

**ADDENDUM to CLINICAL REVIEW of ORIGINAL BLA**

Application Type	Original Application
STN	125562/0
CBER Received Date	March 10, 2014
PDUFA Goal Date	March 25, 2015
Division / Office	DHCR/OBRR
Priority Review	Yes
Reviewer Name(s)	L. Ross Pierce, M.D.
Addendum Review Completion Date / Stamped Date	(Original Clinical Review Dated Dec 31, 2014, Stamped Jan 2015)
Supervisory Concurrence	
Applicant	Cangene
Established Name	<b>Anthrax Immune Globulin Intravenous (Human)</b>
(Proposed) Trade Name	<b>Anthrasil</b>
Pharmacologic Class	Hyperimmune immunoglobulin
Formulation(s), including Adjuvants, etc	The formulation contains purified human antibodies to Bacillus anthracis stabilized with 10 % maltose and 0.03% polysorbate 80.
Dosage Form(s) and Route(s) of Administration	Liquid for Intravenous Administration in 50 mL glass vials
Dosing Regimen	Single dose
Indication(s) and Intended	ANTHRASIL is an Anthrax Immune Globulin Intravenous (Human) indicated for the treatment

Population(s)	of toxemia associated with inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs.
Orphan Designated (Yes/No)	Yes, for treatment of toxemia associated with inhalational anthrax (OP letter dated 29 July 2008 re: designation request # 08-2630)

**RECOMMENDATION:** The original BLA, as amended with the draft package insert submitted 03 March 2015, may be approved under the Animal Rule from the clinical perspective.

**Addendum Review:**

This addendum covers

- (a) the sponsor's response to FDA comments regarding
  - (i) the Field Study PMR Synopsis included in the original submission,
  - (ii) the sponsor responses to FDA follow-up comments on the sponsor's revised synopses of the 2-part clinical PMR, protocols AX-003A (field study in inhalational anthrax) and AX-003B (additional data collection and analysis in sporadic systemic anthrax cases) and
  - (iii) the FDA query regarding the hospital discharge status of six injectional anthrax cases, as conveyed by information request dated 2014,
- (b) the sponsor's responses to requests for changes to the draft package insert conveyed by FDA information requests dated 19 Dec 2014, 26 January 2015, 02 February 2015, and 27 February 2015, and
- (c) the sponsor's subsequent submissions of a revised draft package insert, most recently submitted 03 March 2015.
- (d) The analysis of serious adverse events and serious adverse reactions among patients with systemic anthrax who received AIGIV.

In addition, appendices to this addendum include tables of demographics, AIGIV lot numbers administered, and IND regulatory status of systemic anthrax patients who were administered AIGIV.

**(a) Sponsor's 15 Dec 2014 (amendment 17) response to FDA comments regarding the Field Study PMR Synopsis included in the original submission and regarding the hospital discharge status of Six Injectional Anthrax cases, as conveyed by information request to the Sponsor dated 17 Nov 2014**

**1.1 Postmarketing Requirement (PMR) Field Study Protocol AX-003**

**A. We request the PMR be split into two components:**

**i. Field study to confirm efficacy, safety, and the appropriateness of the recommended dosing regimen in persons exposed in a “broad [anthrax] exposure event scenario.”**

**ii. A requirement to periodically submit and analyze cumulative data from use of AIGIV in sporadic systemic anthrax cases.**

**B. Please submit a draft protocol or protocols by 15 December 2014.**

***Sponsor Response:***

*Cangene will develop a protocol for broad anthrax exposure event scenario (i.e., field study AX-003A) to evaluate clinical benefit and safety of AIGIV in patients with confirmed or suspected inhalational anthrax. In addition, Cangene will develop a protocol for use of AIGIV in sporadic systemic anthrax cases (i.e., study AX-003B), including other types of anthrax exposure, such as ingestion or injection anthrax. Detailed synopses for AX-003A and AX-003B are provided and eCTD sections 2.7.6 Synopses of Individual Studies and 5.2.1 Tabular Listing of All Clinical Studies have been updated. As discussed at the pre-BLA meeting (2014-03-18 CRMTS 9270 Pre-BLA mtg min), Cangene proposed to include a synopsis for the PMR field study evaluating clinical benefit and safety of AIGIV with the BLA and submit the final protocol post-licensure; the agency agreed with this approach. Cangene understands that both protocols are being requested under the Animal Rule guidance; the field study as outlined under 21 CFR 601.91, and the sporadic systemic case study to provide information supportive of improving the understanding of the actions, safety, and efficacy of AIGIV in inhalational anthrax.*

*It is anticipated that the appropriate study will be executed after AIGIV is distributed under license from the Strategic National Stockpile (SNS) by the Centers for Disease Control and Prevention (CDC) for either a broad exposure scenario or sporadic systemic anthrax cases. As AIGIV disseminated from the SNS will be commercially labeled, it will be administered under an approved label; therefore, both protocols are primarily observational in nature. Sample collection for pharmacokinetic, and potentially pharmacodynamic, analysis will be requested under patient informed consent.*

*For the sporadic systemic anthrax case study, AX-003B, Cangene's interpretation is that this observational study is not intended to be a well-controlled study to support a significant change*

*in the labeling, and that the route of administration and dosing will be consistent with the labeled dosing with no significant increase in risks associated with AIGIV. As a result, AX-003B does not fall within the applicability of the IND regulations. The two protocols will be submitted to the IND, but the studies will be conducted as observational studies (i.e. , not under IND regulations). FDA has offered feedback that for those sporadic systemic anthrax patients whose route of exposure was other than inhalational, it would be appropriate to conduct the study under an IND and it would also be preferable for a single protocol to cover all sporadic systemic anthrax cases, including both inhalational cases and those with non-inhalational routes of exposure. Cangene does not see how such a study is feasible under IND regulations. To conduct a study under IND, the sponsor must ensure appropriate labeling of the investigational drug (21 CFR 312.6) and ensure selection of investigations [sic] , control of drug and obtaining information from the investigator before participation (21 CFR 312.53). As Cangene will not control distribution of AIGIV for the sporadic systemic anthrax case study, compliance with IND regulations is not possible. As such, Cangene proposes that the study be conducted in accordance with the regulations in 45 CFR part 46 governing research supported by a government funding agency.*

*Anthrax is an extremely rare illness in the United States, with only 11 cases of systemic anthrax documented after a broad exposure in 2001 (1) and only three cases of systemic anthrax occurring post-2001 (2, 3, 4, 5). As such, Cangene requests periodic (annual) agency dialog on the requirement for the sporadic systemic anthrax case study should there be no enrollment or should the broad exposure study be executed and completed. Study AX-003B will be a case study, with each systemic anthrax case summarized and provided to the agency. No formal statistics are planned for this study. Cangene proposes to provide the complete draft protocols for the PMR studies post-approval. Cangene has expanded the original AX-003 synopsis into a synopsis for a broad anthrax exposure event scenario field study AX-003A, including a schedule of events, and has generated a synopsis for AX-003B with schedule of events for the sporadic systemic anthrax case study. As these are complex studies with multiple federal agencies involved, Cangene would like to build in time to work with the CDC to gain feedback on optimized work flow and data collection, as well as sample handling and testing.*

*Please refer to Table 1 below for submission timelines of draft and final protocol/case report forms (CRFs) for AX-003A and AX-003B. These proposed timelines are consistent with timelines for PMR protocols of other products licensed under the Animal Rule (e.g., Raxibacumab, Levaquin® and BAT®).*

**Table 1 Timelines for Submission of Post-marketing Requirement Protocols**

	<b>AX-003A Submission Timeline<sup>a</sup> (broad anthrax exposure scenario)</b>	<b>AX-003B Submission Timeline<sup>a</sup> (sporadic systemic anthrax cases)</b>
Draft protocol/CRFs	July 2015	July 2015
Final protocol/CRFs	October 2015 <sup>b</sup>	October 2015 <sup>b</sup>

<sup>a</sup> Submission timeline is based on AIGIV PDUFA date of March 25, 2015.

<sup>b</sup> Based on the assumption the agency will review draft protocols/CRFs within 30 days of submission.

**Reviewer Comment:**

- Contrary to the sponsor’s statement, FDA did not indicate its agreement with the sponsor’s counter-proposal to submit the final protocol for the PMR field study evaluating clinical benefit and safety of AIGIV post-approval.
- Although the sponsor states, “As AIGIV disseminated from the SNS will be commercially labeled, it will be administered under an approved label; therefore, both protocols are primarily observational in nature,” it does not necessarily follow that all PMR trials and studies of licensed products are primarily observational in nature. CBER has many examples of phase 4 PMC trials of approved/licensed products that are clinical trials conducted under IND and I am not aware of any regulation that would preclude a PMR study from being conducted under an IND.
- The sponsor states “For the sporadic systemic anthrax case study, AX-003B, Cangene’s interpretation is that this observational study is not intended to be a well-controlled study to support a significant change in the labeling, and that the route of administration and dosing will be consistent with the labeled dosing with no significant increase in risks associated with AIGIV,” and concludes, “As a result, AX-003B does not fall within the applicability of the IND regulations.” While the route of administration of the product in non-inhalational systemic anthrax cases is likely to be the same, it is possible that optimal dosing in injectional anthrax could differ from that in inhalational anthrax. For example, a large area of necrotizing fasciitis in the case of injectional anthrax may require higher and/or a larger number of repeated doses because of a reduced rate of diffusion of the product into the affected tissue, thus prolonging the tissue as a source of ongoing production and diffusion of anthrax toxins into the systemic circulation. (b) (4)

Whether the protocol AX-003B would be exempt from IND regulations may require further internal discussion following submission of the full protocol.

- The sponsor states “As Cangene will not control distribution of AIGIV for the sporadic systemic anthrax case study, compliance with IND regulations is not possible.” It is not clear to this reviewer that this is a true statement. Many sponsors routinely delegate the enumerated tasks of running clinical trials to contract research organizations (CROs). It would appear that Cangene could enter into a similar agreement with the CDC such that IND regulations for the sporadic systemic anthrax case study could be satisfied.
- The Raxibacumab approval letter provides a milestone for performance of a PMR field study with submission of a final protocol by June 2013, which is six months following the December 2012 approval. Cangene proposes to submit the final protocol by October 2015, which is seven months following the ADD. This is acceptable. However, I recommend the sponsor submit a draft protocol prior to the ADD. [The sponsor subsequently agreed to submit the draft protocols for the PMR studies by 20 March 2015, prior to the ADD.]

**C. Please submit a draft case report form (CRF) or forms by 12 January 2015.**

***Sponsor Response:***

*Draft and final case report forms (CRFs) will be developed and submitted in conjunction with the draft and final protocols according to the timelines identified in Table 1. It has been our experience that the amount of data requested is directly related to the responsiveness of the treating facilities. As such, we would like time to ascertain more carefully the type of information requested from the treating facilities and to build in adequate time for CDC feedback from the experience in data collection from their BB-IND 13026 emergency use AIGIV protocol. The type of data to be collected has been outlined in the protocol synopses provided.*

**Reviewer Comment:**

**I recommend the sponsor provide the date by which they expect to submit the CRF for this PMR.** This should be no more than 2 to 3 months following submission of the final protocol. [The sponsor subsequently submitted an acceptable target date for submitting the CRF.]

**D. Please submit with the draft field study protocol proposed relative timelines at this time in relation to initiation of the protocol for completion of enrollment, completion of data collection, and for submission of the final study report. We request calendar date timelines be submitted for the collection, analysis, and submission of the final study report for the component of the PMR dealing with sporadic anthrax cases.**

***Sponsor Response:***

*As it is not possible to predict when, and if, an anthrax exposure event will occur, calendar date timelines cannot be provided. Rather, timelines are provided consistent with other products licensed under the Animal Rule, including BAT®. Please see Table 2 below for submission timelines of final study reports for AX-003A and AX-003B. For AX-003B data collection, analysis, and submission of the final study report, calendar date timelines are not provided as it is difficult to anticipate the occurrence of a first sporadic case in the USA.*

***Table 2 Timelines for Study Enrollment, Data Collection and Study Completion and Submission of Final Study Reports***

	<b>AX-003A (broad anthrax exposure event)</b>	<b>AX-003B (sporadic systemic anthrax cases)</b>
Completion of enrollment	To be determined <sup>a</sup> should a broad anthrax exposure event occur	To be determined <sup>b</sup>
Completion of data collection	12 months after last AIGIV administration following a broad anthrax exposure event	To be determined
Study completion	12 months after last AIGIV administration following a broad anthrax exposure event	To be determined <sup>c</sup>
Submission of final study report	18 months after last AIGIV administration following a broad anthrax exposure event	5 years after final protocol approval <sup>c</sup>

<sup>a</sup> In consultation with the FDA.

<sup>b</sup> The study will be evaluated annually for the first five years after protocol approval. In the event of limited or no enrollment, protocol futility will be discussed with FDA for re-evaluation.

<sup>c</sup> Study may be terminated in case that a broad anthrax exposure scenario occurs. If subjects are enrolled into AX-003B prior to broad exposure event, a final study report on the cases will be generated and submitted to the FDA in conjunction with the final report for the broad exposure scenario.

**Reviewer Comment:**

**The proposed relative timelines for study AX-003A completion are concordant with those in the raxibacumab approval letter, but the proposed milestone for submission of the final study report is discordant with the much shorter time between study completion and final study report submission, if you consider study completion to be near in time to when the last patient is treated with the product. Instead, the sponsor has redefined study completion as the date when data collection has been completed, and proposed this to be 12 months following treatment of the last subject. If there is a mass exposure event, it would seem prudent to expedite analysis of the data to inform treatment during possible subsequent events. I recommend for AX-003A that the sponsor target data collection to be completed within 6 to 9 months of enrollment of the last patient in the study and final study report submission to FDA by 6 months following completion of data collection (12 to 15 months following enrollment of the final patient in the study). For study AX-003B, I**

**recommend the final study report be submitted within 9 to 10 years of final protocol approval, rather than 5 years. [The sponsor agreed to these revised timelines.]**

**E. Please include in both the sporadic and broad exposure study designs a mechanism for studying the use of more than one dose of the product in comparison to use of a single dose.**

*In both protocols we anticipate that AIGIV will be distributed under license and will be administered according to approved Prescribing Information (PI), which will include provisions for re-dosing. The protocol and CRFs for both studies will be designed to capture information on multiple dosing and any sample collection relative to last dose administered. For the broad exposure scenario field study AX-003A, should a sufficient number of patients be treated in each dose group (single dose vs. multiple doses), exploratory analyses can be performed. For the sporadic systemic anthrax case study AX-003B, no formal analysis is planned.*

**Reviewer Comment:**

**The package insert is being revised to recommend a range of initial starting doses from 420 Units to 840 Units and has been revised to include, under defined clinical circumstances, consideration of repeated doses. I recommend the protocol for AX-003A include plans for analysis of survival as well as major morbidity (organ system failure) by the size of the initial dose, by whether single or repeated doses were administered, and by total cumulative dose. These same analyses should be performed in AX-003B to the extent that the data permit such analyses. [The sponsor agreed to these analyses.]**

**F. Please consider for both component s of the PMR including international healthcare providers who may administer AIGIV to patients with inhalational anthrax located overseas.**

***Sponsor Response:***

*The PMR studies will include patients under USA regulatory jurisdiction. Internationally, depending on the scenario, AIGIV could be deployed directly from the CDC or AIGIV could be obtained from a purchase agreement directly with Cangene (doing business as Emergent BioSolutions) and deployed by other regulatory or public health agencies. The regulatory requirements, appropriate distribution agreements, as well as public health and regulatory agency involvement will vary greatly depending on the location of use, and must be considered on a case by case basis. Without knowing the specifics of any overseas deployment or use, we can only commit to including patient populations within the USA jurisdiction, including USA territories and military bases.*

*However, in cases where it may be possible to collect data outside of the USA, we will explore these situations as they arise. If there is an opportunity for co-operation with the FDA and CDC*



*or to work with overseas agencies and get valuable patient data, especially in a broad anthrax exposure scenario, we are willing to discuss and evaluate such scenarios as they occur.*

**Reviewer Comment:**

**I recommend PMR studies AX-003A and AX-003B include overseas administration of the product where feasible.** Given that the product would be obtained from a U.S. source, it seems reasonable for, as a condition of providing said product, the receiving entity to cooperate with collecting and providing clinical outcome data regarding the product's use. This is particularly true when there are uncertainties in the extrapolation of efficacy from animals to humans, uncertainty regarding the optimal dose, and uncertainties in the extrapolation of safety data from healthy human volunteers to severely ill patients with inhalational anthrax. [The sponsor agreed to include overseas sites to the extent feasible.]

**G. As previously requested, please include a pediatric pharmacokinetic protocol as part of your PMR, designed according to the pattern of Heptavalent equine-derived botulinum antitoxin (BLA 125264).**

***Sponsor Response:***

*Like the PMR for Heptavalent equine-derived botulinum antitoxin (BLA 125264), it is anticipated that pediatric patients will be enrolled into the PMR studies. Our intention is to collect samples when it is feasible and ethical for anti-PA testing from all enrolled subjects and then stratify the anti-PA analysis by age category (pediatric, adult). As informed consent will be required for sample collection and analysis for all subjects, a separate pediatric PK protocol is not required.*

**Reviewer Comment:**

**If sufficient pediatric subjects are treated under this PMR, the protocols should include plans to analyze PK data for each of the pediatric age stratum, not just for the overall pediatric population.** [The sponsor subsequently agreed to this request.]

**H. Please consider sampling a subset of patients for lethal factor (LF) before and after administration of AIGIV and exploring the relationship between changes in LF levels in relation to the time of administration of AIGIV and to changes in PA levels in individual patients.**

*Cangene will consider including toxin (lethal factor, LF and protective antigen, PA) testing in both protocols. As Cangene has never had to develop an assay for LF testing during the pre-clinical and clinical development, a collaboration with the CDC will be explored with regards to their validated LF assay, as well as the logistics of handling samples that may still be infectious*

(i.e., samples collected from patients that have been administered antimicrobial therapy for less than 24 hours). In addition, we are assessing the feasibility of utilizing the

(b) (4) PA assay (b) (4) employed for PA testing in the animal studies, due to current equipment limitations. Pending these activities, Cangene will inform the agency whether testing for toxin levels in both protocols is feasible upon provision of the draft protocols (Table 1).

If possible, serum samples will be collected pre- and post-AIGIV infusion in both studies; however, the priority for sample testing will be anti-PA measurements for pharmacokinetics. The LF and PA testing will be only considered if there are sufficient sample quantities.

**Reviewer Comment:**

**Noted.**

**I. Serious adverse events (SAEs), adverse reactions, and suspected adverse reactions should be recorded, analyzed, and reported. Recording and reporting of adverse events that do not fall into one or more of the aforementioned categories need not be reported.**

***Sponsor Response:***

*Cangene is in agreement with the agency; the synopses for AX-003A and AX-003B include wording on collection and analysis of SAEs, adverse reactions and suspected adverse reactions.*

**Reviewer Comment:**

**Noted.**

**J. Please change the secondary endpoint to the frequency of serious suspected adverse reactions plus serious adverse reactions.**

***Sponsor Response:***

*Cangene has included the following secondary endpoints in the synopses for AX-003A and AX-003B:*

- Incidence of serious suspected adverse reactions*
- Incidence of serious adverse reactions.*

**Reviewer Comment:**

**Noted.**

**K. Please add exploratory endpoints consisting of cause-specific mortality, duration of ICU stay, duration of mechanical ventilation, need for dialysis, maximum increase from baseline in SOFA score, and duration of hospitalization.**

***Sponsor Response:***

*Cangene has added the following exploratory endpoints to AX-003A synopsis (broad exposure event):*

- *Cause-specific mortality*
- *Duration of ICU stay*
- *Duration of mechanical ventilation*
- *Maximum increase from baseline in SOFA score*
- *Duration of hospitalization*
- *Requirement for dialysis*

**Reviewer Comment:**

**Noted.**

**L. Please include in the protocol provision for independent assessment by the sponsor of the relatedness of all serious adverse events.**

***Sponsor Response:***

*As included in the synopses for AX-003A and AX-003B, Cangene will independently assess relatedness of all reported serious adverse events.*

**Reviewer Comment:**

**Noted.**

**M. Please define the total of serious suspected adverse reactions plus serious adverse reactions as all SAEs for which any one or more of the following criteria are met:**

- i. SAEs for which the onset was during or within 24 hours of the end of AIGIV infusion.**
- ii. SAEs considered by the healthcare provider or the sponsor to be possibly, probably, or definitely related to administration of AIGIV.**

**iii. SAEs for which the healthcare provider's causality assessment was missing or indeterminate.**

***Sponsor Response:***

*Cangene agrees with the agency's definition of serious suspected adverse reactions and serious adverse reactions; this was included under safety assessment in AX-003A and AX-003B.*

**Reviewer Comment:**

**Noted.**

**N. Please include plans to compare the observed mortality rate to historical controls and to compare the demographics and other pertinent patient characteristics to historical controls.**

***Sponsor Response:***

*The most comprehensive information on historical inhalational anthrax cases was the systematic review of anthrax cases published by Holty et al, 2006 (6), which included all published inhalational anthrax case reports from 1900 to 2005. The authors evaluated the predictors of disease progression and mortality. In the paper, a comparison of disease progression characteristics between the US 2001 patients (11 cases) and pre-2001 patients (71 cases) was performed. The results showed that the patient's age, disease progression (mortality, progression from prodromal to fulminant phase, meningitis), and treatment between the two time periods were significantly different. Changes in the standard of care over time, the type of care and disease state at initiation of treatment are predictors of survival. Since there are many potential factors that impact the mortality rate (Table 3), it is difficult to estimate whether the broad exposure scenario will be comparable to the historical inhalational anthrax cases, which have only limited information available.*

**Table 3 Comparison of Inhalational Anthrax Patient Disease Progression Characteristics – US 2001 Mail Attack Event Cases vs. Pre-2001 Cases**

	<b>US 2001<sup>a</sup> Cases (n=11)</b>	<b>Pre-2001<sup>a</sup> Cases (n=71)</b>	<b>P-value<sup>b</sup></b>
<b>Disease Progression</b>			
Mortality (%)	45 (11)	92 (71)	<0.001
Progression from prodromal to fulminant phase for all cases (%)	45 (11)	94 (71)	<0.001
Progression from fulminant phase to death (%)	100 (5)	97 (67)	1.00
Meningitis (%)	9 (11)	42 (71)	0.045
<b>Treatment</b>			
Mean time from symptom onset to antibiotics or anthrax antiserum (days) <sup>c, d</sup>	4.1 (11)	4.3 (26)	0.80
Therapy (antibiotics or antiserum) started in prodromal phase (%) <sup>c</sup>	64 (11)	13 (71)	<0.001
Mortality if antibiotics or antiserum initiated during prodromal phase (%) <sup>c</sup>	14 (7)	67 (9)	0.060
Mortality if antibiotics or antiserum initiated during fulminant phase (%) <sup>c</sup>	100 (4)	88 (17)	1.0
Multidrug regimen (≥ 2 antibiotics or combined antiserum- antibiotic therapy) if therapy given (%) <sup>c, d</sup>	91 (11)	50 (26)	0.027
Pleural fluid drainage (%)	73 (11)	11 (71)	<0.001

	<b>US 2001<sup>a</sup> Cases (n=11)</b>	<b>Pre-2001<sup>a</sup> Cases (n=71)</b>	<b>P-value<sup>b</sup></b>
Survivors who received pleural fluid drainage (%)	100 (6)	67 (6)	0.45

<sup>a</sup> n represents the total number of cases included for the summary. Due to the missing information for some of the cases, the number of cases used in each analysis is shown in the parentheses.

<sup>b</sup> P-value is for the comparison between US 2001 cases and pre-2001 cases.

<sup>c</sup> Received appropriate antibiotics (≥ 70% of *Bacillus anthracis* strains were susceptible) or anthrax antiserum.

<sup>d</sup> Excluding cases for which antibiotics or anthrax antiserum was not given.

**[Note that the numbers not in parentheses in the middle two columns represent percent and the numbers in parentheses represent the total number of subjects evaluated for the particular feature or treatment.]**

*Due to missing data, including known duration of follow-up, there is a potential bias in the historical control reference mortality rate. Thus, while mortality is a key primary endpoint for evaluation of clinical benefit, it is not meaningful to compare with a historical control mortality rate. For the broad exposure scenario field study AX-003A, the mortality rate will be calculated and summarized with the 95% confidence interval. No formal statistical comparison is planned on the mortality rate.*

*To support the verification of clinical benefit, the secondary endpoint of time to death from symptom onset will be compared with the historical control reference of 5.2 days based on the*

*upper confidence interval from the Hotly et al systematic review (6); mean time to death was 4.7 days from symptom onset, the 95% confidence interval was 4.1 to 5.2 days. The analysis will be limited to fatal cases to avoid the potential bias of the unknown follow-up period for the historical survival cases. In consideration of all potential factors that could impact the observed mortality rate, Cangene is proposing to compare the early mortality rate (at Day 14) to late mortality rate (at Day 30). Early mortality rate is considered as an early disease-attributable mortality rate, which takes all of the confounding factors into consideration. This early disease-attributable mortality rate is treated as the control rate and may be compared with the late survival rate at Day 30 to demonstrate the clinical treatment benefit. Based upon the natural history of disease progression for inhalational anthrax cases, this early disease-attributable mortality has been fairly consistent despite the confounding factors and potential treatments. Additional exploratory analysis will be performed to examine the relationship between the mortality rate and the exploratory endpoints (as outlined in AX-003A), if sufficient data is available.*

*The demographic and other patient characteristics will be listed and summarized for both sporadic systemic anthrax cases and the broad exposure scenario. There is no plan to perform formal statistical comparison of demography or other patient characteristics to historical controls.*

#### **Reviewer Comment:**

**The sponsor's proposal to use the secondary endpoint of time to death from symptom onset, with the analysis limited to patients who die despite therapy, in comparison to the historical control reference of 5.2 days from symptom onset until death to support the verification of clinical benefit is not acceptable, in that this interval is not clearly related to clinical benefit. In addition, it is not clear how the relationship between mortality through day 14 and mortality through day 30 would relate to efficacy of AIGIV.** The sponsor states that it is not meaningful to compare the mortality rate in patients administered AIGIV to an historical control rate, due to missing data, including the known duration of follow-up. This is likely true for the pre-2001 cases, **but a comparison to the mortality rate among the 2001 U.S. inhalational anthrax attack cases would be both appropriate and informative, provided the demographics, time between onset of symptoms and initiation of treatment with antibiotics, and whether the above treatments are initiated in the prodromal stage or in the fulminant stage in the patients in the two datasets are examined and taken into account in the analysis.** In my opinion, depending on the size of the AX-003A study, the finding of a sufficient trend (e.g.,  $p < 0.10$  or  $< 0.20$ ) suggesting increased survival with AIGIV plus antibiotics over and above the 45% survival observed for the 2001 U.S. anthrax attack cases would be supportive of a conclusion of added benefit and conversion of the Animal Rule BLA to a full approval. [The sponsor agreed to revise the primary endpoint to be all-cause mortality through day 7. This may be revised to all-cause mortality through day 30 after the protocol is submitted. The analysis comparing the

mortality rate in AX-003A to that in the 2001 US anthrax incident will also be performed if the comparison cohorts are sufficiently comparable in pre-defined variables.]

**O. Please analyze both efficacy and safety outcomes by age, sex, body mass index, race, and ethnicity.**

***Sponsor Response:***

*Cangene will analyze primary and secondary endpoints of AX-003A and AX-003B by age, gender, body mass index, race and ethnicity.*

**Reviewer Comment:**

**Noted. The sponsor is also asked to analyze primary and secondary endpoints by body weight (in addition to body mass index).** [The sponsor agreed.]

**1.2 Injectional Anthrax Patients**

**2. Please indicate whether the following individuals who were administered AIGIV for injectional anthrax were discharged from the hospital: patients (b) (6)**  
**(b) (6)**

***Sponsor Response:***

*Patient (b) (6) was discharged from the hospital on April 4, 2010 (source: Annual Report for BB-IND 13026, reporting period June 8, 2009 to July 2, 2010); this information was erroneously omitted from the Patient Experience Report.*

*Cangene has reached out to the CDC for the other patients and the CDC has indicated that no new data on discharge dates are available.*

**Reviewer Comment:**

**We understand that you and the CDC do not currently have the hospital discharge dates for injectional anthrax cases patients (b) (6), and (b) (6). However, please endeavor to obtain the hospital discharge status of these patients. If these data cannot be obtained, FDA will consider the survival status of these patients unknown and the draft package insert will require revision accordingly. [The sponsor was subsequently at FDA request able to provide the hospital discharge dates for five of these 6 patients.]**

**The following FDA comments, based on the sponsor's amendment 17 dated 15 Dec 2014, were conveyed to the sponsor on 26 January 2015. The sponsor's replies, in an amendment dated 09 February 2015, are listed below each FDA comment, followed by my reviewer comments.**

1. Whether the protocol AX-003B would be exempt from IND regulations may require further discussion following submission of the full protocol.

***Sponsor Response:***

*Cangene understands and agrees with evaluating this further upon full protocol review.*

**Reviewer Comment:**

**Both AX-003A and AX-003B should be conducted under Cangene's AIGIV IND. Both protocols will include PK sampling for anti-PA antibodies and anthrax lethal factor, which would not necessarily be part of standard of care use of a licensed product. Cangene, as IND sponsor, may enter into a CRO type of agreement with the CDC for the performance of certain tasks, such as investigator selection and control of the investigational agent.**

2. Your proposal to submit the final protocol by October 2015, which is seven months following the action due date (ADD), is acceptable. However, we request you submit a draft protocol prior to the **ADD**.

***Sponsor Response:***

*Cangene will submit draft protocols for AX-003A and AX-003B prior to the action due date (i.e., in March 2015). However, these protocols will be submitted to the Centers for Disease Control and Prevention (CDC) simultaneously and as such, any recommendations by the CDC will be incorporated with the final protocol submissions in October 2015.*

**Reviewer Comment:**

**Noted. The sponsor has been asked to specify the date prior to the ADD by which it expects to submit the draft protocols.**

3. Please provide the date by which you expect to submit the case report form (CRF) for this PMR.

***Sponsor Response:***

*Cangene will provide draft case report forms (CRFs) for each of the protocols in July 2015. The final protocols and final CRFs will be provided in October 2015. Submission timelines are summarized in Table 1.*

**Table 1 Timelines for Submission of Post-marketing Requirement Protocols**



	<b>AX-003A Submission Timeline<sup>a</sup> (broad anthrax exposure scenario)</b>	<b>AX-003B Submission Timeline<sup>a</sup> (sporadic systemic anthrax cases)</b>
Draft protocol	March 2015 <sup>a</sup>	March 2015 <sup>a</sup>
Draft CRFs	July 2015	July 2015
Final protocol/CRFs	October 2015 <sup>b</sup>	October 2015 <sup>b</sup>

<sup>a</sup> Submission timeline is based on AIGIV PDUFA date of March 25, 2015.

<sup>b</sup> Based on the assumption the agency will review draft protocols/CRFs within 30 days of submission.

**Reviewer Comment:**

**Noted.**

- Please revise your milestones for AX-003A such that you target data collection to be completed within 6 to 9 months of enrollment of the last patient in the study and final study report submission to FDA by 6 months following completion of data collection (12 to 15 months following enrollment of the final patient in the study). For study AX-003B, please revise your milestone for submission of the final study report to be within 9 to 10 years of final protocol approval, rather than 5 years.

***Sponsor Response:***

*For AX-003A, Cangene will complete data collection within nine months of the last patient enrollment and submit the final study report to FDA within six months of data collection (i.e., 15 months after last patient enrollment).*

*For AX-003B, Cangene will submit the final study report within nine years after final protocol approval. A modified Table 2 is provided.*

**Table 2 Timelines for Study Enrollment, Data Collection and Study Completion and Submission of Final Study Reports**

	<b>AX-003A (broad anthrax exposure event)</b>	<b>AX-003B (sporadic systemic anthrax cases)</b>
Completion of enrollment	To be determined <sup>a</sup> should a broad anthrax exposure event occur	To be determined <sup>b</sup>
Completion of data collection	9 months after last AIGIV administration following a broad anthrax exposure event	To be determined
Study completion	9 months after last AIGIV administration following a broad anthrax exposure event	To be determined <sup>c</sup>
Submission of final study report	15 months after last AIGIV administration following a broad anthrax exposure event	9 years after final protocol approval <sup>c</sup>

<sup>a</sup> In consultation with the FDA.

<sup>b</sup> The study will be evaluated annually for the first five years after protocol approval. In the event of limited or no enrollment, protocol futility will be discussed with FDA for re-evaluation.

<sup>c</sup> Study may be terminated in case that a broad anthrax exposure scenario occurs. If subjects are enrolled into AX-003B prior to broad exposure event, a final study report on the cases will be generated and submitted to the FDA in conjunction with the final report for the broad exposure scenario.

#### **Reviewer Comment:**

#### **Noted.**

- Please include in the protocol for AX-003A plans for analysis of survival as well as major morbidity (organ system failure) by the size of the initial dose, by whether single or repeated doses were administered, and by total cumulative dose. Please conduct these same analyses for study AX-003B to the extent that the data permit such analyses.

#### ***Sponsor Response:***

*Cangene will include in the draft protocol for AX-003A plans for analysis of survival as well as major morbidity by initial dose of 420 U TNA and repeat dose(s) of 420 U TNA as well as cumulative dose [initial plus repeat dose(s)]. The same analyses will be proposed for AX-003B to the extent that the data permit.*

*The currently proposed dosing regimen ([Prescribing Information](#)) is based on individual doses of 420 U TNA:*

*The initial dose of ANTHRASIL for the treatment of inhalational anthrax in adults in combination with appropriate antimicrobial therapy is 420 units (seven vials). Data in animal models suggest that administration of higher doses may result in improved survival [See 13.2 Animal Toxicology and/or Pharmacology]. As a result, a higher total dose than 420 units may be considered, depending on the clinical scenario and baseline symptomatology as well as the patient's response to the initial dose. A second dose of 420 units (seven vials) may be administered for a total dose of 840 units (14 vials).*

*A double dose of ANTHRASIL (840 units) was administered to healthy adults in a clinical trial with no serious adverse effects [see 6.1 Clinical Trials Experience].*

*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.*

*Cangene's rationale for this dosing recommendation is multifactorial and includes:*

- An equivalent dose in animals exposed to a large Bacillus anthracis spore challenge (200 x LD50) resulted in neutralization of PA. The goal of AIGIV treatment is to neutralize toxin, which in combination with antibiotics, can prevent further disease progression and allow recovery.*
- The benefit of a larger dose is not clear. An improvement in survival with dose was observed in non-human primate monotherapy dose ranging studies where bacteremia, and hence toxin production, was not controlled by antimicrobial therapy. The benefit of larger doses of AIGIV in combination with antibiotics has not been observed in non-human primate combination therapy study.*
- In three inhalational anthrax patients who were administered a dose of 420 U, anti-PA levels were sustained.*
- Baseline symptoms will allow physicians to assess whether an antitoxin is required in addition to antibiotics, but may not guide the appropriate dose. Ongoing patient monitoring based on change in symptoms can better guide the need for repeat doses.*
- The concept of an initial dose followed by subsequent dosing is consistent with VIGIV, which recommends a starting dose of 6000 Units/kg followed by higher doses in the event that a patient does not respond.*
- The range of doses may be confusing for pediatric patients.*

*As such, the analysis will include comparison of survival as well as major morbidity (organ system failure) by 420 U dose and repeat dose(s) and cumulative dose.*

**Reviewer Comment:**

**FDA has considered the sponsor's arguments and has concluded that physicians treating inhalational anthrax patients need flexibility in selecting the initial dose from within the range of 420 units to 840 units, depending on the severity of the**

patient's symptoms. Patients presenting at the fulminant stage of the disease historically have had a very high mortality rate despite combination antibiotic therapy and aggressive supportive care. The sponsor's dose-response modeling, which takes into account all available data from the rabbit, NHP, and phase 1 healthy volunteer studies predicts higher survival with a single 840 unit dose as compared to a 420 unit dose. The sponsor acknowledges that it is unknown whether the 420 unit dose is sufficient to neutralize all lethal toxin and edema toxin in humans as these have not been directly measured. No direct measurement of quantitative PA inactivation by anti-PA was made in the clinical cases of inhalational anthrax in which AIGIV was administered, so it has not been ruled out that the 420 unit dose administered may not have inactivated all circulating and tissue PA moieties. It is known that lethal factor remained detectable for several days following AIGIV dosing in some systemic anthrax patients, although levels did decrease following therapy. While the sponsor points out that, in the three inhalational anthrax patients who were administered a dose of 420 U, anti-PA levels were sustained, this was very likely due, as noted in the literature, to the contribution from endogenous anti-PA antibody synthesis by the patients while exogenous antibody from AIGIV was being cleared. Not all inhalational anthrax patients are expected to have prompt sufficient antibody responses and for these patients, administration of a larger initial AIGIV dose may be important to maximize the chances for survival. The lower 420 unit initial dose may be considered for patients who present very early following the onset of symptoms in the prodromal stage. Because some inhalational anthrax patients progress to the fulminant stage quite suddenly and exhibit rapid clinical deterioration at that point, waiting even 24 hours to decide whether to administer a follow-up dose after an initial 420 unit dose in such patients may permit the disease to advance to the point where survival is not possible despite repeat therapy. The sponsor's analogy to the use of VIGIV in complications of varicella vaccination is flawed in that the pathophysiology in that setting is markedly different from that in inhalational anthrax. As for the suggestion by the sponsor that the range of dosing for pediatric patients would be "confusing," the footnotes in the pediatric dosing table advise the prescriber to select the initial dose based on clinical severity and explains that the lower end of the dose range for each weight category corresponds to the 420 unit adult dose and that the upper end of the dose range for each weight class corresponds to the 840 unit adult dose.

6. We note that, in cases where it may be possible to collect data outside of the USA, you have indicated you will explore these situations as they arise. For PMR studies AX-003A and AX-003B please include overseas cases of administration of the product where feasible.

***Sponsor Response:***

*Cangene will attempt to enroll patients outside the US jurisdictions where AIGIV is deployed by the CDC from the Strategic National Stockpile (SNS).*

*As prospective enrollment may be difficult due to appropriate regulatory and ethics approvals in other jurisdictions and sample collection may not be possible, Cangene proposes to allow for retrospective data collection provided there is cooperation with foreign investigators.*

These provisions will be included in the protocols for AX-003A and AX-003B.

**Reviewer Comment:**

**Noted and accepted.**

7. If sufficient pediatric subjects are treated under this PMR, the protocols should include plans to analyze PK data for each of the pediatric age stratum, not just for the overall pediatric population.

***Sponsor Response:***

*Cangene will include plans to analyze pharmacokinetic data for each pediatric age stratum if sufficient numbers of pediatric patients are treated under the post-marketing requirement.*

**Reviewer Comment:**

**Noted.**

8. Your proposal to use the secondary endpoint of time to death from symptom onset, with the analysis limited to patients who die despite therapy, in comparison to the historical control reference of 5.2 days from symptom onset until death to support the verification of clinical benefit is not acceptable in that this interval is not clearly related to clinical benefit. In addition, it is not clear how the relationship between mortality through day 14 and mortality through day 30 would relate to efficacy of AIGIV. You state that it is not meaningful to compare the mortality rate in patients administered AIGIV to an historical control rate, due to missing data, including the known duration of follow-up. We agree that this is likely true for the pre-2001 cases, but we regard a comparison to the mortality rate among the 2001 U.S. inhalational anthrax attack cases to be appropriate and potentially informative, provided the demographics, time between onset of symptoms and initiation of treatment with antibiotics, and whether the above treatments are initiated in the prodromal stage or in the fulminant stage in the patients in the two datasets are examined and taken into account in the analysis. Please modify your analysis plan accordingly.

***Sponsor Response:***

*To assess statistical comparison to historical mortality rate among the 2001 U.S.*

*inhalational anthrax attack cases, Cangene calculated 95% confidence interval (CI) associated with the overall mortality rate, as well as 95% CI for mortality rates of patients that had antibiotic therapy initiated in either prodromal and fulminant stage of anthrax disease (Table 3).*

**Table 3 95% Confidence Intervals for Mortality Rates from 2001 US Inhalational Anthrax Attack Cases**

	<b>Mortality (Rate)</b>	<b>95% Confidence Interval</b>
Overall Mortality	5/11 patients (45%)	17–77%
Prodromal Stage Mortality <sup>a</sup>	1/7 patients (14%)	0–58%
Fulminant Stage Mortality <sup>b</sup>	4/4 patients (100%)	40–100%

<sup>a</sup> Mortality in patients that had antibiotics or antiserum therapy initiated during prodromal stage of anthrax disease.

<sup>b</sup> Mortality in patients that had antibiotics or antiserum therapy initiated during fulminant stage of anthrax disease.

*The overall mortality rate from 2001 US inhalational anthrax attack cases is based on a small group of patients (n=11) and as evident from the wide confidence intervals indicated in Table 3, it would not be reliable to compare with the lower CI limit and perform a statistical comparison to demonstrate clinical benefit of AIGIV treatment in any of the three scenarios (overall, prodromal stage or fulminant stage). In addition, a comparison to an overall historical mortality rate (derived from a small sample size) may not be relevant if the mass exposure scenario is large and results in different demographic variables (age, co-morbidities) and limitations in standard of care therapies (e.g., pulmonary fluid drainage, mechanical ventilation not available due to overwhelming the medical system), which are all factors that influence mortality rate, that were not observed in the historical reference. As there are too many intrinsic factors that would be unpredictable in a mass exposure scenario, a statistical comparison of the mortality rate to a historical reference (based on one mass anthrax exposure) is unreliable and will not be planned for the PMR studies.*

*Cangene proposes to evaluate primary endpoint as all-cause mortality rate at Day 7 post- AIGIV administration; this would accommodate 5.2 days from symptom onset to death observed in 2001 US inhalational anthrax attack cases.*

*Additional exploratory analysis will be performed to examine the relationship between the mortality rate and time from symptom onset to initiation of antibiotic therapy. To evaluate clinical benefit of AIGIV, treated patients will be stratified on the basis of the time from symptom onset to AIGIV administration. It is anticipated that in patients that are treated later with AIGIV, a limited clinical benefit may be observed (based on the mechanism of action), thus a mortality analysis based on time to treatment may allow for the evaluation of overall clinical benefit. The exploratory analysis will be examined through the logistic regression model to take the time from symptom onset to initiation of AIGIV administration, time from symptom onset to initiation of antibiotics into*

*consideration.*

**Reviewer Comment:**

**Noted.** All-cause mortality is an acceptable primary outcome measure, however I recommend mortality status be assessed through day 30 of hospitalization, or through the date of hospital discharge, whichever comes earlier. Although the confidence intervals are wide around the point estimates of survival in the 2001 U.S. anthrax incident, a proper statistical test of the difference in the mortality rates in the two data sets will also take into account the size of the field study, so such a comparison may be meaningful, provided the demographics, delay between onset of symptoms and antibiotic therapy, stage of disease (prodrome vs. fulminant), and prevalence of medically important pre-existing baseline morbidities are taken into account. The sponsor was asked in a follow-up information request dated 03 March 2015 to confirm that it would perform , pursuant to the discussion during the teleconference between FDA and the sponsor held Monday 23 February 2015, for study AX-003A, a comparison of the mortality rate observed in field study AX-003A to the mortality observed among patients with inhalation anthrax observed during the 2001 U.S. anthrax incident, providing there are sufficient similarities between the two data sets in the demographics, extent of pre-existing co-morbidities, time between onset of symptoms and initiation of treatment with antibiotics, and whether the antibiotic treatments are initiated in the prodromal stage or in the fulminant stage in the patients in the two datasets. [The sponsor agreed to this request in the amendment submitted 04 March 2015.] Regarding footnote b to the sponsor's table, I am not aware that any patients in the 2001 US anthrax attack received anti-anthrax anti-serum.

9. Please analyze primary and secondary endpoints by body weight (in addition to body mass index).

***Sponsor Response:***

*Cangene will analyze primary and secondary endpoints by body weight as well as body mass index.*

**Reviewer Comment:**

**Noted.**

10. Regarding testing of patients pre- and post- AIGIV administration for lethal factor/lethal toxin, we understand that the assay using mass spectrometry developed at the CDC would be suitable in this regard. It is our understanding that universal precautions are deemed adequate for handling clinical specimens from anthrax-infected patients. Please see [http://www.cdc.gov/anthrax/labs/recommended\\_specimen.html](http://www.cdc.gov/anthrax/labs/recommended_specimen.html) and

<http://www.cdc.gov/anthrax/labs/cdcspecimens.html>.

*Sponsor Response:*

*Testing of LF levels pre- and post-AIGIV administration is pending CDC agreement to test these samples (if available for testing).*

*Cangene will include the specimen recommendations in the protocols for AX-003A and AX-003B.*

**Reviewer Comment:**

**Noted.**

11. For the secondary endpoint in AX-003A and AX-003B, incidence of serious suspected adverse

reactions (SSARS), please combine this with the incidence of serious adverse reactions (SARs).

*Sponsor Response:*

*Cangene will include the incidence of serious suspected adverse reactions with the incidence of serious adverse reactions in the protocols for AX-003A and AX-003B.*

**Reviewer Comment:**

**Noted.**

12. For studies AX-003A and AX-003B, please record the volume(s) and dates of pleural and ascitic fluid removal.

*Sponsor Response:*

*Cangene will include the volume(s) and dates of pleural and ascetic fluid removal parameters in the data collection tools for AX-003A and AX-003B.*

**Reviewer Comment:**

**Noted.**

13. For studies AX-003A and AX-003B, you state you plan to collect the date of discharge from the ICU and/or hospital. Please collect both the date of discharge from the ICU as well as the date of hospital discharge.

*Sponsor Response:*

*Cangene will include the date of discharge from the ICU as well as the date of hospital*



discharge parameters in the data collection tools for AX-003A and AX-003B.

**Reviewer Comment:**

**Noted**

14. We understand that you and the CDC do not currently have the hospital discharge dates for injectional anthrax cases patients (b) (6) and (b) (6). Please endeavor to obtain the hospital discharge *status* of these patients. If these data cannot be obtained, FDA will consider the survival status of these patients unknown and the draft package insert will require revision accordingly.

***Sponsor Response:***

*Please see Table 4 below for discharge dates. Cangene was able to obtain this information from recent CDC correspondence for (b) (6) and (b) (6). In addition, for (b) (6), Cangene has confirmation from the treating physician ((b) (4)) that the information will be provided. Once received, this information will be reported to the FDA and an updated Patient Experience Report recording the appropriate discharge data will be provided.*

**Table 4 Discharge Dates for Injectional Anthrax Patients**

Patient ID	Hospital Discharge Date
(b) (6)	February 02, 2010
(b) (6)	Information pending
(b) (6)	March 12, 2010
(b) (6)	July 05, 2010
(b) (6)	May 14, 2010
(b) (6)	August 02, 2010

**Reviewer Comment:**

**Noted.** Only the date of discharge of subject (b) (6) has not been provided by the sponsor.

**(b) Sponsor's 12 January 2015 response to FDA comments conveyed 19 Dec 2014 requesting changes to the draft package insert (PI) with reviewer comments as indicated.**

## **1 GENERAL**

**1. Ensure that the PI is proof-read for editorial errors.**

***Sponsor Response:***

*The Prescribing Information (PI) was proof-read for editorial errors.*

**2. Use command language whenever possible.**

***Sponsor Response:***

*The PI was reviewed to ensure command language was used whenever possible.*

**3. The FULL PRESCRIBING INFORMATION should contain only headings and subheadings. We recommended revising the 5 WARNINGS AND PRECAUTIONS and 13 NONCLINICAL TOXICOLOGY sections to remove the sub-subheadings under the subheadings. In any case, do not separately number subsections of subsections (e.g. use 5.11 but not 5.11.1, 5.11.2, etc.).**

***Sponsor Response:***

*The third level numbering and titles in sections 5 WARNINGS AND PRECAUTIONS have been removed. The numbering has been removed from sub-sections within 13.2 Animal Toxicology and/or Pharmacology; however, the titles have been left for clarity.*

**Reviewer Comment: Noted.**

**4. [Blank]**

## **2 HIGHLIGHTS**

**5. Please ensure that the HIGHLIGHTS, excluding the Boxed Warning section, are limited in length to one-half page.**

***Sponsor Response:***

*The HIGHLIGHTS section was condensed by removing the suggested additional text within INDICATIONS AND USAGE (response to Question 9). Similar to the maltose warning that is included in the black box warning, the bullet for thrombosis under WARNINGS AND PRECAUTIONS (response to Question 7) was also removed.*

**Reviewer Comment: Noted.**

**6. Please add the following language to the boxed warning in both HIGHLIGHTS and**

*the FPI sections:*

**WARNING: THROMBOSIS**

- *Thrombosis may occur with immune globulin products, including Anthrasil. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.*
- *For patients at risk of thrombosis, administer Anthrasil at the minimum infusion rate practicable. Ensure adequate hydration in patients before administration.*
- *Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.*

**Sponsor Response:**

*The suggested language has been added to the boxed warning in both HIGHLIGHTS and the Full Prescribing Information (FPI). In addition, "... AND THROMBOSIS" was added to the black box title and the second and third bullets were merged. Reference to the black box warning was added in [2.5 Clinical Overview](#).*

**Reviewer Comment: Noted.**

*7. Replace the second bullet under WARNINGS AND PRECAUTIONS in the HIGHLIGHTS section with the bulleted statement "Thrombosis may occur following treatment with immune globulin products including Anthrasil. (5.3)" Change the fourth bullet to read "Acute intravascular hemolysis may occur. Monitor for clinical signs and symptoms of hemolysis and hemolytic anemia. (5.5)" Move the fifth bullet down to be the next-to-the-last bullet in this section. Move the eighth bullet down to be the last bullet in this section.*

**Sponsor Response:**

*The bullet for thrombosis under WARNINGS AND PRECAUTIONS in the HIGHLIGHTS section was removed as it is already included in the black box warning. As hemolysis in general, and not specifically intravascular hemolysis, is a class warning, the fourth bullet has been revised to read:*

*Hemolysis can occur subsequent to immune globulin intravenous therapy. Monitor for clinical signs and symptoms of hemolysis and hemolytic anemia (5.5).*

*This wording is consistent with other intravenous immune globulin products.*

*In addition, the sections for Transfusion-related Acute Lung Injury (TRALI) and Transmission of Infectious Agents from Human Plasma in the FPI were moved below Interference with Laboratory Testing and renumbered appropriately for consistency with the revised order in the HIGHLIGHTS section.*

**Reviewer Comment: Noted.**

**3 HIGHLIGHTS (AND, FOR SOME ITEMS, ALSO FULL PRESCRIBER INFORMATION)**

*8. Please change the first paragraph of the INDICATIONS AND USAGE sections in HIGHLIGHTS and the full prescribing information (FPI) to read:  
ANTHRASIL is an Anthrax Immune Globulin Intravenous (Human) indicated for the treatment of toxemia associated with inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs.*

**Sponsor Response:**

*The first paragraph of the INDICATIONS AND USAGE section in both the HIGHLIGHTS and FPI has been revised and [2.2 Introduction](#) has been updated accordingly.*

**Reviewer Comment: Noted.**

*9. Following the second paragraph in the INDICATIONS AND USAGE sections in HIGHLIGHTS and the FPI please add the following statement:*

*Although survival in rabbits and monkeys with inhalational anthrax was greatest among animals that received AIGIV plus antibiotic therapy, a statistically significant independent contribution to efficacy (survival) of ANTHRASIL above and beyond that conferred by appropriate antibiotic therapy was not demonstrated in animal efficacy trials (13.2). Although the efficacy of ANTHRASIL monotherapy was demonstrated with animal treatment models of inhalational anthrax, ANTHRASIL should be administered in combination with appropriate antibiotic therapy.*

**Sponsor Response:**

*As per the FDA request to condense the HIGHLIGHTS section (Question 5), the wording as suggested by FDA was only added to the second paragraph of INDICATIONS AND USAGE in the FPI. Minor changes including changing “Although” to “While”, “monkeys” to “cynomolgus macaques” and addition of “... , indicating a potential for added benefit with ANTHRASIL (1)” with a literature reference by [Kammanadiminti et al. \(2014\)](#) were incorporated. In addition, the following statement was added within the second paragraph of Monotherapeutic Studies in Animal Models under 13.2 Animal Toxicology and/or Pharmacology:  
There was no significant difference between the survival rates observed for 30 U and 15 Units per kg dose groups.*

**Reviewer Comment:** Noted and accepted. [The statement, “There was no significant difference between the survival rates observed for 30 U and 15 Units per kg dose groups” was later deleted at FDA request, as it was redundant with the statement that the differences in survival between the three active dosage groups were not statistically significant.]

**10. Please delete the first sentence in the third paragraph under the INDICATIONS AND USAGE sections in HIGHLIGHTS. Please move the second sentence in the third paragraph in the INDICATIONS AND USAGE sections in HIGHLIGHTS to the DOSAGE AND ADMINISTRATION section and change it to read “Pediatric dosing was derived using from allometric scaling. Please add this modified sentence to the beginning of the fourth bullet in to the DOSAGE AND ADMINISTRATION section of the FPI. Please add the statement “There have been no studies of ANTHRASIL in the pediatric, geriatric, or obese populations to the INDICATIONS AND USAGE section in the FPI. Please add the following statement to the DOSAGE AND ADMINISTRATION section in HIGHLIGHTS: “See section 2.1 for considerations regarding repeat dosing.”**

**Sponsor Response:**

*The requested changes to the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections in HIGHLIGHTS and the FPI were completed. In addition, the statement above 2.2 Preparation was revised from “pharmacokinetic simulations” to “allometric scaling”:*

*The pediatric dosing in Table 2 is derived from allometric scaling based on observed adult exposure to ANTHRASIL at 420 Units by TNA dose.*

**Reviewer Comment:** Noted. However the statement regarding pediatric dosing in Table 2 was changed to reflect scaling from both the 420 unit and 840 unit adult doses, given that a dosage range for the initial dose is recommended for both adults and pediatric patients.

**11. In the boxed warning in the HIGHLIGHTS and FPI sections, please spell out IGIV as Immune Globulin Intravenous (Human).**

**Sponsor Response:**

*In the boxed warning (HIGHLIGHTS AND FPI) as well as throughout the FPI, IGIV has been spelled out as Immune Globulin Intravenous (Human).*

**12. In the DOSAGE AND ADMINISTRATION sections of HIGHLIGHTS, please state the adult dosage range and indicate that the dose in pediatric patients under age 13 (corresponding to a body weight of approximately 60 kg or less) is determined by body weight.**

**Sponsor Response:**

*In the DOSAGE AND ADMINISTRATION sections of HIGHLIGHTS, the adult dose of seven vials has been included and a statement about dosing for pediatric patients  $\leq 16$  years has been added. The proposed dose is 420 Units rather than a range; please refer to the response for Question 16 for justification. The pediatric age range of patients  $\leq 16$  years is based on the Draft Guidance for Industry and Review Staff Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling (February 2013), which states that “adolescents are 12 years to younger than 17 years” and is consistent with the request in Question 13 below.*

**Reviewer Comment: Noted. However the initial adult dose is expressed as a range from 7 to 14 vials (420 to 840 units), depending on clinical severity.**

***13. In the dosing table showing infusion rates in the DOSAGE AND ADMINISTRATION sections of HIGHLIGHTS and the FPI, please change the Dose column entries to 7-14 vials for adults and 1-14 vials for Pediatric <1 year to  $\leq 16$  years, and correct the fourth column to reflect for pediatric subjects incremental infusion rates if tolerated of 0.02 mL/kg/min. Eliminate the separate row for pediatric subjects <1 year.***

***Sponsor Response:***

*As stated in the response to Question 12 above, the proposed dose is 420 Units rather than a range; refer to the response for Question 16 below for the rationale. The pediatric age range has been modified to <1 year to  $\leq 16$  years for consistency with the Draft Guidance for Industry and Review Staff Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling (February 2013). As requested, the incremental infusion rate has been modified to 0.02 mL/kg/min and the separate row for pediatric patients <1 year has been removed.*

*The corresponding changes were incorporated in [2.5 Clinical Overview](#).*

**Reviewer Comment: Response unacceptable. The initial adult dose is expressed as a range from 7 to 14 vials (420 to 840 units), depending on clinical severity. The pediatric doses, by weight ranges, subsequently were modified at FDA request to reflect scaling from the two extremes of the adult dosage range.**

***14. In the CONTRAINDICATIONS section in HIGHLIGHTS, please revise the first bullet to include the word “immune” before globulins.***

***Sponsor Response:***

*In the CONTRAINDICATIONS section in HIGHLIGHTS, the first bullet was revised to include the word “immune” before globulins.*

***15. In the USE IN SPECIFIC POPULATIONS section in HIGHLIGHTS, change the last bullet to read “Pediatric dosing is based on allometric scaling.”***

***Sponsor Response:***

*In the USE IN SPECIFIC POPULATIONS section in HIGHLIGHTS, the last bullet was changed as suggested.*

**4 FULL PRESCRIBER INFORMATION (FPI)**

***16. In the Full Prescriber Information please change the recommended dose for adults from 420 U to the following language:***

***The minimum dose of ANTHRASIL for the treatment of inhalational anthrax in adults in combination with appropriate antimicrobial therapy is 420 U (7 vials). Animal data suggest that administration of the human equivalent of approximately 840 U (14 vials) may result in improved survival. It may be necessary to take into account the condition of the patient and/or availability of the product in relation to the size of the inhalational anthrax outbreak in determining the appropriate initial dose from a public health perspective.***

***Sponsor Response:***

*Cangene has revised the FPI for the recommended adult dose to the following language:*

*The initial dose of ANTHRASIL for the treatment of inhalational anthrax in adults in combination with appropriate antimicrobial therapy is 420 Units (seven vials). In animal studies, doses equivalent to 420 Units were efficacious (survival) when ANTHRASIL was used as a monotherapy. Data suggests that administration of higher doses may result in improved survival [see 13.2 Animal Toxicology and/or Pharmacology]. As a result, higher doses may be considered based upon the clinical scenario and baseline symptomatology as well as the patient's response to the initial dose. A second dose of 420 Units (seven vials) may be necessary for a total dose of 840 Units (14 vials).*

*The data from animal monotherapy and combination studies indicate that the human equivalent dose of 420 Units rapidly neutralizes the protective antigen (PA) toxin, while anti-PA data from three inhalational anthrax patients treated with 420 Units dose (in combination with antibiotics) suggest that anti-PA levels are maintained for five days after administration. Therefore, the initial dose is proposed at 420 Units (seven vials).*

*As repeat dosing is a consideration based on the patient's clinical condition, Cangene proposes a second dose of 420 Units (seven vials) for a total dose of 840 Units (14 vials). As Cangene does not have safety data for doses that exceed 840 Units, the initial and repeat dose(s) are proposed at 420 Units (for a total dose of 840 Units or 14 vials) to be in line with the existing safety data as well as for ease of determining the dosing by the treating physician.*

*It should be noted that the survival benefit observed with a higher dosage of AIGIV in the cynomolgus macaque monotherapy study was not statistically different from the 15 U/kg dose. In addition, the benefit of higher doses in combination with antibiotics could not be assessed due to*

*limitations in conducting combination studies in cynomolgus macaques and rabbit specific dose-limiting toxicity in New Zealand white rabbits.*

**Reviewer Comment:** Response unacceptable. The language was further modified based on FDA request to read:

**The minimum initial dose of ANTHRASIL for the treatment of inhalational anthrax in adults in combination with appropriate antimicrobial therapy is 420 units (seven vials). Data in animal models suggest that administration of higher doses may result in improved survival. An initial dose higher than 420 units (up to 840 units or 14 vials) may be considered, depending on the clinical status of the patient.**

**It was decided not to state in the PI that the decision regarding initial dose may take into account the size of the anthrax outbreak in relation to availability of the product. Depending on one's assumptions and interpretation of the animal efficacy model data, it is possible that overall survival could be greater using the 840 unit dose for all patients even under conditions where availability was limiting, but this cannot be predicted with certainty.**

***17. Change the fifth bullet under DOSAGE AND ADMINISTRATION to read as follows: 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.***

***Sponsor Response:***

The bullet for repeat dosing under DOSAGE AND ADMINISTRATION was changed to read as indicated above and the information was added to [2.5 Clinical Overview](#).

**Reviewer Comment:** Noted.

***18. Consider adding the following statement to the DOSAGE AND ADMINISTRATION section:***

***The patient's clinical status and, where available, results of testing for serum/pleural/peritoneal levels of anti-protective antigen and of anthrax lethal factor following dosing with ANTHRASIL may be taken into account in evaluating the adequacy of dosing.***

***Sponsor Response:***

*At this time, Cangene cannot commit to this statement as there may be considerable variation in assays for testing of anti-PA antigen and toxin levels as they are without*



standardization. Monitoring the patient's clinical status and, when available through postmarketing commitment study results for anti-PA and anthrax toxins, may allow evaluation of dose and advisement on re-dosing. Cangene will attempt to collect this information in the post-marketing commitment study based on the feasibility of standard assays and sample availability for testing of anti-PA and toxin levels.

**Reviewer Comment: Noted and accepted. Inclusion of this recommendation in the PI should be reconsidered after review of data from the clinical PMR, AX-003A and/or AX-003B.**

**19. Please modify your dosing algorithm for pediatric patients as follows:**

**Table 2 Pediatric Dosing Guide for ANTHRASIL<sup>1</sup>:**

Body wt (kg)	Number of ANTHRASIL Vials <sup>2</sup>
<5	1
5-<10	1 - 2
10-<18	2 - 4
18-<25	3 - 6
25-<35	4 - 8
35-<50	5 - 10
50-<60	6 - 12
≥60	7 - 14

1 The pediatric dosing in Table 2 is derived from allometric scaling based on observed adult exposure to

ANTHRASIL at 420 or 840 Units by TNA dose.

2The lower number in each range is based on a 420 unit adult dose and the higher number is based on an 840 unit adult dose.

***Sponsor Response:***

*The table has been modified to the following:*

**Table 2 Pediatric Dosing Guide for ANTHRASIL<sup>a</sup>**

Body Weight (kg)	Number of ANTHRASIL Vials per Dose <sup>b</sup>
<10	1
10 to <18	2
18 to <25	3
25 to <35	4
35 to <50	5

50 to <60	6
≥60	7

a The pediatric dosing is derived from allometric scaling based on observed adult exposure to ANTHRASIL at 420 Units by TNA dose.

b Initial dose and repeat dose (if necessary, based on patient's condition after administration of initial dose).

*Rather than providing a range of doses to health care providers, the dosing schedule for pediatric patients is now the same as the adult dosing schedule with the initial dose*

*(scaled by body weight; one to seven vials) and the repeat dose (if necessary) that would be the same as the initial dose (one to seven vials), for a total dose that can range from two to 14 vials, depending on the body weight (see response to Question 16 for adult dosing). The pediatric dosing table in [2.5 Clinical Overview](#), [Human Dose Justification](#) and [Pharmacovigilance Plan](#) has been revised accordingly.*

**Reviewer Comment:** The sponsor's counterproposal to have a single fixed initial dose rather than a range is unacceptable. Depending on the clinical condition of the patient, the higher range of the FDA-requested dosage range may be appropriate, such as in patients with fulminant inhalational anthrax who may not survive if the initial dose is insufficient. [The sponsor subsequently accepted the FDA proposal for an initial adult dose range from 420 to 840 units, depending on the clinical severity. A range of pediatric doses by weight class was scaled accordingly.]

*Please correct the exposure to protein in pediatric patients in section 5.4 accordingly.*

**Sponsor Response:**

*Correct protein exposure in pediatric patients has been verified based on each allometric scaled dose equivalent to the adult dose of 420 U. Assuming a maximum fill volume of (b) (4), a maximum ANTHRASIL protein level of 70 mg/mL and a minimum pediatric body weight of 2.5 kg, the protein exposure per dose in pediatric patients is 0.32 to 1.26 g per kg of body weight as presented in section 5.4 Aseptic Meningitis Syndrome (AMS).*

**Reviewer Comment:** Per management recommendation, the protein content for the range of adult and pediatric doses was subsequently moved to section 11 DESCRIPTION of the PI.

**20. Under DRUG INTERACTIONS in HIGHLIGHTS, change the first bullet to read "Based on animal studies, ANTHRASIL did not interfere with therapy with the antibiotics levofloxacin or ciprofloxacin."**

**Sponsor Response:**

*Under DRUG INTERACTIONS in HIGHLIGHTS, the first bullet was changed to read:*

*Based on animal studies, ANTHRASIL did not interfere with the antibiotics levofloxacin or ciprofloxacin.*

*In addition, the third bullet (“Antibodies in ANTHRASIL may interfere with some serological tests”) was removed. In the Prescribing Information submitted in eCTD sequence 0007, section 7.3 Drug/Laboratory Interactions was moved to 5.11 Interference with Laboratory Testing but the associated bullet in the HIGHLIGHTS was inadvertently not removed.*

**Reviewer Comment: Noted.**

**21. Change the last bullet in HIGHLIGHTS under WARNINGS AND PRECAUTIONS to read “Interference with blood and urine glucose testing (5.11).”**

**Sponsor Response:**

The bullet for *Interference with laboratory testing* under WARNINGS AND PRECAUTIONS in HIGHLIGHTS was revised as recommended. Note that based on the edits for Question 7 this is now the third last bullet within the section.

**Reviewer Comment: Noted.**

**22. Please change the statement in section 2.2 Preparation to read “Once punctured, the thawed vials should be used to prepare the infusion bag within 6 hours.”**

**Sponsor Response:**

*“Once punctured” was removed and the bullet was moved from the last position to the first position of item 5 within section 2.2 Preparation for clarity. The 48 hour stability is based on compatibility studies as discussed in [3.2.P.2 Pharmaceutical Development, Compatibility](#) where it was concluded that AIGIV was stable in infusion bags after 48 hours at room temperature, which exceeds the normal clinical thaw/infusion time period. This statement is also consistent with section 16.2 Storage and Handling of the Prescribing Information where it states that “It is recommended to use ANTHRASIL within 48 hours of thawing.”*

**Reviewer Comment: Response unacceptable. The statement was subsequently changed at FDA request to read:**

**“Once punctured, use the vial contents to prepare the infusion bag and administer as soon as possible. ANTHRASIL contains no preservative.”**

**FDA concluded that the submitted data did not support lack of the possibility of microbial growth 48 hours following puncturing of the vials.**

**23. Change the first sentence in section 5.1 Hypersensitivity Reactions to read “Acute systemic allergic reactions were not seen in the clinical trial with ANTHRASIL”.**

**Sponsor Response:**

*The FDA proposed edits to the first sentence have been accepted. For consistency with other immune globulin intravenous class warnings, the IgA specific hypersensitivity statement has been revised and moved to the end the section.*

*In addition, “acute hypersensitivity” was revised to “anaphylactic” in the last statement of the third paragraph in section 5.1 Hypersensitivity Reactions so the sentence reads: Medications such as epinephrine should be available for immediate treatment of anaphylactic reactions.*

**Reviewer Comment: Noted and accepted.**

**24. In section 5.2 Interference with Blood Glucose Testing, change the second sentence to read “Maltose in ANTHRASIL and in Immune Globulin Intravenous (Human) products has been shown...”**

**Sponsor Response:**

*The requested changes were made to the second statement within section 5.2 Interference with Blood Glucose Testing.*

**25. In section 5.4 Aseptic Meningitis Syndrome (AMS), move the 2nd and 3rd sentences in the third paragraph to the top of section 5.2 and change them to read “For ANTHRASIL at the recommended adult dosages of 420 Units (seven vials) and 840 U (14 vials), an adult patient may be exposed to up to 0.368 g or 0.736 g protein per kg body weight, respectively. Exposure to protein in pediatric patients due to ANTHRASIL administration may range from 0.378 g per kg to 2.0 g per kg, depending on the pediatric dose (for body weight-dependent pediatric dosing; see Table 2 in 2.1 Dosage and Administration).” Precede these sentences at the top of section 5.2 with the statement, “The incidence and/or severity of some adverse reactions to ANTHRASIL and other Immune Globulin Intravenous (Human) products may be related to the total protein/polyclonal antibody load administered.”**

**Sponsor Response:**

*The requested changes have been reviewed and revised as follows to reflect the proposed initial dose of 420 U (seven vials) with repeat dosing up to 840 U (14 vials) as indicated in response to Question 16.*

*For each recommended adult dosage of 420 Units (seven vials) of ANTHRASIL, an adult patient may be exposed up to 0.368 g protein per kg body weight. Exposure to protein in pediatric patients due to ANTHRASIL administration may range from 0.32 g per kg to 1.26 g per kg, depending on the pediatric dose (for body weight dependent pediatric dosing, see Table 2 in 2.1 Dosage and Administration).*

*In addition, the information was moved to the top of section 5.4 Aseptic Meningitis Syndrome (AMS) rather than section 5.2 Interference with Blood Glucose Testing as suggested.*

**Reviewer Comment:** The sponsor revised this language to include the adult and maximum pediatric protein loads corresponding to the 840 unit adult dose. This information was moved to section 11 DESCRIPTION.

**26. In section 5.5 Hemolysis, change the second sentence in the third paragraph to read “Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours, and again approximately 7-10 days post infusion.”**

***Sponsor Response:***

*The addition of “..., and again approximately seven to 10 days post infusion” was accepted in section 5.5 Hemolysis and the [Pharmacovigilance Plan](#) was updated accordingly.*

**27. In section 6 ADVERSE REACTIONS, change the second sentence to read “This includes those adverse events (AEs) with an incidence of 5% or greater which were dose-dependent, and/or considered related by the Clinical Investigator, and/or which demonstrated a temporal relationship (within 72 hours of ANTHRASIL administration).” Please provide the data listing and SAS code for identifying the most common adverse reactions as defined above and as included in Table 3 in section 6.1. What criteria were applied to determine if AEs were dose-dependent?**

***Sponsor Response:***

*The revision for section 6 ADVERSE REACTIONS has been accepted although “incidence of 5% or greater” was changed to “incidence of greater than 5%” for consistency with Table 3 in section 6.1 Clinical Trials Experience. The data listings package for identifying the most common adverse reactions is provided (5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports), which includes adverse events, infusion log, adverse reactions confirmed by the Principal Investigator and the temporal related adverse events. The corresponding SAS codes to identify the adverse reactions and the temporal adverse events are provided, together with the SAS code for generating Table 3 in the Prescribing Information.*

*The criteria applied to determine dose dependency is discussed in detail in response to Question 28D below, and an updated Table 3 is provided in response to Question 28E.*

**Reviewer Comment:** At FDA management request, the operational definition of adverse reaction was removed from the PI.

**28. In section 6.1 Clinical Trials experience:**

**A. Change the first sentence in the fifth paragraph of section 6.1 to read “No serious adverse reactions were reported during the clinical study. Change the second sentence in this paragraph to read “Infusion of ANTHRASIL was stopped for four subjects due to adverse reactions (ARs). Change the next sentence to read “One**

***subject was withdrawn due to an AR consisting of chest discomfort, flushing, tachycardia, throat tightness, and headache.”***

***Sponsor Response:***

*The suggested changes have been accepted with the following exception. Subject (b) (6) withdrew due to an AR consisting of chest discomfort, flushing, tachycardia and throat tightness. The headache in this subject occurred 21 days after the ANTHRASIL infusion was stopped. This adverse event was not a reason for withdrawal, nor was it temporally related or deemed related to ANTHRASIL by the Principal Investigator. As a result, headache has been deleted from the suggested revisions.*

**Reviewer Comment: Noted and accepted.**

***B. Replace the adverse drug reaction (ADR) with adverse reaction (AR).***

***Sponsor Response:***

*Adverse drug reaction (ADR) has been replaced with adverse reaction (AR) throughout section 6.1 Clinical Trials Experience.*

***C. Strike the sentence in the 7th paragraph which begins “This includes all dose dependent AEs...”***

***Sponsor Response:***

*The statement noted above has been removed.*

***D. Change the first sentence in the 8th paragraph to read “Headache, pain (including back pain and pharyngolaryngeal pain), and cough were reported in a dose-dependent fashion. In addition, nasal congestion, rhinorrhea, and neck pain occurred more frequently with higher doses of ANTHRASIL.” Please clarify the criteria used to determine these two categories of [possibly] dose-related ARs.***

***Sponsor Response:***

*To determine if a dose-dependent relationship exists between AE onset and AIGIV administration, the frequency of events reported in the AX-001 clinical trial was compared across all treatment groups (placebo and AIGIV dosing groups). The clinical study report includes an analysis of the incidence of AEs between the dose groups, which could be considered as a dose trending statistical analysis. Generalized Fisher’s exact test was used to determine if the number of subjects who experienced a particular event in each treatment group was statistically different across the groups. If a difference was determined to be statistically significant, then multiple comparison methods were used among the individual dose groups. The analysis results showed that the only significant different AE across dose groups was infusion site pain.*

*However, the significant difference was due to the high incidence of AEs (four subjects with 22.2% incidence) in the 210 Unit dose group. Further analysis of multiple comparisons illustrated that no significant differences between individual groups were observed. Therefore, infusion site pain was not a dose dependent AE. No other incidence rates differed significantly, with the exception of headaches, which showed a trend toward significance. Headaches were common across the AIGIV groups, especially the 420 Unit group (50% subjects) and 840 Unit blinded group (44% of subjects).*

*As there was no significant change revealed during the statistical analysis between incidence of AEs in different dosing groups, AEs were qualitatively examined for dose dependent trends by reviewing the AE tables by treatment group. The criterion that was used to identify a possible dose dependent relationship was increased frequency of an AE with increasing dosage of the product. The determination of the dose dependent relationship was based on the data from all 74 subjects that received AIGIV compared to placebo. Isolated adverse events occurring in any one group were not considered.*

*Two AEs that exhibited dose dependent relationship are headaches and back pain. A review of all reported AEs across treatment groups revealed that headaches were more frequently reported at AIGIV doses of 420 Units and higher. As mentioned above in the statistical analysis, there were 45 instances of headache reported by 28 subjects (37.8%) who received AIGIV at doses of 210 U, 420 U or 840 U, compared to five events of headache reported by three subjects (16.7%) from the placebo group. The dose dependent increase in the number of headaches reported by AIGIV treated subjects is observed at dosages of 420 U and 840 U. Nine subjects (50%) from 420 Unit group reported nine headaches and eight subjects (44%) from the 840 U blinded group reported 19 headaches whereas eight subjects (40%) from the 840 U open label group reported 12. Five headaches were reported by three subjects from 210 U AIGIV group and the same number of headaches was reported by three subjects from the placebo group).*

*Back pain was reported more frequently in subjects who received 840 U AIGIV dose (10.5% of subjects) when compared to subjects who received AIGIV at 210 U or 420 U dose (0% of subjects). There were seven AEs of back pain reported by six subjects in the AX-001 study including one back pain reported by a subject from a placebo group. The six remaining AEs of back pain were reported by subjects from the 840 U group (two AEs in blinded and four in open label group) indicating dose dependent relationship to the occurrence of back pain.*

*In addition, when criteria for examining dose dependent AEs was applied to all AEs occurring in the AX-001 study by treatment group, the following AEs were identified with a potential dose dependent relationship: pain, neck pain, pharyngolaryngeal pain, cough, nasal congestion, Rhinorrhea, urticaria and pruritus. A conclusive relationship for dose dependency of these AEs could not be determined. We have further reexamined this list and taken into consideration the Principal Investigator assessment and temporal relationship to AIGIV administration. We also examined the incidence in the higher dose groups (420 Units and/or 840 Units) compared to either the placebo or 210 Unit dose group, to determine dose dependency.*

*While pain, neck pain, pharyngolaryngeal pain, cough, nasal congestion and Rhinorrhea showed a potential trend towards higher incidence in higher dose groups, when investigator assessment (ARs) and temporal relationship were examined, these AEs do not appear to be dose dependent. As a result, we do not consider these AEs as dose dependent.*

*Urticaria and pruritis occurred in only one subject in the 420 Unit group, with five instances of each AE in this subject. Because these events were not reported in any other subjects (even at higher dose) a dose relationship could not be confirmed.*

*Events of low frequency (i.e. two events or fewer) were not considered as having a dose dependency even if only observed at the 840 U high dose group. This would exclude AEs of:*

- Oral herpes occurred in two subjects who both received 840 U (one in blinded cohort and the other in the open-label cohort); incidence of 2/38 or 5.3% of the 840 U dose. Both were deemed unrelated by the Principal Investigator and both occurred >72 hours after administration.*
- Haematuria occurred in two subjects who both received 840 U in the blinded cohort. One case was deemed unrelated due to menses and both cases occurred within 72 hours of administration.*
- Erythema occurred in two subjects who both received 840 U in the blinded cohort. Both cases occurred within 72 hours of administration; however, one was deemed related and the other unrelated due to heating pad use.*
- All other AEs that occurred in only one subject in the 840 U groups.*

*We have revised the AE table (response to Question 28E) to include only those ARs that occurred in >5% of subjects, and in addition, we have elevated back pain to be included in this table as there was a potential dose dependency. Of note, these higher frequency ARs were also temporally related to AIGIV administration. The first statement in 6 ADVERSE REACTIONS and the HIGHLIGHTS sections has been revised to read:*

*The most common adverse reactions to ANTHRASIL observed in >5% of subjects in the healthy volunteer clinical trial [see 14.1 Safety and Pharmacokinetics of ANTHRASIL in Healthy Volunteers] were headache, infusion site pain, nausea, infusion site swelling and back pain.*

*The side effects in the PATIENT INFORMATION were updated accordingly.*

*The statement regarding dose dependency has been revised to the following:*

*Headache and back pain were reported in a dose dependent fashion.*

*The dose-related AR information has been updated in the following supportive documents:*

- 2.5 Clinical Overview*
- 2.7.4 Summary of Clinical Safety*
- Pharmacovigilance Plan*
- Human Dose Justification*

**Reviewer Comment: Noted and accepted. I concur with the sponsor's reasoning regarding the analysis of potentially dose-related adverse reactions.**



***E. Please redesign Table 3 to provide the numbers of subjects and events which occurred in the placebo group for the corresponding rows. Limit the data for the active subjects to the randomized, double-blind portion of the study. Include a narrative or separate tabular listing of the cumulative incidence by subject and event type for common ARs using all 74 subjects exposed to AIGIV for only those additional ARs not included in Table 3. Change the title of Table 3 to read “Adverse Reactions Observed in >5% of Subjects Administered ANTHRASIL or Placebo in Healthy Volunteer Clinical Trial.” Please note that healthy volunteers were not “treated” with ANTHRASIL because they did not have anthrax.***

***Sponsor Response:***

*Table 3 has been redesigned to include data from the randomized, double blind portion of the study. When examining differences between the AIGIV groups in the blinded portion (n=54) and the total AIGIV population (n=74), there is not an obvious difference in the frequency of ARs with the exception of back pain, which is dose dependent and discussed in response to Question 28D above. As a result, we have added a footnote regarding back pain but have not included a separate table for the overall population of n=74. The table title has been changed as requested.*

**Table 3 Adverse Reactions Observed in >5% of Subjects Administered ANTHRASIL or Placebo in a Healthy Volunteer Clinical Trial**

**H**

System Organ Class	Preferred Term	AIGIV Blinded Randomized Group (N=54)			Placebo (N=18)		
		No. of Events	No. of Subjects	% of Subjects	No. of Events	No. of Subjects	% of Subjects
Gastrointestinal disorders	Nausea	5	5	9.3	2	1	5.6
General disorders and administration site reactions	Infusion site	7	5	9.3	0	0	0.0
	Infusion site swelling	5	4	7.4	0	0	0.0
System Organ Class	Preferred Term	AIGIV Blinded Randomized Group (N=54)			Placebo (N=18)		
		No. of Events	No. of Subjects	% of Subjects	No. of Events	No. of Subjects	% of Subjects
Musculoskeletal and connective tissue disorders	Back pain <sup>a</sup>	2	2	3.7	1	1	5.6
Nervous system	Headache	15	11	20.4	3	1	5.6

Adverse Events are classified according to MedDRA Version 10.0

a Back pain is included as there was an increase in incidence observed at the 840 Unit dose group including the open label group receiving 840 Units (n=20). Back pain occurred in two out of 54 (3.7%) subjects in the randomized portion of the clinical trial; however, this event occurred

in additional three subjects who received 840 U ANTHRASIL dose from the open label portion of the clinical trial. Overall, five out of 74 subjects (6.8%) receiving ANTHRASIL experienced back pain.

The updated table was included in the following supportive documents:

- [2.5 Clinical Overview](#)
- [2.7.4 Summary of Clinical Safety](#)
- [Pharmacovigilance Plan](#)
- [Human Dose Justification](#)

**Reviewer Comment:** Noted and accepted.

*F. Change the last sentence to read “In addition to the reported ARs, dose-related elevations in urine glucose were noted transiently following dosing [see 5.11 Elevated Glucose in Urine].*

**Sponsor Response:**

*The last sentence in section 6.1 Clinical Trials Experience was revised. Note that the reference was changed to 5.9 Interference with Laboratory Testing as a result of the reorganization of WARNINGS AND PRECAUTIONS in response to Question 7 and removal of subheadings in response to Question 3.*

**Reviewer Comment:** Noted.

*29. Change the last sentence in subsection 7.1 Ciprofloxacin and Levofloxacin to read “Concomitant administration of ANTHRASIL with levofloxacin or ciprofloxacin in exposed rabbits and cynomolgus macaques, respectively, did not reduce the efficacy of antibacterial therapy.”*

**Sponsor Response:**

*The last sentence in subsection 7.1 Ciprofloxacin and Levofloxacin was changed as requested.*

*30. Change subsection 8.4 Pediatric Use to read as follows:*

*Safety and effectiveness of ANTHRASIL in the pediatric population (<16 yrs of age) have not been studied. Allometric scaling was used to derive dosing regimens to provide pediatric patients with exposure comparable to the observed exposure in adults receiving 420 to 840 Units. The dose for pediatric patients is based on body weight.*

**Sponsor Response:**

*The changes to section 8.4 Pediatric Use were completed with the following exceptions. Based on the Draft Guidance for Industry and Review Staff Pediatric Information*

*Incorporated into Human Prescription Drug and Biological Products Labeling (February 2013), the pediatric age was revised from <17 yrs of age to ≤16 yrs of age throughout the HIGHLIGHTS and FPI. Since the proposed dose is 420 Units (see response to Question 16), 840 Units was excluded. Section 2.7.4 Summary of Clinical Safety was also updated to reflect the change in age range and additional information.*

**Reviewer Comment: Noted. However the inclusion of the pediatric dose scaling from the 840 unit adult dose was subsequently included per FDA request.**

**31. Change subsection 8.5 Geriatric Use to read as follows:**  
*Safety and effectiveness of ANTHRASIL in the geriatric population (>65 yrs of age) have not been studied. No safety data are available in elderly patients from either the AX-001 healthy volunteer study or from the compassionate use of AIGIV in patients with systemic anthrax.*

**Sponsor Response:**

The changes to section 8.5 Geriatric Use were completed.

**32. Change subsection 8.7 Use in Obese Population to read as follows:**  
*Safety and effectiveness of ANTHRASIL in the obese population have not been studied. Although empirically-based guidance for dosing for Immune Globulin Intravenous (Human) in morbidly obese patients has been reported in the medical literature, pharmacokinetic data for ANTHRASIL or IGIV in obese patients are lacking.*

**Sponsor Response:**

The changes to section 8.7 Use in Obese Population were completed and information regarding the obese population was added to 2.7.4 Summary of Clinical Safety and the [Pharmacovigilance Plan](#).

**Reviewer Comment: Noted. However, per management request, the statement about empirically-based guidance from the literature regarding dosing of IGIV in obese patients was subsequently removed.**

**33. Add the following statement to section 12.1 Mechanism of Action:**  
*ANTHRASIL is administered in combination with appropriate antibiotic therapy as the product by itself is not known to have bactericidal activity against anthrax bacteria which otherwise may continue to grow and produce anthrax toxins.*

**Sponsor Response:**

The statement was added to section 12.1 Mechanism of Action in the Prescribing Information and [3.2.S.1.3 General Properties](#), [2.2 Introduction](#) and [2.3.S.1 General Information](#) have been updated accordingly.

**Reviewer Comment: Noted.**

**34. In section 12.3 Pharmacokinetics:**

**A. In Table 5, delete AUC(0-7d) and provide all PK parameters as arithmetic means with the exception of Tmax.**

***Sponsor Response:***

Table 5 within section 12.3 Pharmacokinetics and the associated Table 28 in 2.7.2 Summary of Clinical Pharmacology Studies were revised.

B. Insert a new paragraph under Table 5 which reads “It is expected that the clearance of anti-PA antibodies from ANTHRASIL administration will be greater and the AUC will be lower in patients with inhalational anthrax compared to healthy subjects.”

***Sponsor Response:***

*We agree with the nature of the proposed statement, and have revised it as follows: In comparison to healthy subjects, patients with inhalational anthrax are expected to initially have greater clearance of anti-PA antibodies and lower AUC from ANTHRASIL administration due to the presence of PA antigen.*

*The pharmacokinetic differences of AIGIV between affected and healthy animals were examined. In rabbits, in both monotherapy and combination therapy studied, Cmax and AUC0-7 were lower than in healthy animals. In non-human primates, similar conclusions could not be reached, perhaps due to limitations in study design or due to development of anti-PA with innate immunity. In surviving animals, anti-PA levels increased or remained steady over time. [emphasis added]*

**Reviewer Comment: Noted. Increased rate of protein catabolism in sepsis would also be expected to raise clearance values in individuals with systemic anthrax. While IgG levels have been well-documented in the literature to be low in sepsis, I am not aware of IgG clearance studies in sepsis.**

***C. Change the next paragraph to read as follows:***

***Mean PK results (TNA data) were evaluated by sex and revealed no sex-related differences over the dose range studies. Systemic exposure of ANTHRASIL increased in a dose-proportional manner over the dose range studied. ANTHRASIL has a serum elimination half-life of 24 to 28 days in humans.***

***Sponsor Response:***

The paragraph was revised as indicated by FDA.

**D. Change the next paragraph to read as follows:**

*In compassionate use/ expanded access programs [see 14.2 Compassionate Use/Expanded Access Program], inhalational anthrax patients concomitantly treated with antibiotics and a single ANTHRASIL dose of 420 Units TNA 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. The peak anti-PA levels in these patients following ANTHRASIL administration (132 to 160 mcg/mL, mean 145 mcg/mL) overlapped with those obtained with the 420 Units ANTHRASIL dose in healthy volunteers (135 to 250 mcg/mL, median 192 mcg/mL), although mean levels were approximately 25% lower in the inhalational anthrax patients. In the three inhalational anthrax patients, serum and pleural levels of lethal factor declined after initiation of antibiotics and further decreased over the period of five days following ANTHRASIL administration. Unlike the situation in the animal treatment model studies, plasma levels of lethal factor remained detectable 1 to 2 days following ANTHRASIL administration, despite their decline.*

**Sponsor Response:**

*The suggested edits have been accepted with the following exceptions. The opening statement was revised to “In expanded access patient experience [see 14.2 Patient Experience (Expanded Access)], ...” for consistency with the response to Question 42, and the final sentence was excluded. It should be clarified that PA levels were measured in animal studies but lethal factor was not measured. In the CDC expanded access patient experience, lethal factor, anti-PA and TNA were measured but not PA. The anti-PA in ANTHRASIL is measured as a component of release testing, as is the corresponding potency in toxin neutralization activity units. **While ANTHRASIL contains antibodies to other antigens present in BioThrax®, including lethal factor, these antibodies are not measured as part of the product release. It is unknown whether ANTHRASIL contains sufficient levels of antibodies to lethal factor to fully neutralize this toxin component in either animals or patients. [emphasis added]** Due to the presence of anti-PA in ANTHRASIL, PA neutralization was observed post dosing in animal studies. While in animal studies lethal factor was not measured, it can be hypothesized that lethal factor may remain in circulation until it has decayed or until the anthrax infection has cleared. Cangene does not have sufficient data to compare the observations made in patients for lethal factor to animal studies. The mechanism of action of ANTHRASIL is such that neutralization of protective antigen will prevent cellular entry of lethal factor. The significance of lethal factor levels is not known and cannot be fully evaluated with the limited data available. As anti-PA levels were sustained in inhalational anthrax patients, it appears that PA was neutralized.*

**Reviewer Comment:** Further FDA-requested edits were made, including that plasma levels of lethal factor remained detectable two to five days following ANTHRASIL administration, despite their decline. The fact that “It is unknown whether ANTHRASIL

contains sufficient levels of antibodies to lethal factor to fully neutralize this toxin component in either animals or patients,” together with the lack of direct demonstration of complete neutralization of PA load by the product in humans, underscores the uncertainty regarding whether the recommended dosing range is necessarily optimal to stoichiometrically neutralize all anthrax toxins in the body in inhalational anthrax.

*E. Change the last paragraph to read as follows:*

*Because the effectiveness of ANTHRASIL cannot ethically be tested in placebo-controlled trials in humans, a comparison of ANTHRASIL exposures achieved in healthy human subjects to those observed in animal models of inhalational anthrax in therapeutic efficacy studies is necessary to support the dosage regimen of 420 Units to 840 Units IV as a single (or initial) dose for the treatment of inhalational anthrax in humans.*

**Sponsor Response:**

*Based on the proposed dosing (see response to Question 16), the text has been revised as follows:*

*Because the effectiveness of ANTHRASIL cannot ethically be tested in placebo-controlled trials in humans, a comparison of ANTHRASIL exposures achieved in healthy human subjects to those observed in animal models of inhalational anthrax in therapeutic efficacy studies was necessary to support the dosage regimen. A dose of 420 Units has a similar exposure to the efficacious dose of 15 U/kg administered to New Zealand white rabbits and cynomolgus macaques. In cynomolgus macaques with ANTHRASIL monotherapy, a higher dose of 30 U/kg, with a similar exposure to a human dose of 840 Units, may result in improved survival [see 13.2 Animal Toxicology and/or Pharmacology]. As a result, the dosing regimen includes the potential for repeat dosing after the initial dose of 420 Units.*

**Reviewer Comment:** This language was further revised at FDA request to include the 840 unit initial dose option.

**35. Change the heading for section 13 to NONCLINICAL TOXICOLOGY AND PHARMACOLOGY. Change the second paragraph in this section to read as follows:**

*The evaluation of new treatment options for anthrax using placebo controlled human trials is unethical and infeasible. Therefore, the effectiveness of ANTHRASIL for treatment of inhalational anthrax is based on controlled efficacy studies conducted in rabbits and cynomolgus macaques.*

**Sponsor Response:**

*The revisions to section 13 NONCLINICAL TOXICOLOGY were completed as outlined*

above.

**36. Change the second sentence in sub-subsection 13.2.2 to read “No significant difference between the control (normal immune globulin [IGIV] plus levofloxacin) and treatment groups (ANTHRASIL plus levofloxacin) was seen when combination treatment was delayed up to 60 hours post-challenge.**

**Sponsor Response:**

The sentence was revised.

**Reviewer Comment: Noted.**

**37. Change the third sentence in the third paragraph of sub-subsection 13.2.2 to read “Of the animals that survived to be treated (19% of those challenged), antibacterial drug plus ANTHRASIL (15 Units per kg) resulted in (58%) [sponsor fill in (number of surviving animals/number of animals surviving to be treated)] survival compared to 39% [sponsor fill in (number of surviving animals/number of animals surviving to be treated)] survival in rabbits treated with antibacterial drug and IGIV placebo ( $p = 0.21$ ).” Round off the  $p$  value in the next paragraph to 0.02.**

**Sponsor Response:**

The values for (number of surviving animals/number of animals surviving to be treated) were added and the  $p$  value was corrected from 0.21 to 0.14 (Z-test). The  $p$  value in the following paragraph was rounded as requested.

**Reviewer Comment: Noted. Product reviewer to review in conjunction with FDA statistician.**

**38. Please add the  $p$  value in parentheses for the survival difference in the cynomolgus macaque combination treatment study in the paragraph under Table 7 in subsubsection 13.2.2.**

**Sponsor Response:**

The  $p$  value of 1 was added for the survival difference in the cynomolgus macaque combination treatment study in the paragraph under Table 7 in 13.2 Animal Toxicology and/or Pharmacology.

**Reviewer Comment: Noted**

**39. Please modify the paragraph presently under 13.2.3 ANTHRASIL in Post-exposure prophylaxis to include the results to those in animals who were determined to be anti-PA positive, and both anti-PA positive and bacteremia at the time of dosing. Exclude**

**the presentation of data from challenge dosing at 20 hours.**

***Sponsor Response:***

*The presentation of data from challenge dosing at 20 hours was removed from information under the sub-heading of ANTHRASIL in Post-exposure Prophylaxis in 13.2 Animal Toxicology and/or Pharmacology. The paragraph was also modified to include survival results in animals that were determined to be bacteremic and toxemic at the time of treatment; i.e. 22% (2/9) survival with a dose of 15 Units TNA per kg.*

**Reviewer Comment: Noted. Product reviewer to review.**

***40. In section 14, please change the first sentence to read “Because it is not ethical or feasible to conduct placebo-controlled clinical trials in humans with inhalational anthrax..” Change the last sentence in this paragraph to read “The safety has been tested in healthy adults and evaluated in a limited number of patients with anthrax who were treated with ANTHRASIL under compassionate use or CDC’s expanded use programs.”***

***Sponsor Response:***

*The first sentence within section 14 CLINICAL STUDIES was changed as requested. The last sentence was changed to read:*

*The safety has been tested in healthy adults and evaluated in a limited number of patients with anthrax who were treated with ANTHRASIL under expanded access use.*

*Cangene is leaving the wording of the CDC held IND study as “Expanded Access” (i.e., dropping “program”) throughout the FPI. Please refer to the response to Question 42 for the rationale.*

**Reviewer Comment: Noted and accepted.**

***41. Strike the last sentence in section 14.1 which begins “The data collected in this study demonstrated...” as it is promotional in tone.***

***Sponsor Response:***

*The last sentence in section 14.1 Safety and Pharmacokinetics of ANTHRASIL in Healthy Volunteers has been removed.*

***42. Change the title of subsection 14.2 to read Patient Experience (Compassionate Use/Expanded Access Program). (Note that not all human cases of systemic anthrax treated with AIGIV received the product under the Expanded Access Program.)***

***Sponsor Response:***



*The title of subsection 14.2 was changed to read Patient Experience (Expanded Access). The rationale is as follows:*

- Prior to 2009, subjects were treated under “emergency use” INDs; CDC protocols for the first two patients were titled to include “one-time emergency use”.*
- After 2009 Subpart I of 21 CFR 312, which is specific for “Expanded Access to Investigational Drugs for Treatment Use”, went into effect. Expanded access includes:*

- 1. Individual patients, including for emergency use*
- 2. Intermediate-size patient populations*
- 3. Treatment IND or treatment protocol.*

*Thus by the current regulation, the term “expanded access” includes both emergency use and treatment protocols.*

*There is no definition or mention of “compassionate use” found in the regulations or FDA guidance documents for investigational drugs. However, on FDA websites, expanded access and compassionate use are used synonymously (<http://www.fda.gov/forpatients/other/expandedaccess/default.htm>): Expanded access, also called “compassionate use” is a regulation that makes promising drugs and devices available to patients with serious or immediately life-threatening diseases. As a result, we believe “expanded access” best defines the CDC program that both includes individual emergency IND patients and patients enrolled under a larger treatment protocol. This term is also consistent with regulations presented in 21 CFR 312, subpart I.*

**Reviewer Comment: Noted and accepted.**

***43. Strike the sentence in the first paragraph of section 14.2 which reads “To provide additional support...”***

***Sponsor Response:***

The sentence noted in the first paragraph of 14.2 Patient Experience (Expanded Access) has been removed.

***44. Change the second paragraph of section 14.2 to read “For the ANTHRASIL indication of inhalational anthrax, two out of three patients treated with ANTHRASIL plus appropriate antimicrobial therapy survived and one died from progression of anthrax disease. In all three patients, therapy included aggressive supportive measures including mechanical ventilation and pulmonary fluid drainage.”***

The second paragraph of 14.2 Patient Experience (Expanded Access) has been changed.

**Reviewer Comment: Noted.**

**45. Change the third paragraph of section 14.2 to read “In the three inhalational patients, the ANTHRASIL 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 rising antibody production by the patient at the same time that the exogenously-administered antibody was being cleared.”**

**Sponsor Response:**

The third paragraph of 14.2 Patient Experience (Expanded Access) has been changed.

**Reviewer Comment: Noted.**

**46. Add a fourth paragraph to section 14.2 to read as follows:**

*Unlike the case in animals, serum lethal factor remained detectable in patients’ serum following administration of ANTHRASIL, although substantial declines following product administration were observed. 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-ANTHRASIL peak levels by 24 hours following ANTHRASIL administration.*

**Sponsor Response:**

*As discussed in response to Question 34D, lethal factor was not measured in animal studies. In addition, the levels of antibodies to lethal factor in ANTHRASIL are not measured. Parallels between lethal factor measurements in patients by the CDC and protective antigen measurements in animal studies cannot be made. As a result, we do not feel that the first statement regarding lethal factor can be included as this time. We are exploring whether the post-marketing commitment study can address this particular question.*

*The second statement regarding injectional anthrax patient anti-PA levels has been included, with the addition of:*

*ANTHRASIL has not been studied in injectional anthrax animal models.*

**Reviewer Comment: Noted and accepted.**

**47. In section 17 PATIENT COUNSELING INFORMATION change the term “legal guardian” to “legally authorized representative” in the first sentence. In the last bullet in this section, change the last sentence to read “The safety of ANTHRASIL has been tested in healthy adults, but no safety data are available in the pediatric population, the elderly, or pregnant women [see 8 USE IN SPECIFIC POPULATIONS].**

***Sponsor Response:***

The requested changes in section 17 PATIENT COUNSELING INFORMATION have been made.

**5 DRAFT CARTON AND CONTAINER LABELS**

***48. The proper name of the product on the carton and container label shall be placed above any trademark or trade name identifying the product.***

***Sponsor Response:***

As per 21 CFR 610.62(a), the logo for Anthrasil has been revised such that the proper name of the product is above the trademark or trade name. An updated **commercial shelf carton label** and **commercial vial label** have been provided.

**Sponsor's 09 February 2015 response to FDA comments conveyed 25 Jan 2015 and 02 Feb 2015 requesting changes to the draft package insert (PI).**

1 DOSAGE AND ADMINISTRATION (HIGHLIGHTS AND FULL PRESCRIBING INFORMATION)

***Sponsor Response:***

*Cangene would like to revert back to the previous dosing proposal until we can better understand the FDA's proposal of a dose range. We consider that the proposed dose range may complicate dosing decisions by a treating physician as well as distribution of Anthrasil (AIGIV) vials by the Centers for Disease Control and Prevention (CDC).*

*The dose range may be confusing for a treating physician that may not have sufficient experience in treating an anthrax patient to determine the appropriate starting dose. For an ease-of-use approach, a physician can give an initial dose (420 Unit dose) and then make a decision based on progression, stabilization or improvement of symptoms whether to give a second dose to the patient. In addition, a dose range within the Anthrasil Prescribing Information may create difficulties for the CDC to determine how many vials to deploy in a mass exposure.*

*The dosing scheme that was previously provided (Table 1 and Table 2 below [see Amendment]) will*

*adequately allow for neutralization of the toxin and assessment for re-dosing based on symptomatology.*

*Cangene would like to understand any concerns with Anthrasil dosing the agency may have before making further adjustments to the proposed dosing instructions.*

**Reviewer Comment:**

**FDA does not accept the sponsor's proposal to recommend a single fixed initial dose of 420 U of the product (in combination with appropriate antibiotic therapy) for the treatment of inhalational anthrax. The sponsor's scalings of effective dose from animals to humans were based on estimates of mean clearance. Clearance of anti-PA antibodies varies among healthy individuals and it is likely that clearance varies even more among individuals with systemic anthrax disease. Thus, the sponsor's proposed initial human dose is likely to be suboptimal for many patients, even if one were to assume that the 15 U/kg dose in animals is optimal in the setting of combination therapy with antibiotics. However, FDA notes that in monotherapy animal studies, particularly the monkey, the survival among bacteremic and toxemic animals (as well as among all animals by ITT) was numerically superior in the 30 U/kg groups compared to the 15 U/kg groups, though the differences in survival at these 2 dosages did not achieve statistical significance. In the monkey, which has been acknowledged in the literature to be a better model of human anthrax compared to the rabbit, there was observed a monotonic increase in survival as the dose increased from 7.5 to 15 to 30 U/kg. According to the sponsor and to the FDA Clinical Pharmacology review, 15 U/kg and 30 U/kg in animals scale to approximately 420 U and 840 U respectively in humans with inhalational anthrax. In addition, the sponsor's dose-response models which took into account all available animal and human study data, in both the monotherapy setting as well as in the combined with antibiotics setting, predicts greater survival with 840 U compared to 420 U.**

**Inhalational anthrax is typically a devastating disease with high morbidity and mortality despite antibiotic therapy. Multi-organ failure is common even in surviving patients. Because patients can exhibit rapid deterioration, it is considered important that the initial dose be selected to provide the best likelihood of survival. Some patients who receive an initial suboptimal dose are likely to deteriorate beyond the point where additional therapeutic measures may result in their survival, including administration of additional doses of AIGIV. For these reasons, FDA concluded that a range for the initial AIGIV dose from 420 U to 840 U was more appropriate than a fixed initial dose of 420 U and the option to begin therapy at the higher dose may improve survival. An initial dose of 420 units**

might be considered for patients without major underlying morbidity presenting early in the prodromal period.

It should be noted that the sponsor has acknowledged in an amendment that it is unknown whether the 420 U dose will be sufficient to neutralize the body's burden of anthrax lethal factor in inhalational anthrax:

The anti-PA in ANTHRASIL is measured as a component of release testing, as is the corresponding potency in toxin neutralization activity units. While ANTHRASIL contains antibodies to other antigens present in BioThrax®, including lethal factor, these antibodies are not measured as part of the product release. It is unknown whether ANTHRASIL contains sufficient levels of antibodies to lethal factor to fully neutralize this toxin component in either animals or patients.

For the above reasons, FDA requires that the initial dose for both adults and pediatric patients recommended in the package insert be a range (from 420 to 840 U for adults and the corresponding scaled doses for pediatric patients, as determined by body weight).

## **2.2 Preparation and Administration**

### **FDA Change:**

Use the thawed vials to prepare the infusion bag within 48 hours. ANTHRASIL contains no preservative. Once punctured, administer vial contents within 6 hours.

### ***Sponsor Response:***

*In addition, the last bullet under point 5 of 2.2 Preparation and Administration was revised to clear any confusion about whether the product can be held in vials or the intravenous bag for up to 48 hours. The following statement was also revised in 16.2 Storage and Handling for consistency.*

### ***Sponsor's counterproposal language:***

*Once punctured, use the vial contents to prepare the infusion bag within six hours.*

*Use the prepared infusion bag within 48 hours. ANTHRASIL contains no preservative.*

**Reviewer Comment:** Product reviewer to address. A 48 + 6 hour total time periods from vial puncture until the end of the infusion may present an increased risk of microbial

**growth should the vials become contaminated upon puncture/transfer and this time interval is much longer than for other FDA-approved parenteral products lacking preservative. [This was subsequently changed to “as soon as possible.”]**

## **2 WARNINGS AND PRECAUTIONS**

### ***Sponsor Response:***

*The Infusion Rate Precaution was not removed from the WARNINGS AND PRECAUTIONS section as there is a reference to it within the Highlights section as recommended by FDA:*

- Infuse ANTHRASIL at the minimum rate practicable in patients at risk of thrombosis or renal failure (5.5)*

### **Reviewer Comment:**

**Acceptable. The Infusion Rate Precautions section states:**

**Adverse reactions (such as chills, fever, headache, nausea and vomiting) may be related to the rate of infusion. Follow closely the recommended infusion rate given under 2.1 Dose. Closely monitor and carefully observe patients and their vital signs for any symptoms throughout the infusion period and immediately following an infusion.**

**Given that some practitioners administering AIGIV may not be accustomed to administering IGIV, the inclusion of the above language in this section is acceptable.**

## **3 ADVERSE REACTIONS**

### ***Sponsor Response:***

*The adverse events (AE) discussed under Patient Experience within section 6 ADVERSE REACTIONS was revised from 53 AEs with 34 events considered serious and unrelated to ANTHRASIL administration to 46 AEs with 31 events considered serious and unrelated to administration as a result of the elimination of duplicate events. The events included in the analysis were as follows:*

*Serious AEs (SAEs): Coagulopathy, disseminated intravascular coagulation, cardiac arrest (n=2), ascites, rectal haemorrhage, death, multi-organ failure (n=2), oedema,*

*oedema peripheral, septic shock (n=2), systemic candida, hyperkalemia, metabolic acidosis, renal failure, renal failure acute (n=2), renal impairment (n=2), acute respiratory distress syndrome (n=2), haemothorax, pleural effusion (n=2), pulmonary congestion, pulmonary oedema, respiratory failure, circulatory collapse, hypotension. Non serious AEs: Thrombocytopenia (n=2), cardiovascular disorder, pyrexia (n=2), blood creatinine increased, C-reactive protein increased, haemoglobin decreased, urine output decreased, white blood cell count increased, acidosis, hyponatraemia, convulsion, haemorrhage, hypotension.*

*Cangene would like to clarify that the CDC expanded access INDs planned for capture of data pertained to related adverse reactions only. For the 19 patients treated in this program, the investigator/treating physicians and the CDC reported no adverse reactions to AIGIV. The CDC has reported this to the FDA in annual IND reports, and Cangene has documented the same in the Patient Experience Report as follows:*

*No adverse events (AEs) were captured by the CDC for the 19 patients who received AIGIV. None of the treating physicians reported any AIGIV-related AEs.*

*However, of the 19 patients, there were six deaths reported by the CDC after AIGIV administration, including one inhalational and five injectional anthrax patients. From narrative descriptions provided by the CDC, or in some cases in literature publications, Cangene has captured a total of 46 events and assessed 31 events as serious. Cangene also reported these events in the Patient Experience Report as follows:*

*However, 11 serious adverse event (SAE) cases have been recorded at Cangene from narrative data provided by the CDC. Upon notification and receipt of case narrative information from the CDC for these subjects, SAE cases were generated by Cangene Pharmacovigilance and AE data were captured based on the available data. The SAEs in these patients were related to progression of anthrax or co-morbidities and*

*were not assessed as related to AIGIV by the CDC or treating physicians. As such, these events are not captured as AEs by the CDC.*

*As these events were not directly reported from the investigator or captured by the CDC, the onset time in relation to AIGIV was not always captured. The onset date was captured when available.*

*Cangene causality assessment for these events was consistent with CDC initial assessment that the SAEs were unrelated to AIGIV and most likely related to the underlying anthrax infection and complications.*

*In a healthy volunteer study (AX-001), the assessment of temporally-related adverse events (within 72 hours of administration) was predefined in the protocol. However, in the anthrax patients who received AIGIV, there were underlying symptoms of severe systemic anthrax disease that complicate assessment of temporally related adverse events. Hence, this population is very different from the healthy volunteers. Furthermore, as the events were not reported by investigators but were captured from narratives, we do not agree that this temporal assessment is informative to the safety profile of AIGIV as the events reported were consistent with, and attributed to, the underlying disease.*

*The listings of SAEs for the 11 systemic anthrax cases are provided in Table 3 (inhalational; n=3) and Table 4 (injectational; n=8). Due to the missing AE onset information, all SAEs are included in the listings with AIGIV administration information and the calculated days from AIGIV infusion to AE onset date.*

*Out of nine SAEs reported for inhalational cases, two SAEs are missing AE onset information (‘Renal impairment’ for patient (b) (6) and ‘Renal failure acute’ for patient (b) (6)). Only one SAE occurred within three days post AIGIV administration (‘Acute respiratory distress syndrome’ for patient (b) (6)). See Table 3 for detailed information.*



There are 22 SAEs reported for injection cases. Three out of 22 SAEs have no AE onset information. One SAE ('Multi-organ failure') occurred prior to the AIGIV administration. There is no SAE reported for the single gastrointestinal case.

Table 4 Listing of Serious Adverse Events for Injectional Anthrax Patients

Case No.	Cangene Patient ID	AIGIV Admin Date/Time	AE Onset Date	Time to AE Onset (Days) <sup>a</sup>	System Organ Class	Preferred Term	AE Outcome	Causality <sup>b</sup>	Death
(b) (6)	(b) (6)	19DEC2009/22:30	21DEC2009	2	Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	Unknown	Unrelated	Yes
			22DEC2009	3	Infections and infestations	Septic shock	Fatal	Unrelated	Yes
		21DEC2009/9:00	21DEC2009	0	Renal and urinary disorders	Renal impairment	Fatal	Unrelated	Yes
			22DEC2009	1	Gastrointestinal disorders	Ascites	Unknown	Unrelated	Yes
		29DEC2009/3:00	29DEC2009	0	Blood and lymphatic system disorders	Coagulopathy	Recovering/Resolving	Unrelated	No
			05JAN2010	7	Respiratory, thoracic and mediastinal disorders	Pleural effusion	Recovering/Resolving	Unrelated	No
			15JAN2010	17	Gastrointestinal disorders	Rectal haemorrhage	Recovering/Resolving	Unrelated	No
		02JAN2010/6:45	02JAN2010	0	General disorders and administration site conditions	Oedema peripheral	Not recovered/Not resolved	Unrelated	Yes
			02JAN2010	0	Vascular disorders	Hypotension	Unknown	Unrelated	Yes
			02JAN2010	0	General disorders and administration site conditions	Oedema	Not recovered/Not resolved	Unrelated	Yes
			04JAN2010	2	Renal and urinary disorders	Renal failure	Not recovered/Not resolved	Unrelated	Yes
			04JAN2010	2	Metabolism and nutrition disorders	Metabolic acidosis	Not recovered/Not resolved	Unrelated	Yes
			05JAN2010	3	Renal and urinary disorders	Oliguria	Not recovered/Not resolved	Unrelated	Yes
			05JAN2010	3	Metabolism and nutrition disorders	Hyperkalaemia	Not recovered/Not resolved	Unrelated	Yes
			05JAN2010	3	Cardiac disorders	Cardiac arrest	Fatal	Unrelated	Yes

Case No.	Cangene Patient ID	AIGIV Admin Date/Time	AE Onset Date	Time to AE Onset (Days) <sup>a</sup>	System Organ Class	Preferred Term	AE Outcome	Causality <sup>b</sup>	Death
(b) (6)	(b) (6)	17JAN2010/9:00	24JAN2010	7	Respiratory, thoracic and mediastinal disorders	Respiratory failure	Recovered / Resolved	Unrelated	No
		20JAN2010/3:45	22JAN2010	2	General disorders and administration site conditions	Death	Fatal	Unrelated	Yes
		16FEB2010/5:30	UNK	UNK	Infections and infestations	Septic shock	Fatal	Unrelated	Yes
			01FEB2010	-15	General disorders and administration site conditions	Multi-organ failure	Fatal	Unrelated	Yes
			21FEB2010	5	Respiratory, thoracic and mediastinal disorders	Pulmonary congestion	Fatal	Unrelated	Yes
		26FEB2010/20:45	UNK	UNK	Respiratory, thoracic and mediastinal disorders	Pleural effusion	Recovered / Resolved	Unrelated	No
			UNK	UNK	Respiratory, thoracic and mediastinal disorders	Pulmonary oedema	Recovered / Resolved	Unrelated	No

<sup>a</sup>Time to AE (days) derived as the time from AIGIV Administration to Adverse Event Onset ('AE Onset Date' - 'AIGIV Admin Date')

<sup>b</sup>AEs were collected by the company from the case narratives, which were present in the CDC report and from literature sources. The CDC did not report any of the listed AEs in their report as adverse drug reactions. The company assigned causality on the basis of the following statement found in the report BB-IND 13026 Anthrax Immune Globulin Intravenous (Human) (AIGIV) with reporting period June 08 2011 to June 07 2012: "To date, no AIGIV infusion-related adverse events have been reported for any of the 19 patients who were treated with AIGIV".

UNK = Unknown

Adverse Events are classified according to MedDRA Version 16.0

## Reviewer Response:

**There is no gold standard for the adjudication of individual adverse events (AEs) occurring in individual subjects/patients. The best evidence for a causal relationship between a**

particular type of AE and a therapeutic agent comes from randomized, double-blind, controlled trials demonstrating consistent statistically significant imbalances in the exposure-adjusted incidence of the AE type. Other lines of evidence suggestive of a causal relationship include a close temporal relationship between the administration of the therapeutic agent and the onset of the AE, the clustering of several instances of rare AEs in a modest sized exposed population, and similarity of the AE type to pertinent toxicologic findings in animals. Investigator opinion's regarding causality of AEs in therapeutic trials are subject to bias and error. This is proven by the regular findings of investigator opinions of relatedness of AEs to blinded placebo occurring in the placebo groups of randomized controlled trials.

The sponsor states that *"in the anthrax patients who received AIGIV, there were underlying symptoms of severe systemic anthrax disease that complicate assessment of temporally related adverse events."* FDA would restate this as *"in the anthrax patients who received AIGIV, there were underlying symptoms of severe systemic anthrax disease that complicate assessment of adverse reactions."* Furthermore, it is not completely clear that the sponsor's statement that no adverse events were considered related to ANTHRASIL administration is completely accurate. For example, the most recent ANTHRASIL annual report IND 11982 amendment 198 states in regard to the serious adverse event of ADRS which was diagnosed one day following ANTHRASIL administration in inhalational anthrax case (b) (4)

*On 23 Feb 2006, AIGIV was infused without adverse reactions... On 24 Feb 2006, a chest CT revealed bilateral pulmonary opacities with prominent ground glass appearance consistent with acute respiratory distress syndrome (ARDS). A bronchoscopy result also was consistent with ARDS. From 25 Feb 2006 through 1 Mar 2006, the patient continued to receive mechanical ventilation due to the worsening respiratory function... There was concern that the administration of AIG might have contributed to this deterioration. However, there was clinical and radiological evidence of worsening respiratory status and ARDS occurred prior to administration of AIG. [Published in Walsh et al. Clinical Infectious Disease. 2007;44 :971]*

FDA does not accept at face value either the investigator or sponsor opinions of causality of adverse events in uncontrolled clinical trials. Nor will FDA accept the investigator and sponsor opinion that none of the treatment-emergent adverse events were at least possibly caused by AIGIV administration.

The sponsor also states in the Annual Report IND 11982 amendment 198 that *"Safety information provided for the patients that were treated with AIGIV is limited and therefore not adequate to assess the safety profile of AIGIV in these patients."* Although in the table above in the sponsor's IND Annual Report amendment 198 the cause of death is listed as "unknown" for 3 of the 6 deaths among the 19 patients with systemic anthrax treated with ANTHRASIL, the sponsor repeatedly states *"...there were six anthrax patients who received AIGIV treatment under CDC BB-IND 13026 that died as a result of anthrax disease (Table 1).*

*The deaths in these patients were related to progression of anthrax or co-morbidities and were not assessed as related to AIGIV by the CDC or treating physicians.” Whereas it appears that the sponsor speculates that the cause of death in three systemic anthrax patients was due to progression of anthrax disease or co-morbidities, the sponsor inappropriately states these assumptions as facts. FDA considers it important for the incompleteness of the safety reporting for the patients with systemic anthrax treated with AIGIG to be reflected in the package insert.*

**The sponsor is asked to add a table to the ADVERSE REACTIONS section listing the following [suspected] serious adverse reactions for which the available information suggests that the event began within 3 days/72 hours of ANTHRASIL infusion. A footnote to the table is requested to state that “septic shock” was also reported within 72 hours of ANTHRASIL administration but that these events may have been due to progression of anthrax infection. [Note that the 27 February 2015 FDA edited PI/information request asked, per the recommendation of Dr. Jain, that the information in the table below be instead incorporated into the PI in narrative form.]**

<b>Organ System</b>	<b>Serious Adverse Reaction<sup>1</sup></b>	<b>Number of Patients</b>
<b>Respiratory</b>	Adult Respiratory Distress Syndrome	2
	Pulmonary Edema	1
	Pleural Effusion	1
<b>Renal</b>	Acute Renal Insufficiency/Failure	4
<b>Hematologic</b>	Coagulopathy	1
<b>Cardiovascular/General</b>	Cardiac Arrest/Death NOS <sup>2</sup>	2
<b>Cardiovascular</b>	Hypotension	1
<b>Gastrointestinal</b>	Ascites	1
<b>Metabolic</b>	Metabolic Acidosis	1
	Hyperkalemia	1
<b>General</b>	Edema/Peripheral Edema	1

<sup>1</sup>Two cases of septic shock also occurred within 72 hours of ANTHRASIL infusion but were attributed to progression of anthrax.

<sup>2</sup>Not Otherwise Specified

#### **4 USE IN SPECIFIC POPULATIONS (HIGHLIGHTS AND FULL PRESCRIBING INFORMATION)**

##### ***Sponsor Response:***

*The Pregnancy and Lactation Labeling for sections 8.1 through 8.3 in the Full Prescribing Information and associated HIGHLIGHTS were revised in accordance with the FDA Draft Guidance for Industry Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2014). Considering AIGIV is a stockpiled product and there is a labeling operation planned post-approval that includes addition of the approved package insert with the product, Cangene believed it would be appropriate to incorporate the changes at this time. Note that section 8.3 Females and Males of Reproductive Potential was omitted.*

**Reviewer Comment: Changes are acceptable.**

#### **5 MECHANISM OF ACTION**

##### ***Sponsor Response:***

*The mechanism of action was revised from the FDA suggested wording to reflect the polyclonal nature of AIGIV.*

*FDA wording:*

*The polyclonal immune globulin G in ANTHRASIL is a passive immunizing agent that neutralizes anthrax toxin. ANTHRASIL binds to protective antigen (PA) to prevent binding to its cellular receptors and thus precluding oligomerization of PA and internalization of anthrax edema factor and lethal factor.*

*Proposed wording:*

*The polyclonal immune globulin G in ANTHRASIL is a passive immunizing agent that neutralizes anthrax toxin. ANTHRASIL binds to protective antigen (PA) to prevent PA mediated cellular entry of anthrax edema factor and lethal factor.*

**Reviewer Comment:**

**The sponsor's counterproposal for modified FDA language is acceptable.**

## **6 PHARMACOKINETICS**

***Sponsor Response:***

*The FDA addition of “and an increased rate of protein catabolism” was not accepted for the following statement as we do not have any data to support it:*

*In comparison to healthy subjects, patients with inhalational anthrax are expected to initially have greater clearance of anti-PA antibodies and lower AUC from ANTHRASIL administration due to the presence of PA antigen and an increased rate of catabolism.*

**Reviewer Comment:**

**Accepted. Although it is highly likely that the accelerated general protein catabolism observed in sepsis also pertains to catabolism of IgG , including AIGIV, and low total IgG levels have been documented by many investigators during sepsis (e.g., Shankar-Hari et al., Crit Care 2012;16:206.), I am not aware of published PK studies of IgG during sepsis.**

## **7 ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY**

***Sponsor Response:***

*The data in ANTHRASIL Efficacy in Combination with Antibiotics in section 13.2 ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY (following Table 7 in the Prescribing Information) was reviewed and confirmed to be correct when both PA+ and bacteremic animals were considered for the analysis. One animal from the placebo arm and two from the 15 units/kg AIGIV plus Ciprofloxacin groups were excluded due to non-anthrax related deaths. For 30 U/kg group, one animal was excluded and there were 11 survivors, which is 71% (b) (4) 987-G005780). Although FDA review of study 987 suggested the IGIV + Cipro arm was 69% (9/13), 15 U/kg AIGIV + Cipro was 71% (10/14), and 30 U/kg AIGIV +*

*Cipro was 64% (9/14), the following statement in the Prescribing Information is accurate: ANTHRASIL and antibiotic combination treatment was also studied in the cynomolgus macaque*

*model of inhalational anthrax. In this study, delay of initiation of treatment to 64 hours post anthrax exposure resulted in 75% (9/12) survival in the IGIV placebo plus ciprofloxacin treatment group versus 83% (10/12) survival in the ANTHRASIL (15 Uunits per kg) plus ciprofloxacin group ( $p=1$ ).*

**Reviewer Comment:**

**Product Reviewer to provide comment/response to sponsor's statements.**

## **8 TRADEMARK STATEMENT**

***Sponsor Response:***

*The following trademark statement was not removed as it is consistent with other products that are manufactured by Cangene Corporation doing business as Emergent BioSolutions:*

*ANTHRASIL™ Anthrax Immune Globulin Intravenous (Human) and BioThrax® (Anthrax Vaccine Adsorbed) and any and all Emergent BioSolutions Inc. brand, product, service and feature names, logos, slogans are trademarks or registered trademarks of Emergent BioSolutions Inc. or its subsidiaries in the United States or other countries. All rights reserved.*

**Reviewer Comment:**

**The trademark statement containing reference to Emergent BioSolutions Inc. is unacceptable according to APLB and needs to be removed, notwithstanding similar statements in other approved products' package inserts, which also need to be removed.**

**Review of revised draft package insert submitted 03 March 2015 and sponsor's responses to FDA edited version of the draft PI sent to the sponsor 27 Feb 2015 as an information request, together with reviewer comments as appropriate:**

## **1 USE IN SPECIFIC POPULATIONS (HIGHLIGHTS)**

***Sponsor Response:***

*The language for pregnancy was reverted to that which was previously submitted and the bullet for lactation was removed:*

- *Pregnancy: No human or animal data are available (8.1)*

**Reviewer Comment: noted and accepted.**

## **2 PREPARATION AND ADMINISTRATION**

### ***Sponsor Response:***

*The statement “The volume infused into each subject is dependent upon the product lot.” was removed from sections 2.2 Preparation and Administration and 3 DOSAGE FORMS AND STRENGTHS to eliminate confusion. The variable fill volume is now addressed in section 11 DESCRIPTION (new text in **bold italic** font):*

*The product is a clear or slightly opalescent colorless liquid, free of foreign particles, supplied in a 50 mL vial **with variable fill volume**.*

**Reviewer Comment: noted and accepted.**

## **3 DESCRIPTION**

### ***Sponsor Response:***

*FDA had suggested that a statement regarding activated Factor XI (FXIa) content be added to section 11 DESCRIPTION, followed by a statement that higher levels of FXIa in immunoglobulin products have been associated with thrombotic/thromboembolic events. Cangene has taken this into consideration; however, no statements were added to the recent version of the Prescribing Information. The rationale is based on the submitted evaluation of thrombogenic risk, the alert limit established for FXIa and the action taken to quarantine lots above this alert limit (3.2.S.3.2 Impurities). The alert limit, which considers an additional margin of safety, has been applied to all lots manufactured to date based on a 420 Unit dose and lots with FXIa values above the alert limit have been placed in quarantine. A reassessment is planned based on the potential for dosing using 840 Units; an updated eCTD section 3.2.S.3.2 Impurities will be submitted prior to the action due date of March 25, 2015.*

(b) (4)

*. In addition, FXIa levels for future lots that are manufactured with the*  
(b) (4) *in place are also expected to contain low levels of FXIa.*

**Reviewer Comment: noted and accepted. To the extent that the Product review team is comfortable with the action limit used for determining which lots with high FXIa activity are to be quarantined/continue to be quarantined for predicting thrombogenic safety below that limit, (b) (4)**

(b) (4)

#### 4 TRADEMARK STATEMENT

***Sponsor Response:***

*The trademark statement was replaced with the wording that has been proposed for the commercial vial label and commercial shelf carton label:*

*Anthrasil™ is a trademark of Emergent BioSolutions Inc. or its subsidiaries.*

**Reviewer Comment:**

**Input has been sought from APLB to determine the acceptability of the revised trademark statement. The above trademark statement is not found in the sponsor's revised draft PI submitted 03/03/2015, so the question is moot.**

**(d) Analysis of serious adverse events and serious adverse reactions among patients with systemic anthrax who received AIGIV.**

A total of 16 serious adverse reactions that began within 72 hours of infusion were reported for eight out of 19 (42%) patients with systemic anthrax who were administered a single 420 unit dose AIGIV, as listed in the table below:

Table - Serious Adverse Reactions in Patients with Systemic Anthrax

Organ System	Serious Adverse Reaction <sup>1</sup>	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 <sup>2</sup>	2 (10.5)
Cardiovascular	Hypotension	1 (5.3)
Gastrointestinal	Ascites	1 (5.3)



<b>Metabolic</b>	Metabolic Acidosis	1 (5.3)
	Hyperkalemia	1 (5.3)
<b>General</b>	Edema/Peripheral Edema	1 (5.3)

<sup>1</sup>Two cases of septic shock also occurred within 72 hours of ANTHRASIL infusion but were attributed to progression of anthrax.

<sup>2</sup>Not Otherwise Specified.

Six deaths were reported, including one patient with inhalational anthrax. The cause of death in three of these patients was consistent with progression of anthrax disease or co-morbidities and the cause of death in the remaining three patients was not determined or available.

Most of the suspected 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 (ARDS), acute renal insufficiency, and cardiac arrest/death not otherwise specified. The possible role of circulating immune complexes involving antibodies in AIGIV and anthrax antigens in any of these listed suspected adverse reactions is uncertain, but it is conceivable they could be involved in some reports of renal dysfunction. It is possible that one of the cases reported as ARDS may have represented TRALI, but sufficient clinical details were lacking to permit a differentiation between these clinical entities, and ARDS reports following IGIV administration are rare. 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 pre-existing pleural effusion and/or ascites and to peripheral edema. The latter events are also attributable to inhalational anthrax.

## **APPENDIX**

**Sponsor narratives of subjects whose AIGIV infusions were stopped prematurely due to AEs (other than IV infiltration):**

**Subject <sup>(b) (6)</sup> – 420 units of Lot 24906011 (active AIGIV)**

The infusion for Subject <sup>(b) (6)</sup> was stopped approximately 23.25 minutes after the start of infusion with a 420 U dose of NP-015 (Treatment B) due to the following mild AEs, judged treatment-related: urticaria, pruritis, lip swelling and dry/sore throat. The AEs resolved with and without therapy, which included administration of Benadryl, the use of a cool cloth, ice bag and saline gargle. Subject <sup>(b) (6)</sup> completed the study and their post study physical examination was normal.

**Subject (b) (6) – 840 units of Lot 24906011 (active AIGIV)**

The infusion for Subject No (b) (6) was stopped approximately 2.72 minutes after the start of infusion with an 840 U dose of NP-015 (Treatment C) due to the following mild AEs, judged treatment-related: chest discomfort, flushing, tachycardia and throat tightness. Tachycardia began approximately 2 minutes after dosing and resolved approximately 5 minutes after onset, without therapy. The subject was withdrawn from the study by the Principal Investigator due to these 4 treatment-related AEs, all of which resolved without therapy. The post study physical examination for Subject No (b) (6) was normal.

**Demographics of Anthrax Patients Who were Administered AIGIV****Table 7 Anthrax Patient Population Treated with AIGIV**

CDC Patient ID <sup>a</sup>	Cangene Patient ID	Age (years)	Sex	Date of AIGIV Administration <sup>b</sup>	Survival Status
<b>Inhalational Anthrax</b>					
(b) (6)	(b) (6)	44	M	2006 Feb 23	Lived
		34	M	2008 Oct 27	Died
		61	M	2011 Aug 8	Lived
<b>Gastrointestinal Anthrax</b>					
(b) (6)	(b) (6)	24	F	2009 Dec 25	Lived
<b>Injectional Anthrax</b>					
(b) (6)	(b) (6)	34	M	2009 Dec 19	Died
		44	M	2009 Dec 21	Died
		39	F	2009 Dec 29	Lived
		35	F	2010 Jan 2	Died
		26	F	2010 Jan 17	Lived
		40	M	2010 Jan 18	Lived
		47	M	2010 Feb 5	Lived
		43	M	2010 Feb 5	Lived
	(b) (6)	24	M	2010 Feb 16	Died
		44	M	2010 Feb 26	Lived
		31	M	2010 Feb 26	Lived
		41	M	2010 Apr 10	Lived
		36	M	2010 Apr 29	Lived
		30	M	2010 Jan 20	Died
		38	F	2010 Jul 3	Lived

<sup>a</sup> CDC patient ID refers to patient numbering in CDC dataset.

<sup>b</sup> Date of administration captured from CDC 2010 annual report for BB-IND 13026 (reporting period June 8, 2009 to July 2, 2010), with the exception of patient (b) (6), the date was obtained from CDC 2012 annual report for BB-IND 13026 (reporting period June 8, 2011 to June 7, 2012), patient (b) (6) date obtained from BB-IND 14261, serial 000, and patients (b) (6) correct dates obtained via communication with the CDC.

**Lot Numbers of AIGIV Administered to Anthrax Patients.**

<b>Patient ID</b>	<b>Lot Number of AIGIV</b>	<b>Death?</b>	<b>Delay from Time of Administration of AIGIV Until Death (days)</b>
(b) (6)	24905011, which was later changed to Lot10804812	N	
(b) (6)	10602912	Y	6
(b) (6)	10602912	N	
(b) (6)	10602912	N	
(b) (6)	10602912	Y	2.1
(b) (6)	10602912	Y	1.7
(b) (6)	10602912	Y	3
(b) (6)	10602912	Y	~ 6
(b) (6)	10906491	Y	2
(b) (6)	10602912	N	
(b) (6)	10602912	N	
(b) (6)	10602912	N	
(b) (6)	10906491	N	
(b) (6)	10906491	N	
(b) (6)	10602912	N	
(b) (6)	10602912	N	
(b) (6)	10602912	N	

(b) (6)	10602912	N	
(b) (6)	10602912	N	

**Table 10 Summary of Time Course for Patients who Died**

	<b>Symptom Onset to Death Median Days (Range)</b>	<b>Hospital Admission to Death Median Days (Range)</b>	<b>AIGIV Administration to Death Median Days (Range)</b>
Inhalational (N=1)	14.0	12.0	6 .0
Injectonal (N=5)	7.0 (6–9)	4.0 (3–7)	3.0 (2–5)

Note that a total of 70 confirmed injectonal anthrax cases are listed in Sponsor’s Table 16 the Patient Experience Report, of which 26 (37.1%) died. Subtracting the 15 inhalational anthrax patients treated with AIGIV, of whom 5 died (33%), there remain 55 confirmed inhalational anthrax cases not treated with AIGIV, of whom 26 minus 5 or 21 (38.2%) died. Thus, there was a 5.2% lower mortality rate among those injectonal anthrax patients who were treated with AIGIV (and antibiotics) compared to the rate among those not treated with AIGIV (and, presumably, antibiotics). Given that pertinent baseline information, such as age, sex, duration of symptoms and stage of disease prior to antibiotic therapy, and presence of pre-existing morbidities was not presented for injectonal anthrax patients not treated with AIGIV in the Patient Experience Report in the BLA, it was not possible to determine whether the 5.2% lower mortality rate observed among AIGIV plus antibiotics injectonal anthrax patients was a meaningful comparison.

### **Regulatory Status of Anthrax Patients’ Treatment with AIGIV**

*Source: Patient Experience Report, original BLA ANTHRASIL*

**Table 1 Individual Patient eINDs for AIGIV Administration**

CDC Patient ID <sup>a</sup>	Cangene Patient ID <sup>b</sup>	CDC eIND	CDC Protocol Version
(b) (6)	(b) (6)	12953	eIND treatment protocol <sup>c</sup>
		13867	Protocol CDC IRB #4881 version 4.0, October 25, 2008
		14249	Protocol CDC IRB #4881 version 5.0, December 18, 2009
(b) (6)		14246	Protocol CDC IRB #4881 version 5.0, December 18, 2009
		14247	
		14257	
		14261	
		14272	
		14270	
		14288	
		14297	
		14301	

<sup>a</sup> CDC patient ID refers to patient numbering in CDC dataset. Alternative naming also provided when applicable.

<sup>b</sup> Cangene patient ID is used throughout this report. The naming is based on route of exposure (IH, inhalational; GI, gastrointestinal; IJ, injectional), location to which AIGIV was sent (US, United States; UK, United Kingdom; SL, Scotland) and patient number (chronological or to match CDC numbering).

<sup>c</sup> Subject (b) (6) predates BB-IND 13026. Patient treatment plan was submitted to eIND 12953.

**Table 2 Patients Treated with AIGIV under BB-IND 13026**

CDC Patient ID <sup>a</sup>	Cangene Patient ID	CDC Protocol Version
(b) (6)	(b) (6)	Protocol CDC IRB #5876, version 2.0, March 1, 2010

<sup>a</sup> CDC patient ID refers to patient numbering in the CDC dataset. Alternative naming also provided when applicable. In the CDC dataset, Subject (b) (6) was reassigned to the 2011 Minnesota inhalational case.

**Table 3 Patients Treated with AIGIV Purchased from Cangene**

CDC Patient ID <sup>a</sup>	Cangene Patient ID	Reference Protocol Version
(b) (6)	(b) (6)	Protocol CDC IRB #4881 version 5.0; December 18, 2009

<sup>a</sup> CDC patient ID refers to patient numbering in the CDC dataset.

#### *Literature References Describing Use of AIGIV in Anthrax Patients*

**Table 6 Literature References for AIGIV Treated Patients**

Literature Reference	Patient ID
Walsh et al, 2006. Inhalation anthrax associated with dried animal hides – Pennsylvania and New York City, 2006 (5)	(b) (6)
Walsh et al, 2007. A case of naturally acquired inhalational anthrax: clinical care and analyses of anti-protective antigen immunoglobulin G and lethal factor (6)	
Health Protection Report, 2008. A single case of inhalation anthrax in a drum maker in London (7)	
Anaraki et al, 2008. Investigations and control measures following a case of inhalational anthrax in east London in a drum maker and drummer (8)	
Griffith et al, 2014. Investigation of inhalation anthrax case, United States (9)	
Sprenkle et al, 2014. Lethal factor and anti-protective antigen IgG levels associated with inhalation anthrax, Minnesota, USA (10)	
Mayo et al, 2010. Gastrointestinal anthrax after an animal-hide drumming event – New Hampshire and Massachusetts, 2009 (11)	
Klempner et al, 2010. Case 25-2010: A 24-year-old woman with abdominal pain and shock (12)	
Johns et al, 2011. An unusual case of peritonitis in an intravenous drug user (13)	
Jallali et al, 2011. The surgical management of injectional anthrax (14) Abbara et al, 2014. Lessons for control of heroin-associated anthrax in Europe from 2009-2010 outbreak case studies, London, UK (15)	
National Anthrax Outbreak Control Team, 2011. An outbreak of anthrax among drug users in Scotland, December 2009 to December 2010 (16)	Injectional cases in Scotland including AIGIV treated cases
Booth et al. A review of twenty seven confirmed cases of <i>B. anthracis</i> infection in injection drug users from the 2009 to 2010 outbreak in Scotland (17, 18, 19)	Injectional cases including (b) (6) (b) (6)
Booth et al., 2012. Injection anthrax: an inflammatory response (20)	(b) (6)