SUMMARY BASIS FOR REGULATORY ACTION

Date: May 17, 2012

From: Alexandra Worobec, M.D., Chair of the Review Committee, DVRPA/OVRR

sBLA/STN: 103821/5203

Applicant Name: Emergent BioDefense Operations Lansing Inc.

Date of Submission: February 12, 2010

Date of CBER Receipt: February 16, 2010

Action Due Date: May 17, 2012

Proprietary Name: BioThrax®

Established Name: Anthrax Vaccine Adsorbed

Indication: Active immunization for the prevention of disease caused by *Bacillus anthracis*. For use in persons 18 through 65 years of age at high risk of exposure to *Bacillus anthracis*.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, Division of Vaccines and Related Product Applications/Office of Vaccines Research and Review

√ **I concur with the summary review.**

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

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

Specific documentation used in developing the SBRA	Reviewer Name – Document Date
Clinical Review	Alexandra Worobec, M.D. – 05/15/2012
Statistical Review	Tsai-Lien Lin, Ph.D. – 11/09/2010, 05/14/2012
CMC/Bioassay Review	Leslie Wagner – 10/25/2010
Bioresearch Monitoring (BIMO) Review	Janet White – 10/06/2010
Advertising and Promotional Labeling	Maryann Gallagher – 02/13/2012
Pharmacovigilence (OBE) Review	Damon Green, M.D., M.S – 05/10/2012

I. INTRODUCTION

Anthrax Vaccine Adsorbed (AVA) (BioThrax®) is the only vaccine approved in the U.S. for the prevention of anthrax infection. Initial U.S. approval was granted in 1970. Licensure was based, in addition to chemistry and manufacturing controls (CMC), on a field efficacy study conducted in U.S. woolen mills in the 1950's (Brachman PS, Gold H, Plotkin SA, et al. Field evaluation of a human anthrax vaccine. Am J Public Health. 1962; 52: 632-645), an open label safety study conducted by the National Centers for Disease Control and Prevention (CDC) in the 1960's, and disease surveillance data compiled by the CDC. The vaccination regimen licensed in 1970 consisted of six (6) 0.5 mL doses of vaccine administered subcutaneously (SC) at 0, 2, and 4 weeks and 6, 12, and 18 months with the recommendation of annual boosters thereafter to maintain immunity. On June 20, 2005, Emergent BioDefense Operations Lansing, Inc. (Emergent) submitted a Biologics License Application supplement (sBLA) containing interim immunogenicity and safety data from a CDC sponsored and conducted study, AVA 000 (under IND -(b)(4)- to support proposed changes to the route of administration (from SC to intramuscular (IM)) and vaccination schedule (dropping the Week 2 dose). CBER identified deficiencies within the submission, which were resolved after several review cycles. CBER issued an approval letter on December 11, 2008, granting Emergent approval for the proposed labeling change to administer BioThrax via an alternate route of administration (IM) and an alternate (abbreviated) dosing schedule.

Emergent submitted another sBLA (STN 103821/5203) on February 16, 2010, based on the complete study report of AVA 000, seeking further changes to the vaccination schedule. With AVA 000 completed and safety and immunogenicity data for the entire 43 month study duration (i.e. "the full study report") available, Emergent sought licensure for marketing of BioThrax using an abbreviated schedule that involved elimination of the Month 12 and Month 18 doses of BioThrax. The supplemental was filed on April 13, 2010. The proposal sought a change from the currently approved immunization schedule of a 5-dose primary series given IM or SC at Week 0, Month 1, 6, 12, and Month 18, with yearly boosters thereafter, to an IM or SC immunization using a 3-dose primary series at Week 0, 1 month, and 6 months with recommendation of subsequent booster injections of BioThrax at 3 year intervals for individuals aged 18 through 65 years, who remain at risk.

After reviewing the submitted data, CBER determined that the data did not support the proposed indication of a three dose primary series followed by boosters every three years for individuals determined to be at risk. The data demonstrated a marked decline of immunogenicity between the final dose of the primary series, administered at Month 6, and the three year booster dose, administered at Month 42. In the absence of data establishing a threshold level of antibody needed to protect against the development of anthrax disease following inhalational exposure and with the marked inferiority of antibody levels in the period between the 6 month and 42 month doses, as compared to antibody levels in individuals receiving interim doses in accordance with the licensed schedule, CBER could not grant approval of the reduced dose schedule requested by the sponsor. Additionally, although a robust immune response was seen after the Month 42 dose in individuals receiving only the three dose primary series, the lack of animal challenge data assessing whether this anamnestic response occurred rapidly enough following respiratory exposure to anthrax spores to prevent disease development did not permit approval of this abbreviated regimen. Emergent was sent a CR letter on November 22, 2010, and responded on November 15, 2011, with a proposal to redefine the primary vaccination series as three doses of BioThrax administered intramuscularly at Months 0, 1 and 6 followed by booster doses at 12 and 18 months after initiation of the series, and at 1-year intervals thereafter for persons who remain at risk, which is supported by the data submitted in the sBLA.

II. VACCINE INFORMATION

The proposed indication and usage for BioThrax is active immunization for prevention of disease caused by *Bacillus anthracis* in persons 18 through 65 years of age at high risk of exposure.

BioThrax is prepared from a sterile filtrate culture fluid of a nonencapsulated strain of *Bacillus anthracis* and contains proteins, including the 83kDa protective antigen protein (PA). It is formulated to contain 1.2 mg/mL aluminum, added as aluminum hydroxide in 0.85% sodium chloride and 25 µg/mL (0.0025%) benzethonium chloride and 100 µg/mL (0.0037% formaldehyde), added as preservatives. Lots --(b)(4)--, FAV074, FAV079, FAV087, FAV107, and --(b)(4)-- of vaccine were used in the study.

III. CHEMISTRY, MANUFACTURING, AND CONTROLS

AVA (Anthrax Vaccine Adsorbed, BioThrax) is a licensed vaccine, therefore no new manufacturing processes, methods, specifications, or results of product tests were submitted for review. CMC review for this supplement comprised review of the assay methodology employed in the pivotal clinical study AVA 000.

Review of Assays under STN 103921/5203:

A review of the methodology and validation of the Lethal Toxin Neutralization Assay (TNA) and Anti-PA IgG ELISA was performed by Leslie Wagner and submitted to the file on October 25, 2010. Tests evaluated by Ms. Wagner were those used to evaluate the immunogenicity responses elicited by BioThrax given by an alternative dosing schedule and route of administration to support a claim of non-inferiority relative to the licensed schedule and route of administration. The anti-PA IgG ELISA was previously reviewed on December 9, 2008, for approval of a related supplement (103821/5080) from the same study (AVA 000) for changing the route of administration from SC to IM and dropping the 2 week dose. The ELISA endpoint comparisons were used for both the interim and final analyses.

Ms. Wagner concluded that the immunoassays used to measure the antibody responses to BioThrax were adequate for this application. Demonstration of acceptable performance of the assays was essential for approval of this labeling change because the immunogenicity data provided the basis for comparing the immunogenicity of the proposed revised dosing schedule to the currently licensed schedule.

Immunogenicity Endpoints:

Three primary immunogenicity endpoints, as measured by ELISA, were assessed in study AVA 000: (1) the geometric mean concentration (GMC); (2) the geometric mean titer (GMT); and (3) the four-fold rise in geometric mean titer.

GMC and GMT:

Antibody concentrations and titers less than LLOQ were assigned a non-zero number for the purposes of calculating GMC and GMT endpoints as follows:

1) Antibody concentrations less than the LLOQ --(b)(4)-- were assigned a value of (b)(4) LLOQ --(b)(4)-- .
2) Antibody titers less than the LLOQ (b)(4) were assigned a value of (b)(4) LLOQ.

Use of these definitions required demonstration that the assay accuracy was sufficiently high and variability sufficiently low such that values at or above the assay LLOQ could be measured reliably. Ms. Wagner reviewed the assay validation data provided by the CDC and cross-referenced by the sponsor and concluded that the sponsor provided adequate evidence to support the above definitions.

Four-fold Rise and Threshold Response:
The four-fold rise in antibody titer endpoint was defined as the proportion of subjects who manifest equal to or greater than a four-fold rise in antibody titer as compared to pre-immunization levels. For subjects with an antibody concentration or titer less than the LLOQ pre-immunization, the post-immunization sample needed to be equal to or greater than four times the LLOQ (14.8 µg/mL or 232, respectively). The threshold response immunogenicity endpoint was defined as the proportion of subjects achieving an antibody concentration or titer equal or greater to a pre-defined threshold for antibody concentration -------(b)(4)----------.

Use of the four-fold response definition required demonstration that the assay variability was sufficiently low that, when a four-fold rise was observed, there was a high probability that this represented a true increase rather than random variation. Ms. Wagner reviewed the assay precision data provided and concluded that the assay precision was adequate to support the fourfold response definition.

Toxin Neutralization Assay (TNA)
The TNA measures functional activity of antibodies targeting anthrax PA. For the clinical evaluation, two types of secondary immunogenicity endpoints determined by the TNA were considered: (a) the TNA ED_{50} GMT (ED_{50} defined as the dilution of serum resulting in 50% neutralization of anthrax lethal toxin) and (b) the four-fold rise in TNA ED_{50} GMT. Ms. Wagner did not identify any deficiencies in the TNA methodology or validation. The TNA was evaluated for the following attributes during validation: specificity, dilutional linearity, accuracy, precision, intermediate precision, limits of quantitation (upper and lower), robustness, and ruggedness. The original study protocol specified that all study samples would be analyzed by ELISA, with a subset of subjects (~ 30%) further analyzed by TNA. CBER agreed to TNA testing in a subset of subjects rather than in the full cohort given the inherent complexities of cell-based tests and because the assay was only in the early stages of development when Study AVA 000 was started in 2000. In the final analysis, the sponsor indicated that 48% of total samples collected were tested for both anti-PA IgG using ELISA and TNA. Of the 1563 subjects, 97% had ≥ 1 serum samples evaluated in the TNA assay. These data were from a 30% random selection of samples from study subjects and all serum samples from a 359 subject cohort in the Correlates of Protection (COP) sub-study; a separate study conducted in a subset of subjects from Study AVA 000 that evaluated exploratory endpoints such as cellular immune responses.

TNA GMT:
To calculate the TNA GMT, the LLOQ for TNA ED_{50} titers (36) were assigned a value of ½ LLOQ (18). Ms. Wagner reviewed the assay validation data provided by the CDC and cross-referenced by the sponsor and concluded that the data supported this definition.

TNA 4-fold rise and threshold response:
These immunogenicity endpoints were defined as follows:
(1) The proportion of subjects with equal to or greater than a four-fold rise in TNA ED_{50} titer, as compared to pre-immunization levels. For subjects with TNA ED_{50} titers less than the LLOQ pre-immunization, the post-immunization sample needed to be equal to or greater than four times the LLOQ (144).
(2) The proportion of subjects achieving a TNA ED_{50} titer equal to or greater than a pre-defined threshold for antibody titer (160).

Ms. Wagner reviewed the assay precision data and concluded that the sponsor has provided evidence that the precision was adequate to support the fourfold response definition above.

IV. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Not applicable.

V. CLINICAL PHARMACOLOGY

Not applicable. See Clinical Review below.

VI. CLINICAL/ STATISTICAL

Immunogenicity and Safety

Analysis of efficacy and safety for this BLA efficacy supplement was based on the final study report for AVA 000 (43 months of data) which comprised a single, prospective, randomized, double-blind, placebo-controlled study designed to evaluate the immunogenicity and reactogenicity elicited by BioThrax given by different routes of administration (SC versus IM) and via different dosing regimens. Study subjects were randomized into 1 of 6 study groups with approximately 260 subjects per group. The dose groups and dosing regimens are summarized in Table 1:

Table 1. Anthrax Clinical Trial AVA 000: Schedule of Injections

Study Group and Route	Week 0	Week 2	Week 4	Month 6	Month 12	Month 18	Month 30	Month 42
TRT-8SC	BioThrax	BioThrax	BioThrax	BioThrax	BioThrax	BioThrax	BioThrax	BioThrax
TRT-8IM	BioThrax	BioThrax	BioThrax	BioThrax	BioThrax	BioThrax	BioThrax	BioThrax
TRT-7IM	BioThrax	S	BioThrax	BioThrax	BioThrax	BioThrax	BioThrax	BioThrax
TRT-5IM	BioThrax	S	BioThrax	BioThrax	S	BioThrax	S	BioThrax
TRT-4IM	BioThrax	S	BioThrax	BioThrax	S	S	S	
CNT-8IM	S	S	S	S	S	S	S	S
CNT-8SC	S	S	S	S	S	S	S	S

TRT = Treatment, CNT= Control, S = Saline placebo. *All participants received the same number of injections.

The objectives of this trial were to support one or more abbreviated dosing schedules of BioThrax given via the IM route of administration. On December 11, 2008 the FDA approved a change in Emergent's BLA for BioThrax (STN 103821/5080) to include a change in schedule from 0, 2, 4 weeks and 6, 12, and 18 months of administration of BioThrax to an abbreviated schedule of 0, 4 weeks, and 6, 12, and 18 months. A change in the route of administration from SC to IM also was approved. This prior efficacy supplement was approved based on analysis of data on the first 1005 study participants through month seven of Study AVA 000 (the interim study report). It was the sponsor's intention to further decrease the number of doses of BioThrax and demonstrate non-inferiority of the other abbreviated dosing regimens (TRT-5IM and TRT-4IM), requiring the demonstration of non-inferiority of the respective dosing regimens to the licensed regimen (TRT-8SC group) at later time points in the study. A hierarchical statistical approach was proposed and applied to the non-inferiority analysis utilizing the final study population of 1563 subjects. It is this analysis that constituted the immunogenicity evaluation for the final study report of AVA 000.

Immunogenicity was assessed by assaying serial blood samples obtained from all subjects at the Week 8 and Months 7, 13 19, 31 and 43 time points using ELISA and TNA assays, as previously described.

Immunogenicity evaluation using the unimputed, according-to-protocol (ATP) population in the full study report of AVA 000 involved primary analyses with comparisons to the TRT-8SC group which were hierarchical, as presented in the SAP and listed below:

1. If the TRT-7IM group was non-inferior to the TRT-8SC group at Months 13 and 19, use of the TRT-7IM regimen would be supported (at 0, 1, 6, 12, 18 months and annual boosters).
2. If the TRT-5IM group was non-inferior to the TRT-8SC group at Months 19 and 43, use of the TRT-5IM regimen would be supported (0, 1, 6, 18 months and a booster every 2 years).
3. If the TRT-4IM group was also non-inferior to the TRT-8SC group at Month 43, use of the TRT-4IM regimen would be supported (0, 1, 6 months and a booster every 3 years).

Using the 3-tier hierarchy, TRT-7IM, TRT-5IM, and TRT-4IM were sequentially compared to the Group A licensed active control (TRT-8SC). Non-inferiority had to be achieved for all three primary immunogenicity endpoint comparisons at the previous tier, in order for the next tier to be evaluated.

Immunogenicity Results:

Review of all immunogenicity endpoints evaluated in AVA 000—primary and secondary (including TNA data as secondary endpoints)--demonstrated non-inferiority of the TRT-4IM abbreviated schedule treatment group when compared to the currently licensed regimen of BioThrax (TRT-8SC and TRT-8IM) at Months 7 (under the TRT-COM group) and 43. The immunogenicity observed in response to the abbreviated regimen, however, did not demonstrate non-inferiority during the interim period from Month 12 through Month 42. Primary immunogenicity data are presented in Table 2.

Immune responses for the TRT-4IM (Group F) and TRT-5IM groups (Group E) evaluated at Month 13, 19, and 31 were significantly lower and statistically inferior to those seen for the TRT-8SC and TRT-8IM groups. Conversely, the Month 7 antibody levels of Group D (TRT-7IM) were non-inferior to Month 13 and 19 antibody levels after a 0 and 4 week, and 6 month primary IM series followed by IM booster injections at 12 and 18 months (see Table 2).

Table 2: Primary Immunogenicity Endpoints; (According to Protocol, Unimputed Data)

(*STN 103821/5023, February 16, 2010, Section 10.1.2.1. Primary Efficacy Variable, Table 11, Pages 73-75 of 508)*

	Week 4	Week 8	Month 7	Month 13	Month 19	Month 31	Month 43
Anti-PA Specific IgG GMC, mcg/mL							
	n GMC 95%CI	n GMC 95%CI	n GMC 95%CI	n GMC 95%CI	n GMC 95%CI	n GMC 95%CI	n GMC 95%CI
TRT-8SC	**242** **49.72** **(43.32, 57.06)**	235 94.29 (82.08, 108.31)	219 201.14 (174.71, 231.56)	203 201.67 (174.77, 232.71)	190 193.45 (167.29, 223.69)	167 250.07 (215.38, 290.34)	**144** **216.83** **(185.80, 253.05)**
TRT-7IM*	**723** **2.63** **(2.39, 2.89)**	**698** **46.39** **(42.18, 51.01)**	**636** **206.09** **(187.12, 226.96)**	203 229.86 (203.20, 260.02)	192 204.95 (180.82, 232.29)	169 263.13 (231.09, 299.61)	139 254.80 (222.03, 292.40)
TRT-5IM*				**399** **28.64** **(25.79, 31.81)**	174 293.60 (258.30, 333.73)	153 33.68 (29.48, 38.48)	141 310.02 (270.49, 355.33)
TRT-4IM*					**193** **13.71** **(12.11, 15.53)**	**179** **7.80** **(6.87, 8.86)**	**157** **433.20** **(379.58, 494.40)**
Anti-PA Specific IgG GMT							
	n GMT 95%CI	n GMT 95%CI	n GMT 95%CI	n GMT 95%CI	n GMT 95%CI	n GMT 95%CI	n GMT 95%CI
TRT-8SC	**242** **565.16** **(492.57, 648.45)**	235 1048.50 (913.05, 1204.05)	219 2211.94 (1921.78, 2545.90)	203 2184.59 (1893.62, 2520.26)	190 2080.89 (1799.87, 2405.79)	**167** **2677.97** **(2306.82, 3108.83**)	**144** **2282.36** **(1955.79, 2663.45)**
TRT-7IM*	**723** **36.61** **(33.32, 40.23)**	**698** **514.57** **(468.08, 565.68)**	**636** **2257.09** **(2050.12, 2484.94)**	203 2546.81 (2251.11, 2881.35)	192 2254.56 (1988.85, 2555.75)	169 2867.88 (2518.14, 3266.19)	139 2760.35 (2404.66, 3168.64)
TRT-5IM*				**399** **296.08** **(266.67, 328.74)**	174 3167.26 (2785.88, 3600.85)	153 348.89 (305.33, 398.66)	141 3286.41 (2866.50, 3767.83)
TRT-4IM*					**193** **135.30** **(119.44, 153.26)**	**179** **79.63** **(70.10, 90.44)**	**157** **4683.79** **(4102.99, 5346.80)**

	Week 4	Week 8	Month 7	Month 13	Month 19	Month 31	Month 43
4-fold response							
	n 4-fold response 95%CI	n 4-fold response 95%CI	n 4-fold response 95%CI	n 4-fold response 95%CI	n 4-fold response 95%CI	n 4-fold response 95%CI	n 4-fold response 95%CI
TRT-8SC	**242** **80.99** **(75.47, 85.73)**	235 94.89 (91.25, 97.33)	219 98.63 (96.05, 99.72)	203 99.51 (97.29, 99.99)	190 98.95 (96.25, 99.87)	167 100.00 (97.82, 100.00)	**144** **100.00** **(97.47, 100.00)**
TRT-7IM*	**723** **4.15** **(2.82, 5.87)**	**698** **78.80** **(75.57, 81.77)**	**636** **97.80** **(96.33, 98.79)**	203 100.00 (98.20, 100.00)	192 98.96 (96.29, 99.87)	169 100.00 (97.84, 100.00)	139 100.00 (97.38, 100.00)
TRT-5IM*				**399** **60.40** **(55.41, 65.23)**	174 99.43 (96.84, 99.99)	153 63.40 (55.24, 71.03)	141 99.29 (96.11, 99.98)
TRT-4IM*					**193** **37.82** **(30.96, 45.07)**	**179** **22.35** **(16.47, 29.16)**	**157** **99.36** **(96.50, 99.98)**

CI: Confidence Interval; *Groups TRT-7IM, -5IM, and -4IM combined as group TRT-COM through Month 7 of the study, GMC: geometric mean concentration. GMT: geometric mean titer. IM: Intramuscular; SC: Subcutaneous; NA: not applicable.

Immune responses for the TRT-4IM (Group F) and TRT-5IM groups (Group E) evaluated at Months 13, 19, and 31 were significantly lower and statistically inferior to those seen for the TRT-8SC and TRT-8IM groups. Conversely, the Month 7 antibody levels of Group D (TRT-7IM) were non-inferior to Months 13 and 19 antibody levels after a Weeks 0 and 4, and Month 6 primary IM series followed by IM booster injections at 12 and 18 months (see Table 2).

The immune response data for the TRT-4IM group were high at Month 43. These data provide evidence that, even without doses at Months 12, 18, and 30, a booster dose three years after the Month 6 primary dose can stimulate a vigorous antibody response. Although the high titers seen at Month 43 suggests the stimulation of a robust anamnestic immune response, bridging animal data were not submitted by the sponsor, as originally planned, to evaluate whether this response would develop rapidly enough following inhalational exposure to anthrax spores to provide protection against the development of anthrax disease between Month 6 and Month 42 doses when baseline antibody levels have declined substantially.

Because the study was not carried out beyond Month 43 and duration of the immune response beyond Month 43 was not evaluated, it is not possible to determine whether an indication for tri-annual administration of booster doses, as sought by Emergent, would provide adequate protection in the period between doses.

Immunogenicity evaluation from the interim study report (n=1005 subjects) demonstrated non-inferiority at 7 months (post-3rd vaccination) for both the 4-dose SC (TRT-8SC) and IM (TRT-8IM) vaccination series and the 3-dose series (TRT-COM) for all three primary immunogenicity endpoints (GMC, GMT, and 4-fold rise of anti-PA antibody titer). These data support a redefinition of protection as occurring after receipt of a 3-dose primary series of BioThrax at Week 0 and Months 1 and 6. These results also were consistent with findings of the Brachman study, which supported the initial licensure of BioThrax and suggested that a 3rd dose of BioThrax vaccine at Month 6 was necessary to attain protective antibody levels against *B. anthracis*.

Overall, a gender analysis did not reveal any important differences between male and female subjects in antibody response following vaccination. However, when subset analysis was performed for gender by treatment interaction, there was a statistically significant lower antibody response in males at Month 31 as compared to females at the same time point. This finding was considered an outlier and not clinically significant because similar immune responses between males and females were noted at all other time points in study AVA 000.

When the primary immunogenicity endpoints were compared by age group (< 30 years, 30 to < 40 years of age, 40 to < 50 years of age and > 50 years of age), in general a decrease in antibody response was seen with increasing age category. With few exceptions, within a study group, subjects < 30 years of age mounted an immune response greater than the other groups. This trend for each older age group to have overall lower immune responses was seen throughout the study duration.

Race was represented by 3 categories: “white”, “black” and “other”. When antibody responses were analyzed by race across study groups and by dose results varied with no clear pattern. When statistically significant differences did occur in pairwise comparisons between categories, almost always the antibody responses in “whites” and “other” race categories exceeded the responses in “blacks”.

Immunogenicity Conclusions:

The clinical reviewer concluded that the immunogenicity results of study AVA 000 do not support the originally proposed change in dosing schedule for BioThrax: 0.5 mL given IM at Month 0, 1, and 6 (primary dose series), with tri-annual boosters. The data, however, do support that protective antibody levels are achieved after receiving three BioThrax doses (at Month 0, 1 and month 6), with booster vaccinations required at Months 12 and 18 and yearly thereafter to maintain protective antibody levels.

Recommendations for catch up administration of BioThrax in the scenario where doses may have been missed or delayed, cannot be made at this time, based on the data reviewed in this sBLA.

Statistical Review

Dr. Tsai-Lien Lin conducted the statistical review of sBLA STN 103821/5023, which was completed on November 9, 2010. Dr. Lin noted that overall, although the proportion of subjects in the ATP population dropped substantially over time, as expected for a study with long study duration, the major reasons for subjects being excluded from the ATP population generally appeared not to be 'treatment related'. The lowest percentage of completers was observed in the TRT-8SC group (66%). This was not significantly different from that of the placebo group (70%). The percentage of missing immunogenicity data among ATP subjects was generally small and also showed no pattern relating to treatment. Dr. Lin accordingly deemed the efficacy analysis results to be reliable for the purposes of immunogenicity outcome conclusions.

For immunogenicity analysis, Dr. Lin noted that although the immune response at Month 43 for the proposed dosing regimen (TRT-4IM) was quite high (in fact, about twice as high as the TRT-8SC group), the TRT-4IM data only provided evidence that without doses at Months 12, 18, and 30, an additional dose 3 years after the Month 6 primary dose could produce a high 'boosted' immune response. The TRT-5IM data showed that without the Month 12 dose, a dose at Month 18 would boost to an antibody level that was non-inferior to the TRT-8SC regimen one month following booster vaccination. In addition, the kinetics sub-study showed that it took approximately 9 days to reach peak antibody levels after each vaccination from Month 6 onwards. As stated in Dr. Lin's review, '*it is not known whether circulating antibody is critical for protection after the Month 6 dose and whether the circulating antibody level before reaching the peak is enough to afford protection during the period of low antibody level between the last primary dose and the booster dose 3 years later*'.

The data from Study AVA 000 were not deemed sufficient to confirm that the TRT-4IM dosing regimen could provide adequate protection during the period of low circulating antibody levels between Months 7 and 43 without knowledge of the immune correlate of protection for *Bacillus anthracis*, the role of circulating antibody in protecting against anthrax disease during this period, and the potential for an anamnestic response to develop rapidly enough to provide protection.

Regarding the safety analysis, Dr. Lin noted that IM administration was generally associated with a statistically significant decrease in any solicited local AEs when compared with SC administration, by dose, for the in-clinic dataset. Incidence of any moderate or severe local AEs was consistently lower in the IM groups compared to the SC group. Statistically significant

decreases in any systemic AEs were also observed for the IM groups when compared to the SC group.

Risk Assessment

The pivotal study AVA 000 raised no new safety concerns. In general, the safety and reactogenicity profile of BioThrax under AVA 000 appeared similar to that already discussed in the BioThrax label. Based on the information that is available at this time, a Risk Evaluation and Mitigation Strategy will not be required.

Post Marketing Commitments and Post Marketing Requirements

None under BLA STN 103821/5203.

PREA

The sponsor did not submit clinical data that would support the use of BioThrax in the pediatric population nor did they seek a pediatric indication for BioThrax. The efficacy supplement underwent PeRC review and was granted a full pediatric waiver under the Pediatric Research Equity Act (PREA).

Bioresearch Monitoring

CBER conducted an inspection of three clinical study sites as part of the initial review of this sBLA and a report was submitted on September 17, 2007. A more recent BIMO inspection for the final clinical study report of AVA 000 was conducted in 2010 at two clinical study sites. These inspections did not reveal problems that would impact the data submitted in the application.

VII. SAFETY

Subject safety was evaluated in AVA 000 using several different data sources. Adverse events (AEs) were categorized as solicited or unsolicited local or systemic AEs which were prospectively defined by the sponsor. Serious AEs (SAEs) were evaluated separately using MedDRA body system classification and pregnancy outcomes were included as a distinct subcategory of SAEs.

The safety evaluation for the full AVA 000 study report did not reveal any clinical concerns or safety signals. The majority of AEs were related to cutaneous reactogenicity and were mild to moderate in severity.

In general, following each dose of vaccine, for many local solicited adverse events, the rate of occurrence was significantly lower in all treatment groups that received the vaccine via the IM route as compared to those that received the vaccine via the SC route of administration. Injection site reactions, including warmth, tenderness, itching, erythema, induration, edema, and nodule formation, consistently occurred at lower frequencies and for shorter duration in subjects given BioThrax by the IM route. This same pattern was not consistently observed for solicited systemic adverse events (i.e., fatigue and muscle ache was generally reported more commonly in the TRT-IM study groups compared to the TRT-8SC study group). Female subjects reported a greater frequency of both local and systemic AEs than male subjects.

The most common AEs consisted of local cutaneous reactions (erythema, pain, induration). Cutaneous AEs were highest in frequency for the TRT-8SC group, lowest in the TRT-4IM group (for an active treatment group) and were highest in female subjects throughout the study but

these differences were not statistically significant. The highest frequency of AEs appeared to peak around the second dose of vaccine. Most local and systemic AEs were mild or moderate in severity; the proportion of subjects with 'severe' AEs was generally exceedingly low (< 1%). In the case of fever, it was noted that for all treatment groups, the majority of subjects failed to report fever; hence a statistical comparison of the proportion of subjects with this AE for the different treatment groups was not available.

Evaluation of in-clinic systemic AEs for all treatment groups revealed a slightly higher frequency of fatigue in the TRT-8SC groups vs. the TRT-IM groups and a slightly higher frequency of muscle ache in the TRT-8IM and TRT-7IM groups vs. all other treatment groups. Overall, systemic AEs were low across all treatment groups and moderate-severe systemic AEs were < 3.0% in frequency across all treatment groups.

A review of the most common solicited and unsolicited AEs (occurring in ≥ 10% of subjects) by the MedDRA system organ class and preferred term, where the frequency in the active (BioThrax) treatment group exceeded that of the placebo group is presented in Table 3.

Table 3. Solicited and Unsolicited AEs Occurring in ≥ 10% of Subjects in any Treatment Group, and with a Higher Frequency in at Least One BioThrax Treatment Group, Study AVA 000 Safety Population

(*STN 103821/5023, February 16, 2010, Section 11.3.2.2. Common Adverse Events, Table 120, Pages 219-222 of 508)*

MedDRA Preferred Term	TRT-4IM N=268	TRT-8SC N=259	TRT-8IM N=262	TRT-7IM N=256	TRT-5IM N=258	All IM Groups Combined N=1044	Placebo (IM + SC) N=260
Injection site tenderness	244 (91.0%)	251 (96.9%)	241 (92.0%)	243 (94.9%)	237 (91.9%)	965 (92.4%)	110 (42.3%)
Injection site pain	222 (82.8%)	226 (87.3%)	223 (85.1%)	224 (87.5%)	221 (85.7%)	890 (85.2%)	84 (32.3%)
Injection site erythema	195 (72.8%)	244 (94.2%)	209 (79.8%)	207 (80.9%)	187 (72.5%)	798 (76.4%)	137 (52.7%)
Myalgia	195 (72.8%)	197 (76.1%)	185 (70.6%)	188 (73.4%)	186 (72.1%)	754 (7mw2.2%)	130 (50.0%)
Injection site joint movement impairment	188 (70.2%)	163 (62.9%)	179 (68.3%)	177 (69.1%)	176 (68.2%)	720 (69.0%)	42 (16.2%)
Headache	187 (69.8%)	203 (78.4%)	173 (66.0%)	194 (75.8%)	181 (70.2%)	735 (70.4%)	177 (68.1%)
Injection site swelling/lump	184 (68.7%)	248 (95.8%)	215 (82.1%)	218 (85.2%)	200 (77.5%)	817 (78.3%)	120 (46.2%)
Fatigue	181 (67.5%)	199 (76.8%)	187 (71.4%)	187 (73.1%)	177 (68.6%)	732 (70.1%)	158 (60.8%)
Injection site warmth	106 (39.6%)	223 (86.1%)	154 (58.8%)	140 (54.7%)	122 (47.3%)	522 (50.0%)	36 (13.8%)
Injection site bruising	80 (29.9%)	150 (57.9%)	101 (38.6%)	85 (33.2%)	101 (39.2%)	367 (35.2%)	74 (28.5%)
Injection site pruritus	73 (27.2%)	186 (71.8%)	114 (43.5%)	101 (39.5%)	71 (27.5%)	359 (34.4%)	32 (12.3%)
Nasopharyngitis	62 (23.1%)	64 (24.7%)	61 (23.3%)	58 (22.7%)	59 (22.9%)	240 (23.0%)	56 (21.5%)
Arthalgia	52 (19.4%)	57 (22.0%)	50 (19.1%)	45 (17.6%)	50 (19.4%)	197 (18.9%)	44 (16.9%)
Back Pain	51 (19.0%)	43 (16.6%)	46 (17.6%)	42 (16.4%)	43 (16.7%)	182 (17.4%)	38 (14.6%)
Pharyngolaryngeal	47	53	47	32	53	179	37

MedDRA Preferred Term	TRT-4IM N=268	TRT-8SC N=259	TRT-8IM N=262	TRT-7IM N=256	TRT-5IM N=258	All IM Groups Combined N=1044	Placebo (IM + SC) N=260
pain	(17.5%)	(20.5%)	(17.9%)	(12.5%)	(20.5%)	(17.1%)	(14.2%)
Nausea	36 (13.4%)	31 (12.0%)	26 (9.9%)	22 (8.6%)	25 (9.7%)	109 (10.4%)	26 (10.0%)
Cough	35 (13.1%)	32 (12.4%)	26 (9.9%)	28 (10.9%)	31 (12.0%)	120 (11.5%)	27 (10.4%)
Sinusitis NOS	34 (12.7%)	33 (12.7%)	36 (13.7%)	25 (9.8%)	30 (11.6%)	125 (12.0%)	22 (8.5%)
Dysmenorrhea	30 (11.2%)	22 (8.5%)	21 (8.0%)	27 (10.6%)	17 (6.6%)	95 (9.1%)	25 (9.6%)
Pain in Extremity	28 (10.5%)	29 (7.3%)	26 (9.9%)	27 (10.6%)	24 (9.3%)	105 (10.1%)	19 (7.3%)
Upper respiratory Tract infection NOS	25 (9.3%)	31 (12.0%)	23 (8.8%)	32 (12.5%)	24 (9.3%)	104 (10.0%)	19 (17.3%)
Diarrhea NOS	23 (8.6%)	27 (10.4%)	25 (9.5%)	20 (7.8%)	21 (8.1%)	89 (8.5%)	20 (7.7%)
Pyrexia	21 (7.8%)	38 (14.7%)	29 (11.1%)	21 (8.2%)	26 (10.1%)	97 (9.3%)	25 (9.6%)
Nasal congestion	19 (7.1%)	25 (9.7%)	20 (7.6%)	16 (6.3%)	28 (10.9%)	83 (8.0%)	19 (7.3%)

Deaths and SAEs:
Seven deaths were reported in the study but none were related to vaccine. A total of 231 SAEs were reported in 186 study subjects. The percent of SAEs was similar between the BioThrax combined groups (193/1303 or 1.5%) and the placebo group (38/260 or 1.5%). Seven of these were fatal events and the remaining 224 SAEs were non-fatal. These included 8 SAEs in 6 subjects who received BioThrax that were assessed by the medical monitor as 'possibly related' to study treatment. The remaining SAEs were assessed by the investigator and medical monitor as 'unrelated' or 'likely unrelated' to treatment.

Pregnancy Outcomes:
There were 51 pregnancies reported among 43 subjects during the study, including 4 subjects in the control group. Although pregnancy data seen in the full study report did not raise concerns about prenatal risk, the sponsor has initiated a pregnancy registry study (a post marketing commitment linked to sBLA 103821/5080) to more specifically address pregnancy risk.

VII. LABELING

Labeling and packaging were reviewed and a series of revisions were submitted to the BLA supplement. The current version (May 16, 2012) is acceptable for the approval of this supplement.

VIII. ADVISORY COMMITTEE MEETING

CBER determined that review of the sBLA for BioThrax by the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was not required because of CBER's extensive experience with BioThrax, because the current application was for evaluation of an abbreviated schedule of an approved vaccine and because no concerns or controversial issues were raised during the review of the supplement.

XI. OTHER RELEVANT REGULATORY ISSUES

There were no other relevant regulatory issues discussed during the review of this supplement.

X. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

1. *Recommended Regulatory Action*

Following the review of all supportive product and clinical data, the review committee recommends approval of this application, which redefines the primary vaccination series as three doses of BioThrax administered intramuscularly at Months 0, 1, and 6 followed by booster doses at 12 and 18 months after initiation of the series, and at 1-year intervals thereafter for persons who remain at risk.

2. *Risk/Benefit Assessment*

The quality, efficacy, and safety of this vaccine have been thoroughly reviewed and have been determined to be acceptable for use of this vaccine as indicated in the label.

3. *Recommendation for Postmarketing Risk Management Activities*

There was no recommendation for postmarketing risk management activities.

4. *Recommendation for Postmarketing Activities*

No postmarketing requirements (PMRs) or postmarketing commitments (PMCs) were requested under BLA STN 103821/5203.