



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

MEMORANDUM

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Subject: Pharmacovigilance Plan Review

Applicant: Cangene (doing business as Emergent Biosolutions)

Product: Anthrax Immune Globulin Intravenous (Human) [AIGIV]

Proposed Indication: Treatment of adult and pediatric patients with toxemia
associated with inhalational anthrax

Submission type/number: BLA 125562/0

Submission Receipt Date: July 25, 2014

Action Due Date: March 25, 2015

1. Materials reviewed include:

- BLA cover letter
- Pharmacovigilance Plan
- Proposed package insert
- Medical Literature
- Summary of clinical safety
- Verbal and written input from other discipline reviewers on the BLA team

2. Introduction

2.1 Product description

AIGIV is a sterile gamma globulin (IgG) fraction of human plasma containing antibodies to *Bacillus anthracis*. The product is indicated for the treatment of adult and pediatric patients with toxemia associated with inhalational anthrax. AIGIV is beneficial in combination with appropriate antibacterial drugs. It is prepared from Source Plasma obtained from selected healthy donors who have been immunized with BioThrax® (Anthrax Vaccine Adsorbed [AVA]). AIGIV is a clear or slightly opalescent colorless liquid essentially free of foreign particles that is formulated in 10% maltose and 0.03% polysorbate 80. AIGIV is intended for single use by intravenous (IV) administration. The proposed package insert includes tables for pediatric patient (<17 years old) dose and infusion rate based on body weight. The adult dose is 420 Units (administered as 7 vials) by Toxin Neutralization Assay (TNA) infused gradually up to a maximum rate of 2 mL per minute.

2.2 Regulatory background

Since clinical trials in a population exposed to anthrax were not feasible due to the small number of naturally occurring anthrax cases, and the fact that it is unethical to deliberately expose healthy individuals to a serious life-threatening pathogen, this BLA is being reviewed under the “Animal Rule” (AR) per 21 CFR Part 601 (subpart H). Per AR regulations, in the event of a broad exposure event, the sponsor would be required to conduct a post-marketing study (PMR) to evaluate the clinical benefit/effectiveness of AIGIV in the treatment of patients with inhalational anthrax exposure. For additional details regarding this effectiveness PMR, which would also capture adverse events associated with AIGIV, please see the clinical review memo. CBER granted this submission 1) fast track, 2) priority review, and 3) orphan drug designations in advance of the BLA submission.

2.3 Public health context

Anthrax is a life-threatening disease caused by *Bacillus anthracis* (*B. anthracis*), a Gram positive, rod shaped bacterium that can form highly resistant spores. Different forms of anthrax include cutaneous, gastrointestinal, inhalational and injectional, which involve different routes of exposure. Infection can be initiated by the introduction of spores via the skin (cutaneous), the gastrointestinal tract (gastrointestinal), the respiratory mucosa (inhalational), or intravenously (injectional). Of these four forms, inhalational anthrax is the most serious form of the disease.

Currently, symptomatic anthrax patients are treated with antimicrobial agents with known activity against *B. anthracis* including doxycycline, ciprofloxacin and penicillin. Although these therapies can address bacteremia caused by the organism, they do not directly inhibit toxemia, the main cause of anthrax pathogenesis. Additionally, antibiotic therapy for inhalational anthrax is generally most effective when given within days of exposure and often prior to becoming symptomatic. During the 2001 outbreak in the US, a considerable proportion of patients treated with antibiotics after the onset of symptoms still succumbed to disease during the course of treatment.¹ Thus, delayed antibiotic treatment may not be entirely effective in addressing anthrax toxemia, creating a potential unmet public health need for a therapeutic intervention to target toxemia. A further potential source of added public health value for AIGIV, which is being stored in the strategic national stockpile, could be a potential mass exposure (e.g., bioterrorist) event in which resources (e.g., antibiotics and AVA) are constrained and are not available for timely administration or if tracking down anthrax-exposed individuals takes a considerable amount of time resulting in toxemia for which AVA and/or antibiotics alone may be suboptimal. The sponsor asserts that AIGIV, which is derived from individuals vaccinated with AVA, contains antibodies to protective antigen (PA) which have anthrax toxin neutralizing capabilities that are correlated with protection against anthrax based on animal data.

2.4 Clinical safety

2.4.1 AX-001(safety study in healthy volunteers without anthrax exposure)

Clinical experience with AIGIV is very limited. The safety of AIGIV was evaluated in Cangene's Study AX-001 (n=74; subjects not exposed to anthrax) and in sporadic cases (n=19) of systemic anthrax. Study AX-001 was designed to assess the safety, tolerability and pharmacokinetics of AIGIV at three dose levels (half dose of 210 U [n=18], anticipated regular human dose of 420 U [n=18] and double dose of 840U [n=38; three lots tested]) in healthy adult volunteers. A placebo group (n=18) was included. The sponsor states that overall, AIGIV appeared safe and well tolerated at all dose levels. The most frequently (>10%) reported AEs were headache (38%), sore throat (14%), nausea (12%), cough (11%), and infusion site pain (11%). The sponsor did not assess any AE as serious (which appears consistent with the study data provided). The following table summarizes AEs observed in ≥5% of AIGIV-treated subjects by system organ class (SOC) and preferred term (PT):

¹ Jernigan JA, Stephens DS, Ashford DA, Omenaca C, Topiel MS, Galbraith M, et al. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis.* 2001;7(6):933-44.

Table 5 Summary of Data Available for Anthrax Patients Receiving AIGIV

| System Organ Class (SOC) | Preferred Term (PT) | Overall (N=74) | | | |
|--|------------------------|----------------|-----------------|--|---|
| | | No. of Events | No. of Subjects | % of Subjects Reporting the Event ^a | Reporting Frequency (RF) ^b (%) |
| Gastrointestinal disorders | Nausea | 9 | 9 | 12.2 | 12.2 |
| General disorders and administration site conditions | Chills | 6 | 4 | 5.4 | 8.1 |
| | Fatigue | 4 | 4 | 5.4 | 5.4 |
| | Infusion site pain | 12 | 8 | 10.8 | 16.2 |
| | Infusion site swelling | 5 | 4 | 5.4 | 6.8 |
| | Pain | 8 | 7 | 9.5 | 10.8 |
| Musculoskeletal and connective tissue disorders | Back pain | 6 | 5 | 6.8 | 8.1 |
| | Neck pain | 5 | 4 | 5.4 | 6.8 |
| Nervous system disorders | Headache | 45 | 28 | 37.8 | 60.8 |
| Respiratory, thoracic and mediastinal disorders | Cough | 8 | 8 | 10.8 | 10.8 |
| | Nasal congestion | 5 | 5 | 6.8 | 6.6 |
| | Pharyngolaryngeal pain | 10 | 10 | 13.5 | 13.5 |
| | Rhinorrhoea | 4 | 4 | 5.4 | 5.4 |

2.4.2 Exposure in anthrax-infected patients

Cangene reports that a limited amount of safety data for AIGIV is available through the CDC-sponsored Expanded Access Program (EAP, BB-IND 13026) that collected data from anthrax patients treated with the product. The purpose of this CDC EAP (BB-IND 13026) was to enable the use of investigational AIGIV for patients with severe systemic anthrax on a case-by-case basis. Under this EAP, AIGIV (420 U dose) was administered to 19 confirmed anthrax patients for different forms of anthrax including three patients with inhalational, one patient with gastrointestinal, and fifteen patients with injectional anthrax resulting from the injection of anthrax contaminated heroin². Sixteen patients received AIGIV via the CDC and the remaining three received AIGIV from a direct product purchase by a Scottish government agency. Based on limited available data, 6 (5 injectional and 1 inhalational) of 19 anthrax-infected patients died. None of these cases was assessed by the CDC or the sponsor (or BLA clinical review to date) as being related to AIGIV treatment. The following table summarizes available outcomes for patients who received AIGIV after anthrax exposure:

Table 6 Summary of the Outcomes for Patients Receiving AIGIV for Different Forms of Anthrax Disease

| Form of Anthrax | No. Patients Receiving AIGIV | Outcome | | | | | |
|-----------------|------------------------------|-----------------------|-------------------------|---------------------|------------------|-----------------|------|
| | | Recovered/ Discharged | Scheduled for Discharge | Listed as Improving | Listed as Stable | Outcome Pending | Died |
| Inhalational | 3 | 2 | 0 | 0 | 0 | 0 | 1 |
| GI | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Injectional | 15 | 4 | 1 | 1 | 1 | 3 | 5 |

² Ramsay CN, Stirling A, Smith J, Hawkins G, Brooks T, Hood J, et al. NHS GGC; Scottish National Outbreak Control Teams. An outbreak of infection with *Bacillus anthracis* in injecting drug users in Scotland. Euro Surveill. 2010 Jan 14;15:19465.

2.5 Non-clinical safety

- 2.5.1 The sponsor states that since AIGIV was determined to be well tolerated in trial AX-001, “(b)ased on this safety profile, a separate non-clinical program to evaluate the toxicity of AIGIV in animals is not warranted. Thus, no separate toxicology studies were conducted for AIGIV or its components according to ICH S6 *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.”
- 2.5.2 In non-clinical pharmacokinetic studies in normal healthy rabbits and the cynomolgus macaque, the basic toxicology end points (i.e. body weights, clinical observations) were monitored and thus some non-clinical safety data was collected. The sponsor notes that the safety information from these non-clinical pharmacokinetic studies demonstrated that AIGIV was “safe and well tolerated in both animal models.”

3. Pharmacovigilance

- a. Important identified/potential risks and missing information
- i. Important identified risks: None
 - ii. Important potential risks:
 - 1. Hypersensitivity, anaphylactic and anaphylactoid reactions, e.g., in patients with IgA deficiency or hypersensitivity to human globulin (as with other immune globulin product prepared from human plasma)
 - 2. Transmission of infectious agents from human plasma (as with other immune globulin product prepared from human plasma)
 - 3. Thromboembolic events (as associated with other immune globulin products)³
 - 4. Falsely elevated blood glucose (as associated with maltose interfering with certain blood glucose testing methods)
 - 5. Aseptic meningitis syndrome (as associated with IGIV products)
 - 6. Hemolytic events (as associated with IGIV products)
 - 7. Transfusion-related acute lung injury (as associated with IGIV products)
 - 8. Acute renal dysfunction/failure (as associated with IGIV products)

Note: All important potential risks noted above are included in the CONTRAINDICATIONS and/or WARNINGS and PRECAUTIONS sections of the proposed package insert.

³ Please see CMC review memo for an assessment of AIGIV thrombotic potential. Discussions are ongoing within the product office regarding potential labeling language/section to communicate this concern.

- iii. Important missing information
 - 1. Larger general safety database (small current sample size due to ethical and practical reasons, with resultant utilization of Animal Rule regulatory pathway. There is an associated PMR that would expand the safety database in the event of a mass anthrax exposure event)
 - 2. Predisposing factors that could cause/exacerbate hypersensitivity reactions
 - 3. Class specific effects including potential TEEs, renal impairment, TRALI, aseptic meningitis, and hemolytic anemia
 - 4. Safety information in pregnant or lactating women, pediatric and geriatric populations.
- b. Planned pharmacovigilance actions for above concerns (in 3a): Routine pharmacovigilance including reporting postmarketing adverse experiences to CBER in accordance with 21 CFR 600.80.

4. Review of literature and other information during the managed review process

A PubMed literature review using the search terms “Anthrax” and “immune globulin” conducted on December 2, 2014 identified one publication of interest addressing the human safety of anthrax immune globulin.⁴ This article, for which the lead author’s designated professional affiliation was the same as this BLA’s sponsor, presented the same studies as presented in this BLA. Overall, this literature search did not identify any new safety concerns regarding AIGIV.

5. Integrated risk assessment

The above pharmacovigilance plan proposed by the sponsor appears adequate for the sought indication. Approval for AIGIV is being pursued via the Animal Rule due to the aforementioned feasibility and ethical considerations precluding premarketing human clinical efficacy studies. Given the very limited number of individuals exposed to AIGIV after anthrax exposure (many of whom had severe symptoms attributed to anthrax infection), the overall human safety profile for the sought indication is largely unknown with non-clinical (e.g., animal) studies largely informing the overall safety of this product in accordance with the Animal Rule. Class effect adverse events (e.g., thrombotic events) seen in other immune globulin products could potentially present in association with this product. Under the Animal Rule, a required postmarketing effectiveness study (with safety assessments) would be triggered in the event of a mass exposure (see clinical review). Any safety data collected postmarketing should be interpreted in the context of the risk/benefit profile of a potentially life-saving product intended to be administered

⁴ Mytle N, et. al. Evaluation of intravenous immune globulin for treatment of inhalation anthrax. Antimicrobi Agents Chemother. 2013 Nov; 57(11):5684-92. doi: 10.1128/AAC.00458-13. Epub 2013 Aug 26.

after a potentially fatal exposure to anthrax. In this context, the review team has not identified any known serious risk or signal of a serious risk related to the intravenous administration of AIGIV to date that would warrant additional pharmacovigilance measures.

6. Conclusions/Recommendations

- The sponsor's plan for conducting routine pharmacovigilance practices appears adequate for the sought indication.
- If there is a mass anthrax exposure event, the aforementioned effectiveness study (see clinical review) will be triggered which will secondarily evaluate safety-related outcomes.
- Postmarketing adverse experiences should be reported to CBER in accordance with 21 CFR 600.80.
- Distribution reports should be provided to CBER in accordance with 21 CFR 600.81.
- No REMS is required at this time.