HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BIOTHRAX safely and effectively. See full prescribing information for BIOTHRAX.

BIOTHRAX (Anthrax Vaccine Adsorbed)
Suspension for Intramuscular Injection
Initial U.S. Approval: 1970

----------RECENT MAJOR CHANGES----------
- Indications and Usage (1) December 2008
- Dosage and Administration (2.1, 2.2) December 2008

----------INDICATIONS AND USAGE----------
BioThrax is a vaccine indicated for the active immunization for the prevention of disease caused by *Bacillus anthracis*, in persons between 18 and 65 years of age at high risk of exposure. Since the risk of anthrax infection in the general population is low, routine immunization is not recommended. The safety and efficacy of BioThrax in a post-exposure setting have not been established.

----------DOSAGE AND ADMINISTRATION----------
- Immunization consists of a series of five 0.5 mL intramuscular doses. Administer 1 dose at 0 and 4 weeks and 6, 12, and 18 months.
- Individuals are not considered protected until they have completed the full vaccination series.
- Subsequent booster injections of 0.5 mL of BioThrax at one-year intervals are recommended for those who remain at risk. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Suspension for injection in 5.0 mL multidose vials containing 10 doses each. (3,11)

----------CONTRAINDICATIONS----------
- Severe allergic reaction (e.g. anaphylaxis) after a previous dose of BioThrax. (4)

----------WARNINGS AND PRECAUTIONS----------
- Administer with caution to patients with a possible history of latex sensitivity because the vial stopper contains dry natural rubber and may cause allergic reactions. (5.1).
- Pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination have been determined to outweigh the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this product, the patient should be apprised of the potential hazard to the fetus. (8.1)

----------ADVERSE REACTIONS----------
The most common (≥10%) local (injection-site) adverse reactions observed in clinical studies were tenderness, pain, erythema and arm motion limitation. The most common (≥5%) systemic adverse reactions were muscle aches, fatigue and headache. (6)

Serious allergic reactions, including anaphylactic shock, have been observed during post-marketing surveillance in individuals receiving BioThrax.

To report SUSPECTED ADVERSE REACTIONS, contact Emergent BioSolutions at 1-877-246-8472 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------DRUG INTERACTIONS----------
- Immunosuppressive therapies may diminish the immune response to BioThrax. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Safety and effectiveness of BioThrax have not been established in pregnant women or nursing mothers, or in pediatric or geriatric populations. (5, 8.1, 8.3, 8.4, 8.5)

See Section 17 For PATIENT COUNSELING INFORMATION.

Revised: December 2008

FULL PRESCRIBING INFORMATION CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BioThrax is a vaccine indicated for the active immunization for the prevention of disease caused by *Bacillus anthracis*, in persons between 18 and 65 years of age whose occupation or other activities place them at high risk of exposure.

Since the risk of anthrax infection in the general population is low, routine immunization is not recommended.

The safety and efficacy of BioThrax in a post-exposure setting have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Use a separate 1- or 1½ -inch 23- or 25-gauge sterile needle and syringe for each patient to avoid transmission of viral hepatitis and other infectious agents.

Shake the bottle thoroughly to ensure that the suspension is homogeneous during withdrawal. Inspect visually for particulate matter and discoloration prior to administration. If the product appears discolored or has visible particulate matter, DISCARD THE VIAL.

2.2 Dose and Schedule

Immunization consists of a series of 5 intramuscular doses administered at 0 and 4 weeks and 6, 12 and 18 months. Select a different injection site for each sequential injection of this vaccine. Do not mix with any other product in the syringe. Individuals should not be considered protected until they have received the full series of vaccinations. Do not inject BioThrax intravenously or intradermally.

Yearly booster injections of 0.5 mL intramuscularly are recommended for those who remain at risk.

When medically indicated, such as in persons with coagulation disorders or receiving medications that affect coagulation (e.g. warfarin), BioThrax may be administered by the subcutaneous route.

3 DOSAGE FORMS AND STRENGTHS

BioThrax is available as a sterile suspension in 5 mL multidose vials containing 10 doses each. *See Description section (11)* for the complete listing of ingredients.

4 CONTRAINDICATIONS

The use of BioThrax is contraindicated in persons with a history of anaphylactic or anaphylactic-like reaction following a previous dose of BioThrax.

5 WARNINGS AND PRECAUTIONS

5.1 Latex

Administer with caution to patients with a possible history of latex sensitivity because the vial stopper contains dry natural rubber and may cause allergic reactions.

5.2 Hypersensitivity Reactions

Before administration, the patient's medical immunization history should be reviewed for possible vaccine sensitivities and/or previous vaccination-related adverse reactions, to determine the existence of any contraindications to immunization. *[See Contraindications section (4)]* Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. *[See Contraindications section (4)]*

5.3 Pregnancy

Pregnancy Category D:

Pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination have been determined to outweigh the potential risk to the fetus. Results of a large observational study that examined the rate of birth defects among 37,140 infants born to U.S. military service women who received anthrax vaccine in pregnancy between 1998 and 2004 showed that birth defects were slightly more common in first trimester-exposed infants (odds ratio = 1.18, 95% confidence interval: 0.997, 1.41) when compared with infants of women vaccinated outside of the first trimester and compared to unvaccinated women.[1] While the increased birth defect rates were not statistically significant when compared with infants born to women vaccinated outside of pregnancy, pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination have been determined to outweigh the potential risk to the fetus.

The effect of BioThrax on embryo-fetal and pre-weaning development was evaluated in a developmental toxicity study using pregnant rabbits. One group of rabbits was administered BioThrax twice prior to gestation and during the period of organogenesis (gestation day 7). A second group of rabbits was administered BioThrax twice prior to gestation and on gestation day 17. BioThrax was administered at 0.5 ml/rabbit/occasion, by intramuscular injection. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted in this study.

BioThrax can cause fetal harm when administered to a pregnant woman. If this vaccine is used during pregnancy, or if the patient becomes pregnant during the immunization series, the patient should be apprised of the potential hazard to a fetus.

5.4 History of Anthrax Disease

History of anthrax disease may increase the potential for severe local adverse reactions.

5.5 Altered Immunocompetence

If BioThrax is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

5.6 Limitations of Vaccine Effectiveness

Vaccination with BioThrax may not protect all individuals. The extent to which one is protected prior to completion of the full immunization schedule is unknown.

6 ADVERSE REACTIONS

The most common ($\geq$10%) local (injection-site) adverse reactions observed in clinical studies were tenderness, pain, erythema and arm motion limitation. The most common ($\geq$5%) systemic adverse reactions were muscle aches, headache, and fatigue.

Serious allergic reactions, including anaphylactic shock, have been observed during post-marketing surveillance in individuals receiving BioThrax.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a product cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in clinical practice.

Local and systemic reactions were monitored in an open-label safety study of 15,907 doses of BioThrax administered by the subcutaneous route to approximately 7,000 textile employees, laboratory workers and other at risk individuals. Over the course of the 5-year study the following local reactions were reported: 24 (0.15% of doses administered) severe local reactions (defined as edema or induration measuring greater than 120 mm in diameter or accompanied by marked limitation of arm motion or marked axillary node tenderness), 150 (0.94% of doses administered) moderate local reactions (edema or induration greater than 30 mm but less than 120 mm in diameter), and 1,373 (8.63% of doses administered) mild local reactions (erythema only or induration measuring less than 30 mm in diameter). Four cases of systemic reactions were reported during the 5-year reporting period (<0.06% of doses administered). These reactions, which were reported to have been transient, included fever, chills, nausea and general body aches.

The CDC sponsored a randomized, double-blind, placebo-controlled, multi-center clinical study [NCT00119067] in which 1,564 healthy volunteers were enrolled *[See Clinical Studies section (14)]*. The objective of this study was to evaluate the effect of (1) changing the route of vaccine administration from subcutaneous (SQ) to intramuscular (IM), and (2) of reducing the number of doses on the safety and immunogenicity of BioThrax. A planned analysis of the first 1,005 subjects compared four treatment groups over a period of seven months in which subjects received a total of either three (3) or four (4) doses of BioThrax. Subjects were instructed to complete a 14-day post-vaccination diary card after the first 2 doses and a 28-day diary card after the subsequent doses to capture solicited and unsolicited adverse events. Adverse reaction data were also collected from in-clinic exams, which were performed prior to, and 15 to 60 minutes post each injection, at 1 to 3 days after each injection, and at 28 days after injections 3 and 4. Demographic characteristics for each respective treatment group in the analysis are provided in Table 1.

Table 1: Demographic characteristics: CDC Study

Study Group (Total vaccinated cohort n= 1,005)		**Group A BioThrax SQ Weeks-0-2-4-26 n=165**	**Group B BioThrax IM Weeks-0-2-4-26 n=170**	**Group C BioThrax IM Weeks-0-4-26 n=501**	**Placebo Control n=169**
Characteristic	Parameters or categories	Value or n (%)	Value or n (%)	Value or n (%)	Value or n (%)
Age	< 30 yrs	58 (35.15%)	42 (24.71%)	149 (29.74%)	52 (30.77%)
	30 to < 40 yrs	30 (18.18%)	44 (25.88%)	132 (26.35%)	35 (20.71%)
	40 to < 50 yrs	50 (30.30%)	52 (30.59%)	128 (25.55%)	51 (30.18%)
	≥ 50 yrs	27 (16.36%)	32 (18.82%)	92 (18.36%)	31 (18.34%)
Gender	Female	81 (49%)	87 (51 %)	249 (50 %)	83 (49%)
	Male	84 (51%)	83 (49 %)	252 (50%)	86 (51%)
Race	Caucasian	129 (78%)	126 (74%)	383 (76%)	130 (79%)
	African-American	28 (17%)	32 (19%)	96 (19%)	31 (18%)
	Other	8 (5%)	12 (7%)	22 (4%)	8 (5%)

Shown in Table 2 and Table 3, respectively, are the rates (percentage) of prospectively defined local and systemic solicited adverse reactions observed in the in-clinic exams.

The analysis of injection site (local) reactions demonstrated that administration of the vaccine by the IM route, as compared to the SQ route, resulted in a statistically significant reduction in reactogenicity (i.e. cutaneous adverse reactions). Injection site adverse reactions, including warmth, tenderness, itching, erythema, induration, edema, and nodule, consistently occurred at lower frequencies and for shorter duration in participants given BioThrax by the IM route. Route of administration did not statistically significantly influence the occurrence or duration of systemic adverse reactions, with the exception of muscle ache (increased occurrence only). Most local and systemic adverse reactions were mild or moderate in severity; the proportion of participants with severe adverse reactions reported was very low (< 1%). It was observed in this study that women receiving BioThrax reported significantly more injection-site adverse reactions than did men. This gender-related difference was seen regardless of the route of administration, but was more pronounced in those receiving the vaccine by the SQ route. Women also reported more systemic adverse reactions than men (in particular fatigue, muscle ache and headache), but these gender differences were not influenced by route of administration. A brief pain or burning sensation, felt immediately after vaccine injection, was reported by most study participants. The pain was rated on a visual analog scale as 0-10. It was described as significant (> 3) more often following SQ administration (41%) than IM administration (26%). Female participants generally experienced a higher pain scale rating than male participants.

Serious adverse reactions were infrequently reported during this study but two (2) important serious adverse reactions that were noted to be possibly related to BioThrax administration include: a case of anaphylaxis and a case of an ANA positive autoimmune disorder manifesting as a moderate bilateral arthralgia of the metacarpophalangeal (MCP) joints. The majority of serious adverse reactions reported were unrelated to vaccination. Out of a total of 44 pregnancies reported in this study, no distinct patterns of infant outcome were seen, with the majority of pregnancies uncomplicated and healthy term infants delivered. Of women who received vaccine approximately within the first trimester (n = 15), 2 reports of spontaneous abortion were reported, along with one report of a healthy term infant with mild right clubbed foot abnormality.

Table 2: Local Adverse Reactions: In-Clinic Solicited by Dose Number*

	TREATMENT ARM															
	Group B BioThrax IM Weeks-0-2-4-26				**Group C BioThrax IM Weeks-0-4-26†**				**Placebo SQ/IM Weeks-0-2-4-26‡**				**Group A BioThrax SQ Weeks-0-2-4-26**			
Number of Subjects (N)**	**170**				**501**				**169**				**165**			
	Dose				**Dose**				**Dose**				**Dose**			
	1	2	3	4	1	2†	3	4	1	2	3	4	1	2	3	4
	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
Adverse Reactions																
Warmth	4	8	6	11	3	1	10	9	2	0	0	0	28	37	29	36
Tenderness	51	61	37	42	47	10	52	51	5	6	6	9	67	72	45	60
Itching	1	3	4	9	0	1	3	6	0	0	0	0	4	15	21	19
Pain	23	23	11	17	18	4	23	15	2	2	3	3	18	24	8	16
Arm motion limitation	11	14	5	10	16	1	16	13	1	0	2	0	9	14	6	12
Erythema	13	22	21	31	10	8	20	25	12	10	8	13	52	60	57	63
Induration	5	9	8	11	4	3	9	14	1	2	4	3	26	32	30	43
Edema	4	12	13	16	3	1	13	11	1	4	3	2	14	28	27	29
Nodule	4	2	5	6	2	1	3	6	0	1	0	1	38	45	36	27
Bruise	6	4	3	3	4	3	5	4	4	6	2	4	5	5	5	3
Presence of any local adverse reaction	62	69	52	62	58	25	67	68	20	19	17	23	81	86	79	81
Presence of any moderate/severe local adverse reactions§	6	9	5	8	5	1	9	5	1	0	0	0	6	16	8	10
Presence of any large local adverse reactionl	0	1	3	1	0	0	1	2	0	0	0	0	1	1	5	3

*Per-dose, statistical assessment performed on Intent-to-Treat population data. Evaluations performed at 15-60 minutes and 1-3 days following each injection and prior to the next scheduled injection.

** N is the highest number per treatment arm; denominator (N) varied with dose number due to attrition over time.

†Subjects received saline (instead of BioThrax) for the Week 2 dose.

‡The two saline groups (SQ and IM) were combined.

§Moderate = causes discomfort and interferes with normal daily activities; Severe = incapacitating and completely prevents performing normal daily activities.

lLarge = an occurrence of induration, erythema, edema, nodule and bruise with a largest diameter greater than 120 mm.

Table 3: Systemic Adverse Reactions: In-Clinic Solicited by Dose Number*

	TREATMENT ARM															
	Group B BioThrax IM Weeks-0-2-4-26				**Group C BioThrax IM Weeks-0-4-26†**				**Placebo SQ/IM Weeks-0-2-4-26‡**				**Group A BioThrax SQ Weeks-0-2-4-26**			
Number of Subjects (N)**	**170**				**501**				**169**				**165**			
	Dose				**Dose**				**Dose**				**Dose**			
	1	2	3	4	1	2†	3	4	1	2	3	4	1	2	3	4
	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
Systemic Adverse Reactions																
Fatigue	7	10	12	8	8	5	12	8	5	5	6	5	8	9	7	8
Muscle ache	11	10	6	6	9	2	14	7	1	2	3	3	6	8	3	5
Headache	4	7	9	5	5	5	7	4	2	6	3	1	7	6	8	9
Fever > 100.4 °F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tender/painful axillary adenopathy	0	1	0	1	0	0	1	0	0	0	0	0	1	1	4	1
Presence of any systemic adverse reaction	20	22	21	15	18	10	26	15	8	10	12	8	17	17	17	17
Presence of any moderate/severe systemic adverse reactions§	1	3	3	4	2	1	6	4	1	1	3	2	1	4	3	3

*Per-dose, statistical assessment performed on Intent-to-Treat population data. Evaluations performed at 15-60 minutes and 1-3 days following each injection and prior to the next scheduled injection.

** N is the highest number per treatment arm; denominator (N) varied with dose number due to attrition over time.

†Subjects received saline (instead of BioThrax) for the Week 2 dose.

‡The two saline groups (SQ and IM) were combined.

§Moderate = causes discomfort and interferes with normal daily activities; Severe = incapacitating and completely prevents performing normal daily activities.

Table 4 shows adverse events (excluding injection site reactions) that occurred in ≥2% of participants through Study Month 7, and excluding those that occurred at a lower rate than those observed in the placebo group.

Table 4: Solicited and Unsolicited Adverse Events Occurring in ≥ 2% of Subjects*

MedDRA Preferred Term	Group B BioThrax IM Weeks 0-2-4-26	Group C BioThrax IM Weeks 0-4-26	Placebo SQ/IM Weeks 0-2-4-26‡	Group A BioThrax SQ Weeks 0-2-4-26
Number of Subjects	**170**	**501**	**169**	**165**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Headache	108 (63.5)	312 (62.3)	82 (48.5)	111 (67.3)
Myalgia	105 (61.8)	360 (71.9)	63 (37.3)	101 (61.2)
Fatigue	104 (61.2)	311 (62.1)	82 (48.5)	101 (61.2)
Nasopharyngitis	26 (15.3)	61 (12.2)	13 (7.7)	18 (10.9)
Pharyngolaryngeal Pain	21 (12.4)	58 (11.6)	18 (10.7)	20 (12.1)
Back Pain	15 (8.8)	36 (7.2)	6 (3.6)	11 (6.7)
Diarrhea NOS	13 (7.7)	31 (6.2)	6 (3.6)	7 (4.2)
Dysmenorrhoea	12 (7.1)	36 (7.2)	11 (6.5)	7 (4.2)
Sinusitis NOS	12 (7.1)	24 (4.8)	8 (4.7)	7 (4.2)
Nausea	10 (5.9)	29 (5.8)	8 (4.7)	15 (9.1)
Hypersensitivity NOS	6 (3.5)	12 (2.4)	0 (0.0)	6 (3.6)
Neck Pain	5 (2.9)	16 (3.2)	3 (1.8)	1 (0.6)
Sinus Headache	5 (2.9)	7 (1.4)	0 (0.0)	3 (1.8)
Rigors	4 (2.3)	7 (1.4)	2 (1.2)	0 (0.0)
Upper Respiratory Tract Infection NOS	3 (1.8)	16 (3.2)	2 (1.2)	7 (4.2)
Influenza Like Illness	3 (1.8)	12 (2.4)	2 (1.2)	1 (0.6)
Lymphadenopathy	5 (2.9)	9 (1.8)	2 (1.2)	5 (3.0)
Rash NOS	0 (0.0)	12 (2.4)	1(0.6)	3 (1.8)
Joint Sprain	0 (0.0)	10 (2.0)	3 (1.8)	1 (0.6)
Pruritus	0 (0.0)	10 (2.0)	1 (0.6)	3 (1.8)

* Listed MedDRA terms (N) are limited to those for which the adverse reaction rate for BioThrax (Weeks 0-2-4-26 or Weeks 0-4-26) exceeds the adverse reactions rate for placebo (Weeks 0-2-4-26) through month 7 irrespective of causality and severity; for each MedDRA Preferred Term in this table, an adverse event is only listed once per subject, even if the adverse event occurs more than once during the 7-month observation period; events already listed in Table 2 are not listed here. The denominator includes any subject who was randomized and received at least one dose of vaccine.

‡ The two saline groups (SQ and IM) were combined

6.2 Postmarketing Experience

The following adverse events have been identified during postapproval use of BioThrax. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The reports included below are listed due to one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug.

- **Blood and lymphatic system disorders**
  Lymphadenopathy
- **Immune system disorders**
  Allergic reactions (including anaphylaxis, angioedema, rash, urticaria, pruritus, erythema multiforme, anaphylactoid reaction and Stevens Johnson syndrome)
- **Nervous system disorders**
  Headache, paresthesia syncope, tremor, ulnar nerve neuropathy
- **Musculoskeletal, connective tissue and bone disorders**
  Arthralgia, arthropathy, myalgia, rhabdomyolysis, alopecia
- **General disorders and administration site conditions**
  Injection site reactions (including pain, nodule, edema, induration, erythema, warmth, pruritus, cellulitis), fatigue, pyrexia, flu-like symptoms

Infrequent reports were also received of multisystem disorders defined as chronic symptoms involving at least two of the following three categories: fatigue, mood-cognition and musculoskeletal system.

No fatalities have been determined to have been causally related to the administration of BioThrax.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

No prospective, controlled clinical studies to assess the concomitant administration of BioThrax with other vaccines have been performed. If BioThrax is to be given at the same time as another injectable vaccine(s), the vaccine(s) should be administered at different injection sites.

BioThrax should not be mixed with any other vaccine in the same syringe or vial.

7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including chemotherapy, corticosteroids (used in high-doses longer than 2-weeks), and radiation therapy may reduce the response of BioThrax.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy and Fertility

Pregnancy: Category D. *See Warnings and Precautions section (5)*
Male Fertility: A retrospective study was performed at an in-vitro fertilization clinic to evaluate whether BioThrax may impact reproductive function in men. This study compared semen parameters, embryo quality, and pregnancy outcomes in 254 male clients who stated that they had received BioThrax, with those of 791 male clients who did not.[2] Prior receipt of BioThrax did not influence semen parameters (including concentration, motility and morphology), fertilization rate, embryo quality or clinical pregnancy rates.

8.3 Nursing Mothers
It is not known whether BioThrax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BioThrax is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established for BioThrax.

8.5 Geriatric Use
Clinical studies of BioThrax did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from subjects in the adult population under age 65. Sub-group analysis of study subjects < 30 years, 30 to < 40 years, 40 to < 50 years and > 50 years indicated that subjects in the > 50 years category had statistically insignificant but numerically lower immune responses than younger subjects.

11 DESCRIPTION
BioThrax, Anthrax Vaccine Adsorbed, is a sterile, milky-white suspension for intramuscular injections made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *Bacillus anthracis*. The production cultures are grown in a chemically defined protein-free medium consisting of a mixture of amino acids, vitamins, inorganic salts and sugars. The final product, prepared from the sterile filtrate culture fluid contains proteins, including the 83kDa protective antigen protein, released during the growth period and contains no dead or live bacteria. The final product is formulated to contain 1.2 mg/mL aluminum, added as aluminum hydroxide in 0.85% sodium chloride. The final product is formulated to contain 25 µg/mL benzethonium chloride and 100 µg/mL formaldehyde, added as preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Anthrax is a zoonotic disease caused by the gram-positive, spore-forming bacterium *Bacillus anthracis*. The spore form of *Bacillus anthracis* is the predominant phase of the bacterium in the environment and anthrax disease is contracted largely through the uptake of spores. Spores are markedly resistant to heat, cold, drought, UV light, and gamma radiation. Following germination at the site of infection, the bacilli can also enter the blood and lead to septicemia.

Virulence components of *Bacillus anthracis* include an antiphagocytic polypeptide capsule and three proteins known as protective antigen (PA), lethal factor (LF) and edema factor (EF). Individually these proteins are not cytotoxic but the combination of PA with LF or EF results in the formation of the cytotoxic lethal toxin and edema toxin, respectively. Although an immune correlate of protection is unknown, antibodies raised against PA may contribute to protection by neutralizing the activities of these toxins.[3] *Bacillus anthracis* proteins other than PA may be present in BioThrax, but their contribution to protection has not been determined.

13 NON-CLINICAL TOXICOLOGY
BioThrax has not been evaluated in non-clinical toxicology studies.

14 CLINICAL STUDIES
A controlled field study using an earlier version of a protective antigen-based anthrax vaccine, developed in the 1950's, that consisted of an aluminum potassium sulfate-precipitated cell-free filtrate from an aerobic culture, was conducted from 1955-1959.[4] This study included 1,249 workers [379 received anthrax vaccine, 414 received placebo, 116 received incomplete inoculations (with either vaccine or placebo) and 340 were in the observational group (no treatment)] in four

mills in the northeastern United States that processed imported animal hides. Prior to vaccination, the yearly average number of human anthrax cases (both cutaneous and inhalational) was 1.2 cases per 100 employees in these mills. During the trial, 26 cases of anthrax were reported across the four mills – 5 inhalation and 21 cutaneous. Of the five inhalation cases (four of which were fatal), two received placebo and three were in the observational group. Of the 21 cutaneous cases, 15 received placebo, three were in the observational group, and three received anthrax vaccine. Of those three cases in the vaccine group, one case occurred just prior to administration of the scheduled third dose, one case occurred 13 months after an individual received the third of the scheduled 6 doses (but no subsequent doses), and one case occurred prior to receiving the scheduled fourth dose of vaccine. Because the comparison of anthrax cases between the placebo and vaccine groups included both inhalation and cutaneous cases, the calculated efficacy of the vaccine to prevent all types of anthrax disease combined was 92.5% (lower 95% CI = 65%). The efficacy analysis in this study included all cases of anthrax disease, regardless of the route of exposure or manifestation of the disease.

Between 1962 and 1974, the Centers for Disease Control and Prevention (CDC) collected surveillance data on the occurrence of anthrax disease in mill workers or those living near mills in the United States.[5, 6] In that time period, individuals received either BioThrax or the earlier protective antigen-based anthrax vaccine used in the field trial described above. Of the 27 cases of anthrax identified by CDC, 24 cases occurred in unvaccinated individuals. In vaccinated individuals one case occurred after the person had been given one dose of anthrax vaccine and two cases occurred after individuals had been given two doses of anthrax vaccine. No documented cases of anthrax were reported for individuals who had received at least three doses of the recommended six doses of anthrax vaccine.

Between 2002 and 2008, the CDC sponsored a prospective double-blinded, randomized, placebo-controlled study to evaluate the impact on safety and immunogenicity of changing the administration route from SQ to IM, and reducing the number of doses (i.e. omitting the week 2 dose) [NCT00119067]. This study enrolled a total of 1,564 healthy civilian men and women between the ages of 18 and 61. Subjects were randomized to one of six groups. A planned analysis of the first 1005 subjects enrolled with 7 month follow-up was conducted to compare safety and immunogenicity of study groups at Week 8 (four weeks after the Week-4 dose) and Month 7 (one month after the Month-6 dose). These designations are used when referring to the data analyses of study groups:

Group A (N=165) received BioThrax via the SQ route of administration at Weeks 0, 2, 4 and Months 6, 12, 18 followed by 2 annual boosters (initial U.S. licensed route/schedule). Group A served as the active control in this study.

Group B (N=170) received BioThrax via the IM route of administration at Weeks 0, 2, 4 and Months 6, 12, 18 followed by 2 annual boosters.

Group C (N=501) received BioThrax via the IM route of administration at Weeks 0, 4 (no Week 2 dose) and Month 6 with various schedules thereafter. (Group C represents data from 3 randomized groups combined for the analysis because the schedules are identical through the Month 6 dose.)

The placebo group (N=169) received saline administered by the IM or SQ route, respectively, using the Weeks 0, 2, 4 and Months 6, 12, 18 schedule, followed by 2 annual boosters.

Immune responses were assessed using an ELISA and were reported as the serum geometric mean concentration (GMC) and geometric mean titers (GMT) of IgG antibodies directed against anthrax protective antigen (PA). Non-inferiority analyses of Group B vs. Group A and Group C vs. Group A were performed. The three immunogenicity endpoints were: (1) Geometric Mean Concentration (GMC) (µg/mL), (2) Geometric Mean Titer (GMT), and (3) percentage with 4-fold rise in anti-PA titer from baseline. These immunogenicity endpoints were assessed at the Week 8 and Month 7 time points. Group B (IM route) was shown to be non-inferior to Group A (SQ route) for all 3 primary endpoints at the Week 8 and Month 7 time points (Tables 5 and 6). Group C (abbreviated IM route) at the Week 8 time point (Table 7) was shown to be non-inferior to Group A for the percentage with 4-fold rise in titer but not non-inferior to Group A for GMCs and GMTs. However, by the Month 7 time point (Table 8). Group C was non-inferior to Group A for all 3 primary endpoints. The elimination of the Week 2 dose did not impact the immune response following the Month 6 vaccination.

The level of protection against *Bacillus anthracis* prior to completion of the full vaccination series is unknown.

In an exploratory subgroup analysis, a diminished immune response was noted in male subjects in Group B (IM route) at the 8 week time point compared to male subjects vaccinated via the SQ route (Group A). The diminished immune response in males was not, however, seen by 7 months (i.e. after the fourth dose of vaccine). At the 7 month time point, non-inferiority was observed between the IM and SQ routes in male subjects. A summary of the gender-by-treatment interaction findings for the three immunogenicity endpoints at the week 8 and month 7 time point is provided in Table 9.

Table 5: Immune Responses at Week 8 - Group A vs. Group B

Endpoint	Group A BioThrax SQ Weeks-0-2-4-26 N=153 point estimate (2-sided 95%CI)	Group B BioThrax IM Weeks 0-2-4-26 N=154 point estimate (2-sided 95%CI)	Comparisons	Non-Inferiority Criteria Passed?
			Ratios (2-sided 97.5% CI)	
Antibody Concentration GMC (µg/mL)	101.92 (88.34, 117.58)	87.78 (74.99, 102.76)	1.161 (0.911, 1.480)	Yes*
Antibody Titer GMT	1250.12 (1079.55, 1447.63)	1080.96 (926.08, 1261.74)	1.156 (0.907, 1.475)	Yes**
			Difference of rates (2-sided 97.5% CI)	
Titer 4-fold increase from baseline[+] (Proportion of Responders)	98.69% (95.36, 99.85)	97.40% (93.49, 99.30)	0.013 (-0.031, 0.062)	Yes***

*****Criteria for non-inferiority of comparisons based on ratios of GMCs: Mean antibody concentration ratio ($GMC_{Group\ A}$ /$GMC_{Group\ B}$). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 1.5.
******Criteria for non-inferiority of comparisons based on ratios of GMTs: Mean antibody titer ratio ($GMT_{Group\ A}$/$GMT_{Group\ B}$). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 1.5.
*******Criteria for non-inferiority of comparisons based on differences in rates of 4-fold rise in antibody titer: 4-fold rise in antibody titer (Group A – Group B). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 0.10.
[+]Baseline values below LLOQ set to ½-empirical LLOQ to calculate post-vaccination 4-fold rise in titer.

Table 6: Immune Responses at Month 7 - Group A vs. Group B

Endpoint	Group A BioThrax SQ Weeks-0-2-4-26 N=139 point estimate (2-sided 95%CI)	Group B BioThrax IM Weeks 0-2-4-26 N=145 point estimate (2-sided 95%CI)	Comparisons	Non-Inferiority Criteria Passed?
			Ratios (2-sided 97.5% CI)	
Antibody Concentration GMC (µg/mL)	218.32 (187.52, 254.17)	262.61 (228.81, 301.41)	0.831 (0.658, 1.050)	Yes*
Antibody Titer GMT	2614.95 (2251.57, 3036.98)	3065.95 (2678.19, 3509.86)	0.853 (0.678, 1.073)	Yes**
			Difference of rates (2-sided 97.5% CI)	
Titer 4-fold increase from baseline[+] (Proportion of Responders)	99.28% (96.06, 99.98)	100% (97.49, 100.0)	-0.007 (-0.048, 0.027)	Yes***

*****Criteria for non-inferiority of comparisons based on ratios of GMCs: Mean antibody concentration ratio ($GMC_{Group\ A}/GMC_{Group\ B}$). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 1.5.
******Criteria for non-inferiority of comparisons based on ratios of GMTs: Mean antibody titer ratio ($GMT_{Group\ A}/GMT_{Group\ B}$). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 1.5.
*******Criteria for non-inferiority of comparisons based on differences in rates of 4-fold rise in antibody titer: 4-fold rise in antibody titer (Group A – Group B). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 0.10.
[+]Baseline values below LLOQ set to ½-empirical LLOQ to calculate post-vaccination 4-fold rise in titer.

Table 7: Immune Responses at Week 8 – Group A vs. Group C

Endpoint	Group A BioThrax SQ Weeks-0-2-4-26 N=153 point estimate (2-sided 95%CI)	Group C BioThrax IM Weeks 0-4-26 N=446 point estimate (2-sided 95%CI)	Comparisons	Non-Inferiority Criteria Passed?
			Ratios (2-sided 97.5% CI)	
Antibody Concentration GMC (µg/mL)	101.92 (88.34, 117.58)	54.21 (49.40, 59.50)	1.880 (1.531, 2.308)	No*
Antibody Titer GMT	1250.12 (1079.55,1447.63)	662.09 (601.13, 729.23)	1.888 (1.527, 2.335)	No**
			Difference of rates (2-sided 97.5% CI)	
Titer 4-fold increase from baseline[+] (Proportion of Responders)	98.69 % (95.36, 99.85)	92.83% (90.02, 95.04)	0.059 (0.014, 0.094)	Yes***

*****Criteria for non-inferiority of comparisons based on ratios of GMCs: Mean antibody concentration ratio ($GMC_{Group\ A}/GMC_{Group\ C}$). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 1.5.
******Criteria for non-inferiority of comparisons based on ratios of GMTs: Mean antibody titer ratio ($GMT_{Group\ A}/GMT_{Group\ C}$). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 1.5.
*******Criteria for non-inferiority of comparisons based on differences in rates of 4-fold rise in antibody titer: 4-fold rise in antibody titer (Group A – Group C). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 0.10.
[+]Baseline values below LLOQ set to ½-empirical LLOQ to calculate post-vaccination 4-fold rise in titer.

Table 8: Immune Responses at Month 7 - Group A vs. Group C

Endpoint	Group A BioThrax SQ Weeks-0-2-4-26 N=139 point estimate (2-sided 95%CI)	Group C BioThrax IM Weeks 0-4-26 N=410 point estimate (2-sided 95%CI)	Comparisons	Non-Inferiority Criteria Passed?
			Ratios (2-sided 97.5% CI)	
Antibody Concentration GMC (µg/mL)	218.32 (187.52, 254.17)	258.13 (232.96, 286.02)	0.846 (0.675, 1.059)	Yes*
Antibody Titer GMT	2614.95 (2251.57, 3036.98)	3087.00 (2785.20, 3421.51)	0.847 (0.676, 1.061)	Yes**
			Difference of rates (2-sided 97.5% CI)	
Titer 4-fold increase from baseline[+] (Proportion of Responders)	99.28% (96.06,99.98)	99.27% (97.88, 99.85)	0.000 (-0.041, 0.019)	Yes***

*****Criteria for non-inferiority of comparisons based on ratios of GMCs: Mean antibody concentration ratio ($GMC_{Group\ A}/GMC_{Group\ C}$). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 1.5.

******Criteria for non-inferiority of comparisons based on ratios of GMTs: Mean antibody titer ratio ($GMT_{Group\ A}/GMT_{Group\ C}$). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 1.5.

*******Criteria for non-inferiority of comparisons based on differences in rates of 4-fold rise in antibody titer: 4-fold rise in antibody titer (Group A – Group C). Non-inferiority is achieved (passed) when the upper 97.5% confidence limit is ≤ 0.10.

[+]Baseline values below LLOQ set to ½-empirical LLOQ to calculate post-vaccination 4-fold rise in titer.

Table 9: Immune Response by Gender: Group A (SQ) vs. Group B (IM)

Immunogenicity Endpoints	Group A BioThrax SQ Weeks-0-2-4-26	Group B BioThrax IM Weeks 0-2-4-26	Ratio (of GMCs, GMTs) or Difference (of rates of 4-fold rise)	2-sided 97.5% CIs of ratios of GMCs, GMTs, or 2-sided 97.5% CI of Difference of rates of 4-fold rise	
	N (Point Estimate) (95% Cl)	N (Point Estimate) (95% Cl)		Lower Limit	Upper Limit
Antibody Concentration GMC (µg/ml): **Males: week 8**	79 94.41 (79.43, 112.21)	73 69.54 (52.92, 91.37)	Ratio of GMCs 1.358	0.946	1.949
Log Antibody Concentration GMC (µg/ml): **Males: month 7**	70 216.66 (177.89, 263.87)	68 263.11 (210.39, 329.05)	Ratio of GMCs 0.823	0.587	1.155
Antibody Concentration GMC (µg/ml): **Females: week 8**	74 110.59 (87.52, 139.74)	81 108.29 (91.96, 127.51)	Ratio of GMCs 1.021	0.742	1.406
Antibody Concentration GMC (µg/ml): **Females: month 7**	69 220.01 (173.56, 278.90)	77 262.17 (220.47, 311.76)	Ratio of GMCs 0.839	0.604	1.166
Antibody Titer GMT : **Males: week 8**	79 1159.35 (974.45, 1379.34)	73 873.23 (670.54, 1137.19)	Ratio of GMTs 1.328	0.932	1.892
Antibody Titer GMT: **Males: month 7**	70 2586.05 (2128.41, 3142.09)	68 3093.38 (2484.02, 3852.21)	Ratio of GMTs 0.836	0.599	1.166
Antibody Titer GMT **Females: week 8**	74 1354.88 (1062.53, 1727.66)	81 1310.19 (1108.37, 1548.76)	Ratio of GMTs 1.034	0.743	1.439
Antibody Titer GMT : **Females: month 7**	69 2644.60 (2095.66, 3337.32)	77 3041.94 (2566.20, 3605.87)	Ratio of GMTs 0.869	0.630	1.201
4-fold rise in Titer (Proportion of responders): **Males: week 8**	79 100% (95.44, 100.00)	73 94.52% (86.56, 98.51)	0.055	-0.007	0.148
4-fold rise in Titer (Proportion of responders): **Males: month 7**	70 100% (94.87, 100.00)	68 100% (94.72, 100.00)	0.000	-0.067	0.069
4-fold rise in Titer (Proportion of responders): **Females: week 8**	74 97.30% (90.58, 99.69)	81 100% (95.55, 100.0)	-0.027	-0.108	0.033
4-fold rise in Titer (Proportion of responders): **Females: Month 7**	69 98.55% (92.20, 99.96)	77 100% (95.32, 100.00)	-0.014	-0.093	0.048

Criteria for non-inferiority based on the ratio of GMCs and GMTs and differences in the rate of 4-fold rise in antibody titer.
Mean antibody concentration ratio ($GMC_{Group\ A}/GMC_{Group\ B}$): Non-inferiority criteria met when the upper 97.5% confidence limit is ≤ 1.5
Mean antibody titer ratio ($GMT_{Group\ A}/GMT_{Group\ B}$): Non-inferiority criteria met when the upper 97.5% confidence limit is ≤ 1.5
4-fold rise in antibody titer (Group A)-(Group B): Non-inferiority criteria met when the upper 97.5% confidence limit is ≤ 0.10.

15 REFERENCES

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3. Brachman, P.; Friedlander, A.; Grabenstein, J., 2008. Anthrax Vaccine. In: Vaccines, Fifth Edition, Plotkin, S.A.: Orenstein W.A. and Offit P.A. (eds.), 111-126
4. Brachman, P., et al., 1962. Field evaluation of a human anthrax vaccine. Amer. J. Public Health, 52:632-645.
5. Food and Drug Administration, 2005, Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Anthrax Vaccine Adsorbed; Final Order. FDA Federal Register 2005; 70(242): 75180-75198.
6. Food and Drug Administration. Biological Products; Bacterial vaccines and toxoids; Implementation of efficacy review. Federal Register (December 13, 1985), 50(240):51002-51117.

16 HOW SUPPLIED/STORAGE AND HANDLING

BioThrax is supplied in 5.0 mL multidose vials containing ten 0.5 mL doses. (NDC 64678-211-05).

Store at 2°C to 8°C (36°F to 46°F). **Do not freeze**. Do not use BioThrax after the expiration date printed on the label.

17 PATIENT COUNSELING INFORMATION

Inform patients of the benefits and risks of immunization with BioThrax.
Instruct patients to report any serious adverse reaction to their health care provider.

Manufactured by:
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Lansing, MI 48906
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