacy Studies

In summary, the efficacy studies performed in the rabbit and NHP models of inhalational anthrax provide consistent evidence that 1) AIGIV is effective as monotherapy, 2) addition of antibiotics does not interfere with the therapeutic effect of AIGIV, and 3) addition of AIGIV therapy to the standard antibiotic therapy may provide added benefit, although this result did not reach statistical significance in either model species. Increasing doses of AIGIV led to decreases in circulating PA levels, however the trend toward increasing efficacy with increasing AIGIV dose was not statistically significant. These results, when combined with modeling to extrapolate the animal AIGIV doses to human AIGIV dosing indicate that it is reasonably likely that the biological product is reasonably likely to provide clinical benefit in humans with inhalational anthrax.

b) Clinical Program

AIGIV was developed under the Animal Rule because its effectiveness could not be ethically tested in placebo-controlled trials in humans and because, in the absence of bioterrorism

events, sporadic cases of inhalational anthrax occur quite infrequently. The clinical development program included a single healthy volunteer safety, tolerability, and pharmacokinetic clinical trial (AX-001) performed at a single site in the U.S. by a single investigator. As required under the Animal Rule, a postmarketing requirement (PMR) study (AX-003a) for the use of the product is to be conducted post-licensure in the event of a mass exposure scenario to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated, when such studies are feasible and ethical. As part of the PMR, Cangene has agreed to conduct a study according to protocol AX-003b, for collection and analysis of data on future sporadic cases of systemic anthrax that are treated with AIGIV.

Healthy Volunteer Clinical Trial

Clinical trial AX-001 for safety enrolled 92 healthy adult human subjects in a two-part study. In part one, 72 subjects were each randomized into one of three dosage strata (cohorts A, B, and C) containing 24 subjects each:6 subjects per dose cohort received saline placebo and 18 subjects received a single fixed doses of 210 U, 420 U, or 840 U of anthrax toxin neutralizing activity (TNA) at infusion rates up to 2 mL/min. In part two of the trial, 20 subjects were randomized in two cohorts of 10 each and administered single doses of 840 U of either of two lots of AIGIV different from the lot studied in part one. No placebo was used in part two of the trial. Blinding in stage one was limited to the subject and caregivers not knowing whether they received active AIGIV or placebo, but study staff presumably knew to which dosage cohort subjects belonged because dosing cohorts were enrolled sequentially at a single center and the number of vials and volume of AIGIV or placebo infused differed between dosage cohorts. Subjects were monitored over 28 days with routine hematology, chemistry, and urinalysis laboratory tests; prothrombin time, activated partial thromboplastin time, fibrinogen, serology for HBV, HIV 1 & 2, and HCV; nucleic acid testing for Parvovirus B19; adverse event monitoring; ECGs; and were sampled for PK measurements.

In part one, blood glucose was tested at one day prior to AIGIV dosing and one hour after the start of test product infusion by both glucose-specific point-of-care (GS-POC) and glucose-non-specific point-of-care (GNS-POC) monitoring devices and by a laboratory glucose assay. This multiple testing procedure for glucose was performed due to the presence of maltose stabilizer in the AIGIV product, which is known to be misread as glucose by some GS-POC test meters depending on the enzyme used in the test reagent .

The demographics of subjects enrolled in clinical trial AX-001 are depicted in the table below, reproduced from the submission.

Healthy Volunteer Demographics Summary (Cangene Table 11-1).

Characteristic	A Active (N= 18)	B Active (N= 18)	C Active (N= 18)	Active D (N= 10)	E Active (N= 10)	All Placebo (N= 18)
Gender						
Female	8	9	9	5	6	7
Male	10	9	9	5	4	11
Age (Years)						
Mean	30	29	32	29	34	32
Median	27	26	28	23	25	29
SD	10	10	13	12	15	11
Minimum	20	19	19	19	20	20
Maximum	55	52	55	55	55	52
Race						
American Indian or Alaska Native	0	0	2	0	0	1
Asian	3	1	0	1	0	2
Black or African American	3	4	3	0	1	2
White	12	13	13	9	9	13
Ethnicity						
Hispanic or Latino	1	1	1	0	0	0
Not Hispanic or Latino	17	17	17	10	10	18
Weight (kg)						
Mean	73.2	71.5	74.6	71.0	68.1	75.0
Median	73.1	67.6	73.7	71.0	70.9	74.6
SD	7.6	12.1	12.1	11.6	10.6	11.0
Minimum	58.5	49.9	52.6	54.4	50.3	55.8
Maximum	92.1	96.6	91.2	92.5	79.4	94.8
Height (cm)						
Mean	171.4	170.6	173.3	170.6	166.0	173.6
Median	170.0	170.0	173.0	168.5	161.5	173.0
SD	8.7	11.6	8.5	10.6	12.9	9.2
Minimum	157	142	160	157	151	157
Maximum	191	193	188	186	187	188

Source: Table 14.1.3
Treatment A Active = 210 U Anthrax Immune Globulin (Human) Lot Number 24906011
Treatment B Active = 420 U Anthrax Immune Globulin (Human) Lot Number 24906011
Treatment C Active = 840 U Anthrax Immune Globulin (Human) Lot Number 24906011
Treatment D Active = 840 U Anthrax Immune Globulin (Human) Lot Number 10804812
Treatment E Active = 840 U Anthrax Immune Globulin (Human) Lot Number 10804816

The randomization resulted in reasonably good balance between each of the active arms and the placebo arm in age and body weight among the 92 subjects enrolled. There were more Asians in the 210 U low dose group A. Blacks were fairly evenly distributed among the dose-comparison groups A, B, and C and the pooled placebo group. Five subjects discontinued the trial prematurely, all from active treatment arms, including two subjects who were discontinued for noncompliance for not attending follow-up visits starting at days 28 and 42, respectively; two subjects whose IV lines infiltrated during the infusion; and one subject who was discontinued due to an infusional adverse event described in Section 7 below.

Post-AIGIV blood samples tested by GNS-POC monitoring devices demonstrated transient false elevations of glucose, in contrast to GS-POC device determinations. Urinalyses also demonstrated transient [presumably false] positive glycosuria following AIGIV administration. The package insert contains a boxed warning regarding the potential masking of hypoglycemia or the overestimation of glycemic levels due to false elevations of blood

glucose associated with use of glucose non-specific glucose meters. The package insert advises prescribers to use only glucose-specific methods for testing blood glucose when treating a patient with AIGIV.

Expanded Access Use of AIGIV in Patients with Systemic Anthrax

Nineteen adult patients (five females and 14 males) ranging in age from 24 to 61 years (median 38 years) with clinical systemic anthrax disease (three inhalational, one GI, and 15 injectional cases) received AIGIV (plus antibiotics and supportive care) under various regulatory mechanisms, collectively referred to as "expanded access" (see Section 6, Clinical Program, below). All three inhalational anthrax cases were in males aged 34 to 61 years. The GI anthrax case was in a female. The injectional anthrax cases were in four females and 11 males. Overall, there were 6/19 (32%) fatalities among these patients, including one death among the three patients treated for inhalational anthrax.In the three inhalational anthrax patients, the single AIGIV dose of 420 units (by TNA) resulted in increased anti-PA levels (correlating with increased TNA activity). These levels remained comparatively stable up to 7 to 20 days post-administration, probably reflecting the rising antibody production by the patient at the same time that the exogenously-administered antibody was being cleared. (Note that the anti-PA antibody assay used does not distinguish between endogenous antibody produced by the patient and exogenously administered antibody from AIGIV administration.). In the inhalational anthrax patient who died, pleural and serum LF levels gradually declined but were still detectable at four and five days, respectively, following AIGIV administration, while serum and pleural anti-PA IgG rose following treatment and remained at a plateau, with serum levels in the range of 30 – 40 μg/mL.

In some injectional anthrax cases, complicated by substantial hemorrhage and pleural and/or peritoneal fluid losses from thoracentesis and/or paracentesis, serum anti-PA antibody levels fell as much as approximately 90% from their post-AIGIV peak levels by 24 hours following AIGIV administration. The observation of rapidly declining serum anti-PA antibody levels in such patients is also likely to occur in some inhalational anthrax patients due to the possibility of similar clinical presentations. In addition, inspection of the LF blood concentration – time curves in patients with systemic anthrax, including inhalational anthrax, who were administered a single 420 U TNA dose of AIGIV revealed that circulating LF levels do not plummet to zero shortly following administration of the product, but rather persist at detectable levels for several days. This may represent ongoing release of LF/LT into the circulation from anthrax bacteria not yet eliminated by antimicrobial therapy. In some patients, particularly those whose own humoral antibody immune response to anthrax infection is slow in onset/inadequate, one (or more) additional AIGIV doses may be required to block the toxic effects due to the ongoing release of LF into the circulation. Consequently, some patients may benefit from repeated dosing of AIGIV.

Overall, this uncontrolled clinical experience is too limited to confirm efficacy of the product in improving survival.

Rationale for the Initial Dose of AIGIV

The severity and rapid progression frequently observed in inhalational anthrax cases, coupled with dose modeling and the results of monotherapy animal efficacy model studies in rabbits and NHP support an initial dose of 420 units, although an initial dose of 840 units may be considered for severe cases. Repeated dosing may also be considered, depending on the severity of symptoms and the response to treatment, especially in patients experiencing substantial hemorrhage as reflected in large transfusion requirements, patients with significant compartmental fluid losses such as from large volume and/or repeated therapeutic thoracentesis and/or abdominal paracentesis, and in patients whose own immune response may be impaired or delayed.

c) Pediatrics

Cangene's AIGIV was granted orphan product status; thus, the provisions of the Pediatric Research and Equity Act do not apply. No safety or efficacy data for AIGIV were submitted by the applicant or available from the literature for pediatric subjects. This limitation is included in the package insert.

The review committee considered it reasonable to extrapolate efficacy from the preclinical animal efficacy studies to pediatric patients. Allometric scaling[11], rather than PK measurements in pediatric subjects, was used to derive a body weight-based dosing regimen for pediatric patients.

To gain a better understanding of the potential safety of the product among pediatric patients, Cangene provided pediatric safety data for other U.S. licensed Immune Globulin Intravenous (Human) hyperimmune products manufactured by Cangene using similar manufacturing processes. Review of the amendment revealed that the doses (in terms of total protein) of Cangene's other hyperimmune immunoglobulin products were considerably lower than the doses recommended for AIGIV, making extrapolation of the pediatric safety profile of Cangene's other hyperimmune products to AIGIV less reliable. However, review of the pediatric safety profile of various (non-hyperimmune) U.S.-licensed Immune Globulin Intravenous (Human) products, whose recommended total protein doses overlap and often exceed those of AIGIV, allowed the conclusion that the pediatric safety data for such products may reasonably be extrapolated to the expected pediatric safety of AIGIV.

d) Other Special Populations

No safety or efficacy data for AIGIV were submitted by the applicant or available from the literature for special populations. This limitation is included in the package insert.

Extrapolation of the safety profile of non-hyperimmune IGIV in geriatric subjects supported safety of AIGIV in this population.

e) Overall Comparability Assessment

Review of lot-specific clinical safety data for the three product lots used in the healthy adult human volunteer trial AX-001 did not reveal significant lot-specific differences in safety.

f) Bioresearch Monitoring Inspections

During review of the BLA the one study site for the clinical pharmacokinetics study AX-001was inspected under the Agency's Bioresearch Monitoring program. The inspection found no problems and was classified No Action Indicated. In addition, FDA inspected four animal studies conducted at a nonclinical laboratory under The Animal Rule. The studies included (b) (4) 695-G005780, (b) (4) 694-G005681, (b) (4) 828-G005780, and (b) (4) 1207-100005104. The nonclinical inspection revealed issues that do not impact the data submitted in the BLA, and was classified Voluntary Action Indicated.

7. Safety

Safety Assessment of AIGIV from the Healthy Volunteer Safety and PK Trial, AX-001.

No deaths or serious adverse events (SAEs) were reported. Infusion of AIGIV was stopped in four subjects due to adverse reactions. One subject was withdrawn due to an adverse reaction (AR) consisting of chest discomfort, flushing, tachycardia, throat tightness, and headache which began 3 minutes into the infusion and two subjects had only partial infusions due to paravenous infiltration. Another subject had their AIGIV infusion halted after 23 minutes due to urticaria, pruritis, lip swelling and dry/sore throat, which may have represented angioedema, but was not withdrawn from trial participation/follow-up.

There were no serious adverse reactions reported in any of the AIGIV or saline placebo control groups in AX-001. Non-serious adverse events and adverse reactions were more frequent in the active AIGIV dosage groups than in the subjects administered placebo. The most common adverse reactions to AIGIV observed in >5% of subjects in the healthy volunteer clinical trial were headache, infusion site pain, nausea, infusion site swelling, and back pain. Headache and back pain rates occurred in a dose-dependent fashion. Sixty-five of 74 (71%) subjects reported 251 adverse events (AEs), of which 4 were severe (headaches) and 36 were moderate in intensity. Thirty-one subjects (34%) reported 50 headaches during the trial. Of the treatment related AEs, 12 were reported in subjects receiving placebo.

Post-AIGIV blood samples tested by GNS-POC monitoring devices demonstrated transient false elevations of glucose, in contrast to GS-POC device determinations, which did not. Urinalyses also demonstrated transient [presumably false] positive glycosuria following AIGIV administration. The package insert contains a boxed warning regarding the potential

masking of hypoglycemia or falsely elevated glycemic levels when testing with non-specific test glucose meters and advises prescribers to use only glucose-specific methods for testing blood glucose.

The observed safety profile of AIGIV in single doses up to 840 units in this healthy adult volunteer controlled trial (AX-001) was acceptable. FDA expects that adverse reactions that have been causally associated with U.S.-licensed Immune Globulin Intravenous (Human) (IGIV) products may also occur with AIGIV, given the polyclonal nature of the product and the overlap between the recommended doses of AIGIV and those of IGIV. These would include: hypersensitivity reactions, including anaphylaxis, thrombotic events, acute renal dysfunction/failure; hemolysis and hemolytic anemia; aseptic meningitis syndrome; transfusion related acute lung injury; and transmission of infectious agents from human plasma, which are all listed in the WARNINGS AND PRECAUTIONS section of all U.S.-licensed IGIV products and in the AIGIV package insert. AIGIV does not contain sucrose. The majority of reports of renal dysfunction/failure /acute renal injury following IGIV administration have been associated with sucrose-containing products.

Safety Considerations of AIGIV Use in Patients with Inhalational, Injectional, and Gastrointestinal Anthrax

The safety of the product in patients with inhalational anthrax (and other forms of systemic anthrax) may be different from that observed in the healthy volunteer trial AX-001. For example, some anthrax patients have disseminated intravascular coagulation and/or renal dysfunction, which may potentially increase the risk of immunoglobulin-associated thrombosis and/or further renal compromise.

Limited safety data were obtained from patients with systemic anthrax disease who were given a single 420 unit dose of AIGIV. As of the cutoff date for data inclusion in the BLA, 19 adult patients ranging in age from 24 to 61 years with clinical systemic anthrax disease (three inhalational, one GI, and 15 injectional cases) had received AIGIV (plus antibiotics and supportive care) under various regulatory mechanisms (FDA-authorized single-patient Expanded Access Investigational New Drug Applications (IND) for emergency use, CDC's contingency protocol-sponsored BB-IND 13026, or use of AIGIV purchased directly from the manufacturer, collectively referred to as "expanded access"). The total case fatality rate among patients with systemic anthrax treated with Cangene AIGIV was 6/19 or 32 percent, however the hospital discharge status of one of the subjects was unknown.

Among the three patients with inhalational anthrax treated with antibiotics, AIGIV, and supportive care, one died. Among the 15 patients with injectional anthrax treated with antibiotics, AIGIV, and supportive care, five died. Two injectional anthrax patients died from progression of anthrax and the cause of death in the remaining three patients was unknown. The single patient with GI anthrax treated with antibiotics, AIGIV, and supportive care

survived. Overall, this uncontrolled clinical experience is too limited to permit generalization of the observed mortality rate to a larger population and too limited to confirm efficacy of the product in improving survival.

A total of 34 serious adverse events (SAEs) were reported for 11 patients with systemic anthrax. Causality assessment for these SAEs was complicated by the severe pre-existing illness of the patients at the time of treatment with AIGIV, and many if not most of them could have been due to the underlying illness, especially since these SAEs are rarely seen with Ig preparations. The package insert lists as serious adverse reactions those SAEs whose onset was within 72 hours of administration, and which the medical reviewer regarded as at least possibly causally related to AIGIV administration. Among the temporally associated SAEs, two cases of septic shock were not included as serious adverse reactions as they were due to systemic anthrax. These temporally related adverse reactions following AIGIV administration to patients with systemic anthrax are listed in the table below. There were no thrombotic events associated with administration of AIGIV in these patients.

AIGIV administration temporally related adverse reactions in eleven anthrax patients

Organ System	Serious Adverse Reaction[1]	Number (%) of Patients
Respiratory	Adult Respiratory Distress Syndrome	2 (10.5)
	Pulmonary Edema	1 (5.3)
	Pleural Effusion	1 (5.3)
Renal	Acute Renal Insufficiency/Failure	4 (21)
Hematologic	Coagulopathy	1 (5.3)
Cardiovascular/General	Cardiac Arrest/Death NOS[2]	2 (10.5)
Cardiovascular	Hypotension	1 (5.3)
Gastrointestinal	Ascites	1 (5.3)
Metabolic	Metabolic Acidosis	1 (5.3)
	Hyperkalemia	1 (5.3)
General	Edema/Peripheral Edema	1 (5.3)

[1]Two cases of septic shock also occurred within 72 hours of ANTHRASIL infusion but were attributed to progression of anthrax.

[2]Not Otherwise Specified.

Most of the possibly causally related adverse reactions documented in patients who received AIGIV were reported to have occurred in no more than a single patient, with the exceptions of Acute Respiratory Distress Syndrome, acute renal insufficiency, and cardiac arrest/death not otherwise specified. One patient with inhalational anthrax developed multi-organ failure, coagulopathy including DIC, seizures and progressed to cardiac arrest six days after receiving AIGIV. A second patient who developed systemic anthrax after injecting contaminated heroin exhibited hemodynamic instability and died two days after receiving AIGIV. The possible role of circulating immune complexes involving AIGIV antibodies and anthrax antigens in any

of these adverse reactions is uncertain, but it is conceivable they could be involved in some reports of renal dysfunction.

Hypotension has been reported to occur following IGIV and, if severe and prolonged, could lead to metabolic acidosis from under-perfusion of tissues and, thereby, to hyperkalemia. Administration of immune globulin products can contribute to volume overload, which could conceivably result in, or contribute to the magnitude of pleural effusion and/or ascites and peripheral edema.

No safety or efficacy data for AIGIV were submitted or available from the literature for special populations. This limitation is included in the package insert. See Section 6b, *Pediatrics*, for a discussion of extrapolation of pediatric safety data from other U.S.-licensed Immune Globulin Intravenous (Human) products to AIGIV. The review team concluded that the pediatric safety data for such products may reasonably be extrapolated to the expected pediatric safety of AIGIV. A similar line of reasoning may also be applied to geriatric patients.

Given the high mortality associated with systemic anthrax, the observed safety profile of AIGIV in normal subjects and adults with systemic anthrax, and the expected safety profile in special populations is considered acceptable.

8. Advisory Committee Meeting

Justification for Waiver

The review team determined that the animal efficacy models used to approve a monoclonal antibody (raxibacumab) for the treatment of inhalational anthrax were similar to those used to evaluate AIGIV. Since these models were presented to the CDER Anti-Infective Drugs Advisory Committee on two occasions (27 October 2009 and 02 November 2012) and found acceptable at both, the review team concluded that a CBER Blood Products Advisory Committee meeting was not necessary.

9. Other Relevant Regulatory Issues

None.

10. Labeling

The proprietary name “ANTHRASIL” was reviewed by the Advertising and Promotional Labeling Branch and found to be acceptable. The draft package insert underwent a number of revisions at agency request.

The labeling review recommended modifications to the language in the INDICATIONS AND USAGE section in the following respects:

- To make it clearer that the product is to be used in conjunction with appropriate antibacterial therapy
- To include the following limitations:
    - ANTHRASIL does not have direct antibacterial activity.
    - ANTHRASIL does not cross the blood-brain barrier and does not prevent or treat meningitis.
    - There have been no studies of ANTHRASIL in pediatric, geriatric or other special populations

The labeling review also recommended modification of the DOSAGE AND ADMINISTRATION section of the package insert to include the following changes:

- The recommended initial dose for adults is 420 units. An initial dose of 840 units may be considered, depending on clinical severity and according to the judgment of the treating physician. Dosage for pediatric patients is based on weight, and like the adult dose, may be doubled for patients >5 kg.
- Addition of a statement to consider repeat dosing depending on the severity of symptoms and the response to treatment, especially in patients experiencing substantial hemorrhage as reflected in large transfusion requirements, patients with significant compartmental fluid losses such as from large volume and/or repeated therapeutic thoracentesis and/or abdominal paracentesis, and in patients whose own immune response may be impaired/delayed.
- Addition of a statement to clarify repeat dosing by recommending that the magnitude of blood and fluid losses and clinical status of the patient be taken into account to determine the time interval between repeat dosing.

The indication for use was modified to 'treatment of inhalational anthrax in combination with appropriate antibacterial drugs' and the added benefit limitation in the highlights section was removed consistent with FDA's precedent for the approved labeling of raxibacumab.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review team recommends approval; there were no dissenting reviews.

b) Risk/Benefit Assessment

Inhalational anthrax is a serious condition associated with high mortality. The mortality rate with inhalational anthrax treated with antibiotics and intensive supportive care was 45%

during the 2001 U.S. anthrax attack. Surviving patients often experience multiple organ system failure before recovery. Since there is currently only a single approved product to treat anthrax toxemia (raxibacumab) there remains an unmet medical need for additional adjunctive therapies to be combined with appropriate antimicrobial therapy and supportive care in inhalational anthrax.

Benefit Assessment

The activity of AIGIV without concomitant antibiotic therapy in inhalational anthrax has been demonstrated in animal efficacy models in both rabbits and non-human primates. Treatment with AIGIV alone increased survival compared to placebo in anthrax-exposed rabbits and non-human primates. As was observed in the pivotal animal efficacy model study in inhalational anthrax that supported the FDA approval of a monoclonal antibody therapeutic, raxibacumab, survival was higher among rabbits who received both the specific immunoglobulin product (AIGIV) and appropriate antibiotic therapy compared to survival in rabbits receiving antibiotic therapy plus non-specific IGIV, but the survival difference did not reach statistical significance. Thus, the addition of AIGIV to appropriate antimicrobial therapy has the potential to lower the mortality from this serious, life-threatening disease.

Risk Assessment

The safety profile of single doses of AIGIV up to 840 U TNA as observed in the healthy adult volunteer RCT, AX-001 and, as inferred for pediatric patients from review of safety data for other immunoglobulin products (particularly IGIV), is acceptable, given the potential benefits. No serious adverse events were observed in the healthy adult volunteer clinical trial, AX-001, and the most frequent non-serious adverse reactions were headaches and back pain. The safety of a single dose of 840 U TNA is expected to be comparable to the safety of two separate doses of 420 U TNA. Only three patients with inhalational anthrax have received AIGIV, administered as a single 420 unit dose. Limited safety data among these and 16 other patients with injectional or GI forms of systemic anthrax infection who received single doses of 420 units of AIGIV did not reveal any clear pattern of product-associated toxicity, but the analysis of safety of the product in these patients was complicated by their severe illnesses at the time of AIGIV administration, by the lack of a concurrent control group, and by the limitations of data collection in these settings of use. The safety profile of the product may be different in patients with severe inhalational/systemic anthrax compared to that seen in phase 1 clinical trial AX-001. For example, the risk of thrombosis may be different in patients with DIC or coagulopathy due to anthrax, and the risk of renal insufficiency may be greater in patients with systemic anthrax who may be in shock and/or have pre-existing renal dysfunction and be receiving aminoglycosides and other nephrotoxic drugs.

(b) (4)

(b) (4)

The above risks, together with the other known risks of IGIV products including hemolysis, hypersensitivity reactions, and the very low risks of viral transmission and transfusion-associated lung injury, are addressed in the package insert. The presence of maltose in the product can also mask hypoglycemia. Falsely elevated glucose readings in blood and urine are a transient phenomenon following infusion of the product when glucose non-specific test systems are used, such as is the case with some commonly used point-of-care glucose meters. The product carries a boxed warning for the risk of thrombosis and the risk of hypoglycemia from inappropriate administration of insulin in response to falsely elevated glucose readings if glucose non-specific test strips/devices are used to monitor blood sugar. This problem is obviated by using only glucose-specific test methods, which is what is used on most clinical laboratories and some point-of care devices and their associated test strips.

Benefit:Risk Balance

The safety of AIGIV was demonstrated in healthy volunteers and the use of AIGIV in the treatment of sporadic cases of inhalational and injectional anthrax cases provided additional, although limited information on the pharmacodynamics of AIGIV and clearance of anthrax toxins in humans. Efficacy could not be definitively established from these data due to the lack of human control subjects, incomplete documentation of the cases, and the limited number of subjects involved. However, the animal efficacy data provided evidence that the biological product is reasonably likely to provide clinical benefit.

The review team concluded that the potential benefit of the product in the target population, as inferred from the submitted animal efficacy model studies, exceeds the known and expected risks of the product when used in conjunction with appropriate antimicrobial therapy to treat symptomatic inhalational anthrax disease. If a field trial becomes feasible, Cangene is required by Subpart H regulation as a postmarketing requirement to verify the safety and efficacy of the product in humans with inhalational anthrax, and has agreed to design the field trial to verify the appropriateness of the recommended dosing regimen including in pediatric cases. Cangene has also agreed, as part of the postmarketing requirement, to collect and analyze additional data on the use of AIGIV in sporadic cases of systemic anthrax. These data on the use of AIGIV in sporadic cases study are expected to provide information relevant to and supportive of improving the understanding of the actions, safety, and efficacy of AIGIV in inhalational anthrax

c) Recommendation for Postmarketing Risk Management Activities

A Risk Evaluation and Mitigation Strategy was not instituted for this product. The applicant's pharmacovigilance plan was found to be acceptable. Modifications to the package insert to highlight thrombotic risk (b) (4) .

d) Recommendation for Postmarketing Activities

As required under the Animal Rule, Cangene has agreed to conduct a postmarketing requirement study (AX-003a) to be conducted post-licensure in the event of a mass exposure event. This study is intended to verify and describe the AIGIV's clinical benefit and to assess its safety when used as indicated, when such studies are feasible and ethical. As part of the PMR, Cangene has agreed to conduct clinical study AX-003b, which will evaluate the use of AIGIV for the treatment of future sporadic cases of systemic anthrax occuring over the next 9 years.

The applicant has agreed to a postmarketing commitment (PMC) study to obtain pediatric PK data (using sparse sampling) during the postmarketing requirement (PMR) field trial, and when treating future sporadic inhalational anthrax cases in pediatric patients.

Additional CMC PMCs are being requested to (b) (4) A separate PMC is also being requested for Cangene to seek exemption to labeling requirements for AIGIV lots in the SNS.

Subpart H Approval Requirements

Approvals under 21 CFR Part 601, Subpart H (Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible) are subject to three requirements:

1. *Approval with restrictions to ensure safe use.*

   This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that AIGIV can be safely used without restrictions on distribution or use.

2. *Information to be provided to patient recipients.*

This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We have concluded that the FDA-Approved Patient Labeling for AIGIV meets the requirements of this subsection. Cangene was reminded that the Patient Labeling must be available with the product, to be provided, when possible, prior to administration or dispensing of the drug product for the use approved under this subpart.

3. *Postmarketing Studies.*

This subsection requires the applicant to conduct postmarketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical.

With reference to amendments submitted December 15, 2014, February 9, 2015, March 04, 2015, March 17, 2015 and the minutes for the teleconference with Cangene held on March 19, 2005 stating agreement to conduct a field study to evaluate the efficacy, pharmacokinetics, and safety of AIGIV use for the treatment of toxemia due to inhalation anthrax:

1. Cangene agreed to conduct a field study (protocol AX-003A) to evaluate the efficacy, pharmacokinetics, and safety of Anthrax Immune Globulin (Human) for the treatment of toxemia associated with inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs. The primary endpoint of this study will be all-cause mortality.

   Final Protocol Submission: October 31, 2015

   Completion of Enrollment: To be determined in consultation with FDA should a broad anthrax exposure event occur.

   Completion of Data Collection: 9 months after last Anthrax Immune Globulin (Human) administration following a broad anthrax exposure event.

   Study Completion: 12 months after last Anthrax Immune Globulin (Human) administration following a broad anthrax exposure event.

   Final Report Submission: 15 months after last Anthrax Immune Globulin (Human) administration following a broad anthrax exposure event.

2. Cangene agreed to submit annual progress reports as well as interim clinical summary reports including available cumulative clinical and pharmacokinetic data every three years from use of Anthrax Immune Globulin (Human) in sporadic systemic anthrax cases (protocol AX-003B).

   Final Protocol Submission: October 31, 2015

Completion of Enrollment: To be determined in consultation with FDA.

Completion of Data Collection: To be determined.

Study Completion: To be determined.

Final Report Submission: 9 years after final protocol approval.

AGREED UPON POSTMARKETING COMMITMENTS

Per Cangene's written commitments as described in their March 17, 2015 submission and as documented in the minutes for the teleconference held March 19, 2015:

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

3. Cangene committed to (b) (4) Manufacturing will commence pending the availability of funding for the production run(s), and this change will be submitted, with validation data, as a CBE-30 within 5 months of completion of the run(s) or by March 25, 2025, whichever is earlier.

4. Cangene committed to (b) (4) Cangene will submit the final validation report as a Postmarketing Study Commitment – Final Study Report by March 16, 2016.

5. Cangene committed to developing (b) (4) submitted as a CBE-30 by March 16, 2016, and will be applicable to any new lots of Anthrax Immune Globulin (Human) manufactured after you are notified that this PMC is fulfilled.

6. Cangene committed to (b) (4) Postmarketing Study Commitment – Interim Study Report by

September 16, 2015. If the initial assessment is supportive, a complete assessment that includes supportive stability data will be submitted as a Postmarketing Study Commitment – Final Study Report by March 16, 2016.

7. Cangene committed to (b) (4) will be submitted as a CBE-30 to FDA by May 16, 2015.

8. Cangene committed (b) (4) will be submitted as a CBE by March 25, 2016.

9. Cangene committed to submitting a request for exemptions or alternatives to labeling requirements for biological products held by the Strategic National Stockpile per 21 CFR 610.68. This request will include specific lot numbers, the labeling provisions that are the subject of the exemption or alternative request, an explanation why compliance with the labeling regulations could impact the safety, effectiveness, or availability of AIGIV, a description of proposed safeguards to ensure the labeling of the product conveys adequate information for the safe and effective use of the product, and a draft of the proposed labeling. Cangene will submit this information as a CBE30 by April 25, 2015.

12. References

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