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Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 1980N-0208

BioPort Corporation, the sole manufacturer of BioThrax™ Anthrax Vaccine Adsorbed, the only vaccine licensed for protection against anthrax exposure, respectfully submits the following comment in response to the proposed rule and proposed order published by the Food and Drug Administration ("FDA") on December 29, 2004 (29 Fed. Reg. 78281). BioPort's comments address (1) the background of the product's history, (2) current licensed status of the product, (3) the key evidence supporting the efficacy of the vaccine (4) the safety profile of the vaccine and (5) changes in the manufacturing process. As the evidence below establishes, FDA should finalize its proposed order classifying AVA as a Category I Biologic, safe and effective for protection against anthrax infection, regardless of the root of exposure.

1. Background.

Anthrax Vaccine Adsorbed ("AVA"), which BioPort markets under the name "BioThrax," was licensed in 1970 to protect against infections arising out of exposure to *B. anthracis*, which is a deadly spore-forming organism. Anthrax is one of the deadliest bacteria known to man. Indeed, Centers for Disease Control and Prevention ("CDC") lists anthrax as a Category A Bioterrorism Agent/Disease because it poses one of the greatest possible threats to the public health.

When anthrax spores enter the body, they germinate into bacteria that jeopardize the individual's immune response to the anthrax organism. (*See The Anthrax Vaccine: Is It Safe? Does It Work?*, Committee to Assess the Safety and Efficacy of the Anthrax Vaccine, Institute of Medicine, National Academies, National Academy Press, Washington, DC, March 2002 ("IOM Report") at 46.) .The bacteria then multiply in the body and secrete toxins that produce swelling and cause the death of the affected cells. (*Id.* at 46-47.) If the bacteria are carried into the lymph nodes, they will continue to multiply, cause further harm, and enter the bloodstream causing a serious systemic infection. (*Id.* at 47.)

Depending on the route of exposure to anthrax spores, anthrax disease can manifest itself in at least three different syndromes, all of which are characterized by edema (swelling caused by excessive fluids) and necrosis (cell death) of the affected cells. Cutaneous exposure to anthrax typically causes skin lesions with a characteristically black center. Individuals who have been exposed cutaneously also may experience systemic symptoms such as fever,

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swelling of the lymph glands, and headaches. The fatality rate in untreated cases of cutaneous anthrax is estimated to be approximately 20%. (See IOM Report at 43.). Anthrax also may enter the body through contaminated food, which results in a gastrointestinal anthrax infection. The symptoms associated with gastrointestinal anthrax include nausea, vomiting, fever, severe abdominal pain, and bloody diarrhea. Death occurs in 25% to 75% of patients who present with this syndrome. Inhalation (pulmonary) anthrax arises when anthrax spores are inhaled into the lungs. Initial symptoms are non-specific and may include flu-like symptoms such as sore throat, mild fever, coughing, and chest pain. The second stage develops abruptly with findings such as sudden onset of fever and acute respiratory distress, possibly followed by meningitis, shock, or coma. Death usually occurs within 24 hours of the onset of acute symptoms. The fatality rate of inhalation anthrax is estimated to be between 45% and 90%, AVA Package Insert (Jan. 31, 2002)[30] depending on whether aggressive, early treatment is provided. (*See* IOM Report at 45-46. For a more detailed discussion of the epidemiology, clinical presentation, and pathogenesis of anthrax, see *id.* at 40-48.)

AVA is highly effective in protecting against anthrax infections. Indeed, BioPort is aware of no reported deaths in individuals who were exposed to anthrax after having received the full course of immunization. AVA currently is indicated for use in individuals who are at risk of exposure to anthrax, such as military personnel, first responders, and civilians who may be exposed in the workplace. Because the risk of anthrax exposure in the general population is relatively low, AVA is not used for routine immunization. To date, over 5 million doses of AVA have been administered to more than 1 million individuals. As with any pharmaceutical product or medical procedure, the use of a vaccine, including AVA, carries a risk of adverse health effects that must be weighed against the expected health benefit – in this case, preventing deadly anthrax infections in people who are at risk of exposure to anthrax spores. As discussed in detail below, the adverse reactions associated with AVA are generally moderate and are similar to those seen with other licensed vaccines.

Since its licensure in 1970, AVA has been used to protect individuals who are at risk of exposure to anthrax spores. In the 1970s and 1980s, AVA was used principally to protect individuals who were at risk of being exposed to anthrax while working in a laboratory or while working with infected animals or animal products. In the late 1980s, as concerns began to grow about the use of anthrax as a biological weapon, the Department of Defense ("DoD") began to use the vaccine to protect military personnel who were at risk of exposure to weaponized anthrax. At the time of the Gulf War, more than 300,000 doses of AVA were distributed to protect service members deployed to high risk areas. Although it does not appear that anthrax-based weapons were used against troops during Operation Desert Storm, the post-war United Nations inspection of Iraq revealed that 8,000 liters of anthrax spore suspension had been produced and that, during the Gulf War, Iraq had bombs and ballistic missiles containing biological warfare agents. Iraq ultimately admitted that it had, indeed, produced weapons containing anthrax spores. (*See* IOM Report at 49-50 and citations therein.)

In 1998, DoD instituted a mandatory Anthrax Vaccine Immunization Program ("AVIP") to protect all members of the armed services from anthrax exposure. In the years following

DoD's implementation of that program, some service members raised questions about the safety and efficacy of AVA. The government responded to those concerns on multiple fronts.

In December of 2000, the CDC's Advisory Committee on Immunization Practices ("ACIP") – the nation's leading panel of civilian vaccine experts – published a review of the safety and efficacy of BioThrax. The ACIP voted unanimously to recommend the use of AVA to protect certain civilian laboratory workers and other personnel who are at a high risk of exposure to anthrax.[1]

In addition to the work that the CDC was doing, Congress ordered DoD to commission an in-depth study of the safety and efficacy of the vaccine. The Institute of Medicine ("IOM") thus convened the Committee to Assess the Safety and Efficacy of the Anthrax Vaccine. (The IOM, which is an arm of The National Academies, was established in 1970 by the National Academy of Sciences to secure the services of distinguished members of various professions to advise on matters pertaining to public health.) The IOM Committee was comprised of preeminent medical professionals in the fields of immunology, microbiology, epidemiology, biostatistics, and health surveillance, representing many of the nation's leading medical centers (including University of Pennsylvania School of Medicine, Duke University Medical Center, and Harvard Medical School).

The IOM Committee's mandate was to "analyze available information, hold workshops, and make specific recommendations on technical aspects regarding the safety and efficacy of the licensed anthrax vaccine." (IOM Report, Appendix A.) The IOM Committee's Report represents the most comprehensive expert analysis of the safety and efficacy of AVA since the Panel on Review of Bacterial Vaccines and Toxoids issued its report on AVA to FDA in 1983.

The IOM Report was published in March 2002 and contained the following conclusions about AVA:

- AVA, as licensed, is effective to protect against anthrax, including inhalation anthrax.
- It is unlikely that any naturally occurring anthrax strains or potential bioengineered strains would be resistant to AVA.
- AVA is reasonably safe, with the most common adverse events being similar to those seen with other vaccines.
- BioPort has validated its manufacturing processes and renovated its manufacturing facilities. The processes and facilities have been reviewed by FDA. BioPort's renovations resulted in greater consistency in the manufacturing process.
- BioPort manufactures AVA under strict controls, according to current FDA requirements.

In addition, the IOM recommended future efforts with respect to AVA, including continued monitoring of health events following vaccinations, continued exploration of the possibilities for alternative routes of administration and reduced number of doses, and further research regarding post-exposure treatment with AVA in combination with antibiotics. ***Importantly,***

the IOM did not suggest limiting or suspending the current use of AVA in any way.

2. BioThrax is a Fully Licensed Biological Product.

2.1. History.

AVA was licensed in 1970 by the National Institutes of Health ("NIH"), and it remains fully licensed today. Prior to 1972, responsibility for licensing biological products belonged to the Bureau of Biologics of NIH. In 1972, that function was transferred from NIH to FDA. Following that change, FDA established procedures for reviewing the safety, efficacy, and labeling of biological products, including AVA, that already had been licensed by NIH. (21 C.F.R. 601.25.) The biologics review process involves the appointment of advisory panels of independent, qualified experts to evaluate the previously licensed products and to advise FDA as to whether the products are "safe, effective, and not misbranded." (*Id.*) After reviewing a particular panel's recommendation, FDA is to publish the panel's report, along with a proposed order recommending classification of the biological product(s) into one of three categories: Category I (safe, effective, and not misbranded), Category II (unsafe, ineffective, or misbranded), or Category III (not falling within Category I or Category II, because further studies are required). (*Id.*) After a ninety-day comment period, FDA is to review any comments received and then publish a final rule or order classifying the product(s) at issue as Category I, II, or III. (*Id.*)

The review process discussed above is separate and distinct from the licensure of individual biologics. When FDA promulgated the procedures governing the review process, the Agency made clear that the scientific review process itself would not affect the licenses held by individual manufacturers for products under review. After a particular panel completed its work, FDA would review the panel report and determine whether the product licenses at issue would be confirmed (as in the case of AVA), revoked, or permitted to remain in effect pending further study. (38 Fed. Reg. 4319-20 (Feb. 13, 1973)). If a particular license were to be confirmed (Category I), no further FDA action would be required. But if the license were to be revoked, suspended, or amended, FDA would initiate a separate proceeding to effect the necessary changes in licensing status. (*Id.*)

In 1973, FDA appointed the "Panel on Review of Bacterial Vaccines and Toxoids" to review the safety, efficacy, and labeling of certain licensed biological products, including AVA (the "Panel"). The Panel was composed of leading experts in the fields of infectious disease, microbiology, bacterial immunology, and epidemiology. The Panel issued its report in 1983. In that Report, the Panel recommended, unequivocally, that AVA "be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product."

In December 1985, FDA published the Panel's Report, along with the Agency's proposal to place AVA in Category I. (50 Fed. Reg. 51,002 (Dec. 13, 1985).) No comments relating to the proposed classification of AVA were received. In January 2004, FDA issued a final rule classifying AVA as a Category I product that is safe and

effective for protecting against anthrax infection, regardless of the route of exposure. (69 Fed. Reg. 255 (Jan. 5, 2004).)

2.2. The Doe vs. Rumsfeld Lawsuit.

In a lawsuit known as Doe v. Rumsfeld, six unnamed plaintiffs sued the DoD, the Department of Health and Human Services ("HHS"), and FDA to enjoin DoD's mandatory AVIP. That case is pending in the United States District Court for the District of Columbia and in the United States Court of Appeals for the District of Columbia. The plaintiffs in that case argue that AVA was never specifically approved for protection against inhalation anthrax and, therefore, that DoD cannot require military personnel to be inoculated with AVA.

In October 2004, the District Court ruled that FDA's January 2004 final order was ineffective to approve AVA for protection against inhalation anthrax, because FDA failed to comply with the notice and comment requirements contained in FDA's self-established review procedures (21 C.F.R. 601.25). The District Court opinion emphasized that its ruling was not based on "FDA's substantive – and highly technical – determinations regarding the safety of AVA." Rather, the ruling was based solely on a perceived flaw in the way that FDA carried out its notice and comment process. Nonetheless, because of this professed procedural defect, the District Court ordered DoD to halt the mandatory inoculation of troops, pending FDA's compliance with the required procedures. On December 29, 2004, FDA re-initiated the notice and comment process under Section 601.25. (29 Fed. Reg. 78281).

2.3. Licensed Status of BioThrax.

As noted above, during the entire biologics review process, the products under review ***retain their licensed status***. The District Court ruling did not affect the licensed status of BioThrax. It simply returned the status of the vaccine to where it had been before the FDA issued its final rule, at which time BioThrax was a fully licensed and approved biological product.

3. BioThrax is Effective to Protect Against Anthrax Infection, Regardless of the Route of Exposure.

The FDA recommendation to approve AVA as a Category I biological product that is safe and effective to protect against anthrax infection, regardless of the route of exposure, is supported by three categories of data: (1) clinical data from human efficacy studies, (2) research data studying the human serological response to AVA, and (3) studies of the efficacy of AVA in different types of animals.

Two key human studies demonstrate the efficacy of the anthrax vaccine: the oft-cited "Brachman Study"[2] and a CDC study of observational data for the twelve year period from 1962 to 1974.[3] New human clinical trials of AVA are neither feasible nor ethical. (IOM Report at 62.). In situations in which human clinical studies are not possible, FDA recognizes the need to look to both serological studies and animal data. In promulgating the regulations governing the biologics review process, FDA specifically noted that where

controlled clinical trials are not possible, "[a]lternative methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing." (21 C.F.R. 601.25(d)(2).) Indeed, in a proposed rule regarding products such as AVA that are used to protect against bioterrorism, FDA specifically noted that approval should not be withheld on efficacy grounds if the product "has been determined to be effective based on the best human and animal evidence that can be obtained ethically." (*Id.* at 53963.)

Accordingly, in addition to considering the available human field trials of the anthrax vaccine, it is necessary to consider human serological studies and animal studies of the efficacy of AVA to protect against inhalation anthrax.* These studies are discussed below.

3.1. Human Field Trials.

3.1.1. The Brachman Study.[2]

The Brachman study was a randomized, placebo-controlled field study that used an earlier version of the anthrax vaccine. The study was conducted from 1955 to 1959. This study included 1249 workers in four textile mills in the northeastern United States that processed imported animal hides. 379 of the participants in the study received the complete course of anthrax vaccine immunization, 116 received incomplete inoculation courses (vaccine or placebo), 414 received placebo, and 340 received no treatment. (IOM Report at 57-58 and Brachman.[2])† During the trial, 26 cases of anthrax were reported, 21 of which were cutaneous and 5 of which were inhalation cases. ***No anthrax disease was seen in individuals who had received the full course of vaccination.*** Of the 21 individuals who developed cutaneous anthrax, two had received three doses of vaccine, one had received two doses, and ***none had received the full complement of doses.*** Of the five inhalation cases (four of which were fatal), two received placebo and three were in the observational (non-vaccinated) group. ***None of the five individuals who developed inhalation anthrax had been vaccinated at all.*** Although the original FDA Panel stated that "inhalation anthrax occurred too infrequently to assess the protective effect of the vaccine against this form of the disease," FDA correctly disagrees with that statement. (29 Fed. Reg. 78286.)

* Critics of AVA have argued that FDA should not classify AVA as a Category I biologic until it requires additional human clinical trials. New human studies of AVA, however, are neither ethical nor required by law. Humans simply cannot purposefully be exposed to deadly anthrax spores to test the efficacy of the vaccine. FDA explicitly has recognized the need to consider data from serological studies and animal studies when human studies are not possible. (*See, e.g.*, 21 C.F.R. 601.25; 64 Fed. Reg. 53960-64 (Oct. 5, 1999).) There is simply no legal basis to require (and, indeed, it would be impossible to conduct) additional human clinical trials prior to finalizing the classification of AVA as a Category I biologic.

† The dosage schedule used in the Brachman study was 0, 2, and 4 weeks, 6 months, 12 months, and 18 months, with an annual booster thereafter, which is the current FDA-approved dosage schedule for BioThrax.

The fact that none of the immunized subjects suffered inhalation anthrax is strong evidence supporting the efficacy of AVA against inhalation anthrax.*

3.1.2. The CDC Observational Data.

From the years 1962 to 1974, the CDC collected surveillance data on the occurrence of anthrax disease in mill workers or those living near mills in the United States. During that time period, individuals received either BioThrax or the earlier version of the anthrax vaccine. Twenty-seven cases of anthrax disease were identified, all of which were cutaneous. Of those, 24 cases occurred in unvaccinated 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 of the recommended six doses of anthrax vaccine.*** (See IOM Report at 58-59 and 50 Red. Reg. 51002-51017.).

The data from these two studies confirm that BioThrax and its predecessor vaccine have been effective in dramatically reducing the incidence of occupational anthrax in high-risk employees. ***Indeed, no person who has the full course of AVA is known to have developed any form of anthrax infection, cutaneous, inhalation, or otherwise..*** (*See* IOM Report at 58-59.)

3.2. Human Antibody Response Data.

Numerous studies of the ability of the vaccine to elicit antibodies to anthrax in human vaccinees also confirm the efficacy of the vaccine. For example, in a prospective, open-label study to evaluate the immune response following a booster immunization of BioThrax in people who had received one, two, or three priming doses of BioThrax 18 to 24 months earlier, 99% of the participants were found to have detectable antibodies to anthrax.[4] Those subjects who had received two or three priming doses had the highest

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* Critics of AVA have questioned the propriety of considering the Brachman study when analyzing the efficacy of AVA, because the Brachman study used an earlier version of the anthrax vaccine. That criticism is not sound. Longstanding FDA policy permits the Agency to rely on clinical study data from related, but not identical, biological products, provided that the two products are comparable. (*See, e.g.*, FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, FDA Center for Biologics Evaluation and Research (April 1996).) The United States District Court for the District of Columbia explicitly has upheld FDA's practice of relying on clinical studies for comparable biologics. *Berlex Labs. Inc. v. FDA*, 942 F. Supp. 19, 25 (D.D.C. 1996). In *Berlex*, the court stated that: "Neither the [Public Health Service Act ("PHSA")] itself nor FDA's regulations issued under the PHSA provide that the clinical study offered to demonstrate the safety, purity and potency of a new biological product shall have been conducted on that very product." As FDA noted, BioThrax and the anthrax vaccine that was used in the Brachman study are comparable products. (*See* 29 Fed. Reg. 78287.) FDA has determined that the vaccine used in the Brachman study was provided to Dr. Brachman by DoD. (*See id*). Following the Brachman study, DoD modified the manufacturing process to optimize stability and immunogenicity and to increase the scale of manufacture. (*Id.*) DoD then contracted with Merck Sharp & Dohme to standardize large-scale production and to produce the vaccine using an anaerobic method. (*Id.*) DoD subsequently contracted with MDPH to further standardize and scale up production. (*Id.*) The vaccine licensed in 1970 was the result of the DoD-MDPH contract. (*Id.*) FDA specifically has determined that the current vaccine and the vaccine used in the Brachman study are comparable in terms of both safety and efficacy. (*Id.*) Accordingly, it is perfectly appropriate and consistent with long-standing policy for FDA to continue to rely on the Brachman study in connection with its analysis of BioThrax.

levels of antibodies, indicating a strong immune recall to the priming immunizations (*Id*).

The IOM Committee analyzed this study and others and concluded that AVA administered according to its currently licensed dosage schedule (0, 2, and 4 weeks, 6 months, 12 months, and 18 months), as well as by schedules that omit the dose at 2 weeks, "generates substantial antibody responses . . . in 96 to 100 percent of recipients." (See IOM Report at 60) For an in-depth discussion of the antibody-response studies, *see* IOM Report at 59-60 (reviewing Pittman et al., 2002;[4] Johnson-Winegar, 1984;[5] Pittman, 2001;[6] and Pittman et al., 1997[7]).

3.3. Animal Studies.

The IOM Committee concluded that the most appropriate animal studies bearing on the efficacy of AVA against inhalation anthrax are rabbits and macaques (rhesus monkeys). (*See* IOM Report at 69.) The IOM reviewed the data from several different AVA aerosol challenge studies in rabbits and macaques and concluded that AVA was effective in protecting the animals from inhalation exposure to the strains of anthrax tested. (The studies tested three different strains of *Bacillus anthracis*.)

With respect to rabbit studies, the IOM Committee concluded that AVA provided protection from aerosol challenge with anthrax spores (*See* IOM Report at 67-68.) Among the most notable rabbit studies is a study in which New Zealand white rabbits were immunized with two doses of varying dilutions of AVA (1:1, 1:4, 1:16, 1:64, and 1:256). Six weeks later, the rabbits were challenged by inhalation with lethal doses of the Ames strain of *B. anthracis*. All animals in the undiluted and 1:4 dilution groups survived, while 80% of the animals in the 1:16 group and 77% of the animals in the 1:64 group survived. 19 of the 20 rabbits in the 1:256 group and all of the unvaccinated control rabbits died. The levels of antibody at weeks 6 and 10 (determined using anti-PA IgG by ELISA as well as toxin-neutralizing antibody (TNA) assays) correlated strongly with survival.

The principal studies of the efficacy of AVA to protect macaque monkeys against inhalation anthrax – each of which was performed using the currently licensed formulation of AVA – can be summarized as follows:

Summary of Efficacy Studies of BioThrax AVA Against Anthrax Spore Inhalation Challenge in Macaques

Doses (Weeks)	Inhalation Challenge Strain	Challenge Time (Weeks from Initial Immunization)	Challenge Dose (LD_{50})	Survival	Reference
0, 2	Ames	8	437	10/10	Ivins8
0, 2	Ames	38	203	3/3	Ivins8
0, 2	Ames	100	330	7/8	Ivins8
0, 4	Ames	16	899	9/9	Pitt 1996[9]
0, 4	Ames	16	155	5/5	Pitt 2001[10]
0	Ames	6	74	10/10	Ivins 1998[11]
0, 4	Namibia	10	398	10/10	Fellows 2001[12]
0, 4	Turkey	10	1004	8/10	Fellows 2001[12]

In these studies, 62 of the 65 AVA-vaccinated animals survived aerosol challenge. That is a 95% survival rate. Conversely, all unvaccinated animals died. Several key findings can be drawn from these studies:

- One or two doses of AVA provided protection from the virulent Ames strain of *B. anthracis* in 98% of the animals. This is the strain of anthrax that was used in the anthrax letter attacks of 2001.
- Protection was afforded against the Ames, Namibia, and Turkey strains, indicating that AVA protection is not strain specific.
- Protection was demonstrated as early as six weeks following a single dose of AVA.
- Protection was demonstrated as long as two years following two doses of AVA.

In short, the animal challenge studies bolster the results seen in the available human studies – i.e., that BioPort's AVA is effective to protect against inhalation exposure to anthrax spores.

3.4. Efficacy Against Various Strains of *Bacillus anthracis.*

The IOM also was charged with determining whether AVA is likely to be effective to protect against infections caused by exposure to all known strains of anthrax as well as bioengineered strains that may be created by bioterrorists. The IOM concluded that it is unlikely that either naturally occurring or bioengineered strains could evade AVA protection and cause the toxicity associated with anthrax disease. (IOM Report at 71.) The IOM's conclusion was based on (1) the animal studies described above (which tested the efficacy of the Ames, Nambia, and Turkey strains of *B. anthracis*), (2) other human and animal studies involving the Vollum strains and a "broad spectrum" of other strains, and (3) general principles of immunology, based on an analysis of the pathogenesis of anthrax and the way that AVA operates to prevent that pathogenesis in vaccinees. (*See* IOM Report at 69-71 and references cited therein.)

3.5. Conclusion.

Based on all available human and animal data, the IOM Committee correctly concluded that AVA, as licensed, is an effective vaccine to protect against anthrax, including inhalation anthrax, caused by any known or plausible engineered strains of *Bacillus anthracis*. There can be no question that the efficacy of AVA to protect against anthrax infection, regardless of the route of exposure, has been firmly established by human clinical studies, serological studies, and animal studies, all of which are recognized under the federal Food, Drug, and Cosmetic Act as studies sufficient to support a finding of efficacy. (*See* 21 C.F.R. 601.25(d)(2).) Thus, FDA's conclusion that AVA is effective for protection against anthrax, regardless of the route of exposure, is supported by the best available human and animal data, and it should be finalized.

4. The Adverse Events Associated with AVA Are Generally Moderate and Are Comparable to Those Associated with Other Licensed Vaccines.

The health effects of AVA have been studied comprehensively by many qualified scientists and by numerous panels of preeminent medical experts, in what constitutes the most intensive vaccine safety evaluation in modern vaccine history. In each of those studies, AVA has proven to be a safe biologic product, with the most common side effects being moderate reactions similar to those associated with other regularly administered vaccines.

The safety of AVA has been analyzed in more than 20 individual studies (*e.g.*, Lange 2003;[13] Rehme 2002;[14] Sato 2002;[15] Sever, 2002;[16] Sever 2004;[17] Peeler, 1958;[18] Peeler 1965;[19] White, 1974;[20] Pittman 2002;[21] Brachman, 1962;[2] Fed. Reg. 1985;[3] Pittman, 2001; Pittman, 2002b; Canadian Group, 1999;[22] Wasserman, 2003;[23] Gunzenhauser, 2001;[24] Wiesen, 2002;[25] Catherino, 2002;[26] Catherino, 2005;[27] Sulsky 2004;[28] Pittman, 2004[29]), the majority of which have been reviewed by independent expert panels and published in peer-reviewed journals. Those studies demonstrate that (1) the frequency and nature of adverse events occurring shortly after immunization with BioThrax are comparable to that seen with other vaccines; (2) the general health of persons immunized with BioThrax is no different than that of persons who have never received the vaccine; and (3) immunization with BioThrax, even over long periods of time, is not associated with chronic health problems, disabilities, or death.

In 1998 DoD requested that HHS form the Anthrax Vaccine Expert Committee* ("AVEC") to conduct an independent review and evaluation of AVA-related adverse event reports and to assess the relationship, if any, between the anthrax vaccine and the reported health events. The AVEC reviewed more than 1800 adverse event reports submitted between 1998 and 2001. During that time, approximately 2 million doses of BioThrax were administered to over 500,000 individuals. The AVEC reviewed six reports in which the vaccine recipient died at some point after being vaccinated and characterized none of the deaths as being caused by AVA immunization. The AVEC also found no evidence of a high incidence or unusual pattern in the occurrence of medically significant adverse events following

* The membership of AVEC consists of private sector physicians and other scientists recruited through the Expert Witness Program of the Vaccine Injury Compensation Program of HRSA, who have expertise in the fields of statistics, epidemiology, infectious diseases, neurology, rheumatology, and vaccinology.[16]

immunization with AVA and determined that there was no evidence of a significant safety problem with the vaccine. (Sever, 2002;[16] Sever, 2004[17])*

In its 2002 Report, the IOM Committee did an independent, comprehensive analysis of the adverse reactions associated with AVA. (*See* IOM Report at 83-179.) The Committee reviewed historical data, media reports, congressional testimony, epidemiologic studies, reports from the CDC's Vaccine Adverse Event Reporting System ("VAERS"), data from the Defense Medical Surveillance System ("DMSS"), and recent DoD studies on the health effects following AVA vaccination. The IOM also took testimony, both in writing and in person, from recipients of AVA and commissioned an independent study of peer-reviewed articles on the health effects of all vaccines. (*See* IOM Report at 88-89, 102-179.) The Committee concluded that:

- Local reactions to AVA are fairly common and are similar to the events observed following receipt of other adult vaccines. They may include redness, swelling, and nodules at the injection site.
- Systemic reactions to AVA are less common and also are similar to the events observed following receipt of other adult vaccines. They may include fever, malaise, and muscle pain.
- There is no evidence that life-threatening or permanently disabling immediate-onset conditions occur at a higher rate in individuals vaccinated with AVA than in the general population.
- There is no evidence establishing that AVA leads to risks of later-onset health events.

(*See* IOM Report at 12-14.)

In short, exhaustive epidemiological studies have found that the most common adverse reactions to AVA are local injection site reactions and, less frequently, mild systemic reactions. These types of reactions, and the rates at which they occur, are comparable to those seen with other licensed, adult vaccines. (*See* IOM Report at 11; *see also* AVA Product Insert, Jan. 31, 2002[30]) The general health of persons immunized with BioThrax is no different than that of persons who have never received the vaccine, and immunization with BioThrax, even over long periods of time, is not associated with chronic health problems, disabilities, or death.

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* Critics have claimed that the anthrax vaccine is the cause of "Gulf War Syndrome." In its 2000 review, however, the ACIP determined that there is no scientific evidence to support an association between the anthrax vaccine and Gulf War Syndrome. (CDC ACIP, 2000)[1]

5. The Changes that BioPort Has Made to the AVA Manufacturing Process Were Approved by FDA and Did Not Affect the Safety or Efficacy of the Vaccine.

BioPort Corporation manufactures the same vaccine that was licensed by NIH in 1970. As with all regulated drug products, there is an expectation that the equipment, facilities, manufacturing process, and testing processes will be continuously improved to keep up with current good manufacturing practices ("cGMP"). As the IOM recognized, since the time that AVA was licensed in 1970, the regulatory expectations for vaccines and for the companies that manufacture them have become far more stringent. (See IOM Report at 182, 195.) As part of FDA's continuing quality improvement effort, FDA has instituted rigorous process validation requirements for the manufacture of all vaccines. (*Id.*)

Beginning in the late 1990s, in response to FDA's heightened requirements, BioPort implemented a series of changes, including a major renovation of its manufacturing facility, ensure compliance with evolving FDA standards. Since that time, FDA has inspected and approved the changes to the facility and to the manufacturing process. (See, *e.g.*, FDA Response to Citizens Petition, Docket No. 01P-0471/CP1 (Aug. 28, 2002).) FDA has concluded that AVA produced in the renovated facility is safe and effective, and the agency has authorized the release of post-renovation lots. (*Id.*)

Critics of AVA have alleged that changes in the fermentation equipment and filters that are used during the anthrax vaccine manufacturing process substantially changed the product and that FDA has not approved those changes. That is simply not the case. FDA approved a change in two "fermentation trains" in 1993, and the Agency approved the same change to two additional fermentation trains in 2001. (*Id.* at 12.) Similarly, FDA analyzed the effect of the change in filters (from ceramic to nylon) in 2001, including reviewing the lot release protocols and product release test results for all lots of anthrax vaccine released between 1978 and 2001. (*Id.*) FDA concluded that the filter change did not adversely affect the product's safety, purity, or potency. (*Id.*)*

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* Critics of AVA also have asserted that BioPort adds squalene to AVA as an adjuvant and that many lots of AVA are "adulterated" or "contaminated." These statements are simply untrue. Neither the State of Michigan nor BioPort ever added squalene to AVA as an adjuvant or for any other reason. Squalene is a naturally occurring compound that is found in plants, animals, humans, and common food items (including eggs and olive oil). In testing 8 lots anthrax vaccine, FDA found trace levels of squalene. In 2001, follow-up test of more than 30 lots of AVA found measurable quantities of squalene in only *one* lot, and the amount of squalene was minuscule. (*See, e.g.*, IOM Report at 96-97.) If squalene had been added to the vaccine during the manufacturing process, all lots tested would have detected its presence, which simply was not the case. Moreover, BioPort tests each lot of AVA for safety, purity, sterility, potency, and ingredient content under the same FDA requirements and procedures that are applicable to all FDA-approved vaccines. If contaminants are found in any lot of vaccine, the lot is rejected and destroyed. In addition, BioPort sends all of the test results for each lot of AVA to FDA for its review. Before BioPort can distribute or use any lot of AVA, FDA must "release" that lot. Thus, the allegations that BioPort releases adulterated lots of AVA are simply untrue.

In its 2002 Report, the IOM conducted an extensive review of the history of the manufacture of AVA and of the improvements that BioPort, in conjunction with FDA, has made to the manufacturing facilities and processes. The IOM Committee concluded:

- "With high-priority efforts by the manufacturer and FDA, the manufacturing process for AVA has been validated so that vaccine manufactured postrenovation has been approved for release and distribution." (IOM Report at 195.)
- AVA produced in the renovated facility under the newly validated manufacturing processes "has greater assurance of consistency than that produced at the time of original licensure." (*Id.*)

6. Conclusion.

Based on the overwhelming, well-documented body of scientific data and evidence summarized above, the FDA's proposed rule and order confirming that AVA is safe and effective for protection against anthrax, regardless of the route of exposure, should be finalized without revision or delay.

Thank you for the opportunity to comment on the proposed rule and proposed order. If further information would be helpful, please do not hesitate to contact the company.

Respectfully,
BIOPORT CORPORATION

Robert G. Kramer

By Robert G. Kramer, Sr.
President and Chief Executive Officer

Exhibits

References

[1] Centers for Disease Control and Prevention. Use of anthrax vaccine in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2000;49(No. RR-15):[39 pages]

[2] Brachman, P.S., H. Gold, S. Plotkin, F.R. Fekety, M. Werrin, and N.R. Ingraham. 1962. Field evaluation of a human anthrax vaccine. Am. J. Pub. Health, 52: 632-645.

[3] FDA. 1985. Biological Products: bacterial vaccines and toxoids: implementation of efficacy review. Proposed rule. *Federal Register* 50(240): 51002-51117.

[4] Pittman PR, Hack D, Mangiafico J, Gibbs P, McKee KT Jr, Friedlander AM, Sjogren MH. Antibody response to a delayed booster dose of anthrax vaccine and botulinum toxoid. Vaccine. 2002 May 15;20(16):2107-15.

[5] Johnson-Winegar A. 1984. Comparison of enzyme-linked immunosorbent and indirect hemagglutination assays for determining anthrax antibodies. Journal of Clinical Microbiology 20(3):357–361.

[6] Pittman PR. 2001. Anthrax vaccine: the Fort Bragg Booster Study. Presentation to the Institute of Medicine Committee to Assess the Safety and Efficacy of the Anthrax Vaccine, Meeting II, Washington, D.C.

[7] Pittman PR, Sjogren MH, Hack D, Franz D, Makuch RS, Arthur JS. 1997. Serologic response to anthrax and botulinum vaccines. Protocol No. FY92-5, M109, Log No. A5747. Final Report to the Food and Drug administration. Fort Detrick, Md.: U.S. Army Medical Research Institute of Infectious Diseases.

[8] Ivins BE, Fellows PF, Pitt MLM, Estep JE, Welkos SL, Worsham PL, Friedlander AM. 1996. Efficacy of a standard human anthrax vaccine against *Bacillus anthracis* aerosol spore challenge in rhesus monkeys. Salisbury Medical Bulletin 87(Suppl):125–126.

[9] Pitt MLM, Ivins BE, Estep JE, Farchaus J, Friedlander AM. 1996. Comparison of the efficacy of purified protective antigen and MDPH to protect non-human primates from inhalation anthrax. Salisbury Medical Bulletin 87(Suppl):130.

[10] Pitt MLM. 2001. Animal models for anthrax vaccine efficacy. Presentation to the Institute of Medicine Committee to Assess the Safety and Efficacy of the Anthrax Vaccine, Meeting III, Washington, D.C.

[11] Ivins BE, Pitt ML, Fellows PF, Farchaus JW, Benner GE, Waag DM, Little SF, Anderson GW Jr, Gibbs PH, Friedlander AM. 1998. Comparative efficacy of experimental anthrax vaccine candidates against inhalation anthrax in rhesus macaques. Vaccine 16(11–12): 1141–1148.

[12] Fellows PF, Linscott MK, Ivins BE, Pitt ML, Rossi CA, Gibbs PH, Friedlander AM. 2001. Efficacy of a human anthrax vaccine in guinea pigs, rabbits, and rhesus macaques against challenge by *Bacillus anthracis* isolates of diverse geographical origin. Vaccine 19(23–24):3241–3247.

[13] Lange, JL, Leskikar SE, Brundage JF, Rubertone MV. 2003. Comprehensive systematic

surveillance for adverse effects of Anthrax Vaccine Adsorded, US Armed Forces, 1998-2000. Vaccine, 21: 1620-1628.

[14] Rehme PA, Williams, R, Grabenstein JD. 2002. Ambulatory medical visits among anthrax-vaccinated and unvaccinated personnel after return from southwest Asia. Military Medicine, 167: 205-210.

[15] Sato, PA, Reed RJ, Smith TC, Want L. 2002. Monitoring anthrax vaccine safety in US military service members on active duty: surveillance of 1998 hospitalizations in temporal association with anthrax immunization. Vaccine, 20: 2369-2374.

[16] Sever, JL, Brenner AI, Gale AD, Lyle JM, Moulton LH, West DJ, Anthrax Vaccine Expert Committee. 2002. Safety of the anthrax vaccine: a review by the Anthrax Vaccine Expert Committee (AVEC) of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). Pharmacoepidemiology and Drug Safety, 11: 189-202.

[17] Sever, JL, Brenner, AI, Gale AD, Lyle JM, Moulton LH, Ward BJ, West DJ. 2004. Safety of anthrax vaccine: An expanded review and evaluation of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). Pharmacoepidemiology and Drug Safety, 12: 825-40

[18] Peeler RN, Cluff LE, Trever RW. 1958. Hyper-immunization of man. Bulletin of the Johns Hopkins Hospital, 103: 183-198.

[19] Peeler RN, Kadull PJ, Cluf LE. 1965. Intensive immunization of man: evaluation of possible adverse consequences. Ann. Intern. Med., 63: 44-57.

[20] White CS III, Adler WH, McGann VG. 1974. Repeated immunization: possible adverse effects-reevaluation of human subjects at 25 years. Ann. Intern. Med., 81: 594-600.

[21] Pittman, PR, Gibbs PH, Cannon TL, Friedlander AM. 2001. Anthrax vaccine: short-term safety experience in humans. Vaccine 20 (5-6): 972-978.

[22] Canadian Forces Medical Group. Letter from Assistant Chief of Staff Operations to Canadian Clinical Trials and Special Access Program. 15 October 1999.

[23] Wasserman, G, Grabenstein J, Pittman P, Rubertone M, Gibbs P, Wang L, Golder L. 2003. Analysis of adverse events after anthrax immunization in US Army medical personnel. J. Occupational and Environmental Med. 45: 22-33.

[24] Gunzenhauser, JD, Cook JE, Parker ME, Wright I. 2001. Acute side effects of anthrax vaccine in ROTC cadets participating in advanced camp, Fort Lewis, 2000. Med. Surv. Monthly Report, 7: 9-11.

[25] Wiesen, AR, Littell CT. 2002. Relationship between pregnancy anthrax vaccinations and pregnancy and birth outcomes amoung US Army women. J. Am. Med. Assoc. (JAMA), 287: 1556-1560.

[26] Catherino, WH, Levi A, Leondires M, et al. 2002 The anthrax vaccine does not affect semen parameters, embryo quality, or pregnancy outcomes in couples with a vaccinated male military service member. Fertility and Sterility, 78 (3), Suppl. 1 (abstract O-285).

[27] Catherino, WH, Levi A, Kao TC, Leondires MP, McKeeby J, Segars JH. 2005. Anthrax

vaccine does not affect semen parameters, embryo quality, or pregnancy outcome in couples with a vaccinated male military service member. Fertil Steril., 83(2): 480-3.

[28] Sulsky, SI, Grabenstein JD, Delbos RG. 2004. Disability among US Army personnel vaccinated against anthrax. J. Occup. Environ. Med., 46(10): 1065-1075.

[29] Pittman, PR, Coonan KR, Gibbs PH, Scott HM, Cannon TL, McKee KT Jr. 2004. Long-term health effects of repeated exposure to multiple vaccines. Vaccine, 23 (4): 525-536.

[30] BioThrax AVA Product Insert January 31, 2002. Available online at http:\www.bioport.com.