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REPLY TO
ATTENTION OF

Executive Office

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

SUBJECT: Docket Number 1980N-0208, Final Rule and Final Order
Involving Bacterial Vaccines and Toxoids

Ladies & Gentlemen:

The Food & Drug Administration (FDA) proposed language for its Final Rule & Final Order Involving Bacterial Vaccines and Toxoids on December 29, 2004, in the *Federal Register*. Studies with humans and nonhuman primates show that anthrax vaccine adsorbed as licensed is an effective vaccine for the protection of humans against anthrax, including inhalation anthrax. The proposed Final Rule & Final Order rightly finds that anthrax vaccine adsorbed, USP (*BioThrax*, BioPort Corporation), is effective in preventing anthrax, regardless of how anthrax spores enter the body (i.e., route of exposure).

Our staff has been reading some of the public comments submitted to the FDA for this docket. Several of these comments contain factual errors that deserve to be corrected for the purpose of the public record.

VAERS, suppression of: A common misstatement is that the Department of Defense (DoD) suppresses reports to the Vaccine Adverse Events Reporting System (VAERS). On the contrary, DoD sets a minimum standard for VAERS reporting that exceeds requirements under any law or regulation. This standard is repeated in multiple command communications and publicly displayed (e.g., www.anthrax.mil/media/pdf/ClinicalIssues.pdf, www.vaccines.mil/documents/510armymemo.pdf). DoD encourages reporting through its clinical providers, so that reports contain detail needed to enable full evaluation. But anyone is welcome at any time to report any adverse event after any vaccination that they wish. As multiple DoD documents and websites proclaim, the VAERS website is www.vaers.org.

VAERS, overreliance on: A related misconception is that DoD relies solely on VAERS to assess vaccine safety. As seen in Enclosure 1, VAERS reports should not be the primary means of assessing vaccine safety, because they are subject to various kinds of reporting bias and cannot describe the rates of health problems in a population.

80N-0208

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So DoD uses VAERS to identify signals and to act as a kind of patient registry. Then DoD goes further, using cohort studies and other scientifically powerful approaches to assess vaccine safety. These cohort studies are discussed in detail in chapter 6 of the Congressionally directed April 2002 report of the National Academy of Sciences.

Incomplete reporting, other: Another concern is that failure to file a VAERS form means that an adverse event after vaccination has gone unnoticed. On the contrary, DoD's multifaceted public-health surveillance systems collect information automatically from all military hospitals and clinics, removing the reporting bias associated with VAERS reports. Because our surveillance systems systematically collect data on all inpatient and outpatient visits, DoD's surveillance system has advantages over surveillance systems in civilian settings. All medical encounter records are evaluated. No individual action on the part of the vaccine recipient, physician, or nurse is needed to be part of the surveillance net.

Long-term studies, lack of: Some people have reported to this docket that the long-term effects of anthrax vaccination have not been studied. This is incorrect. As one example, DoD has studied the health of vaccinated laboratory workers over the span of decades (White et al., 1974; Pittman et al., 2004). Enclosure 2 provides a bibliography. As a second example, DoD arranged for an evaluation of the effect (if any) of anthrax vaccination on occupational evaluations for disability discharge. The purpose of this study was to identify health problems that might be delayed in appearance after anthrax vaccination or that might have a prolonged effect on physical functioning (Sulsky et al., 2004). Researchers evaluated the Total Army Injury and Health Outcomes Database to assess effects of anthrax vaccination between 1998 and 2001. This study evaluated 716,833 active-duty soldiers (154,456 of whom received anthrax vaccine adsorbed) followed for 4¼ years. The researchers found that rates of evaluation for disability discharge were the same for both vaccinated and unvaccinated personnel (about 4%). Subset analyses found no differences for men alone, women alone, permanent disability, temporary disability, musculoskeletal disability, or neurologic disability.

Side effects in women versus men: DoD investigators showed that women given anthrax vaccine experience more injection-site and systemic adverse events than men. For example, about 60% of women and 30% of men develop swelling less than 1 inch in diameter at the injection site. For both genders, these events typically resolve on their own within 2 to 3 days (Hoffman et al., 2003; Sever et al., 2002; Sever et al., 2004; Wasserman et al., 2003). Within genders, there are no substantive differences in rates for major diseases based on vaccination status (Lange et al., 2003; Sulsky et al., 2004). After DoD investigators reported this gender effect, other investigators analyzed other vaccine adverse events or immune response by gender and found similar differences for influenza vaccine hepatitis B vaccine, and tetanus-diphtheria-pertussis vaccine.

Squalene, "proof" of additive: Multiple comments allege that DoD added squalene to anthrax vaccine adsorbed to stretch the vaccine supply in 1990. Neither DoD nor any other party added squalene in any form to anthrax vaccine adsorbed at any time. Lab assays to detect squalene are complicated by the fact that squalene is naturally present in the human bloodstream and in the oil in human fingerprints at many times the concentration claimed to have been found in the vaccine. Details on the squalene issue appear at Enclosure 3.

Mycoplasma, presence of: In an effort to explain illnesses among veterans of the Persian Gulf War, some have claimed that anthrax vaccine adsorbed was contaminated with mycoplasma bacteria. As published in the journal *Emerging Infectious Diseases* (Hart et al., 2002), contents of 20 vials of anthrax vaccine adsorbed were cultured in three growth media at several dilutions, but mycoplasma did not grow. Testing for the presence of mycoplasma DNA produced negative results for all 10 lots evaluated. To test the ability of mycoplasma to survive in the vaccine, 154 million colony-forming units of live *Mycoplasma fermentans* were intentionally placed into vaccine vials in a laboratory, mixed, incubated, and sampled 24, 48, and 72 hours later. Inactivation of mycoplasma by the preservatives in the vaccine was rapid, as no growth was detected from any of the samples taken at any time point.

Illnesses of Gulf War Veterans, relation to: No published study using objective data has shown the US-made anthrax vaccine adsorbed to be associated with illnesses among Persian Gulf War veterans. Multiple independent civilian review panels found no basis for attributing ill-defined illnesses to anthrax or any vaccine. Gulf War veterans who self-report anthrax vaccination also report lesser degrees of health, but when the analysis is limited to veterans with objective vaccination records the health differential almost disappears (Mahan et al., 2004). Reliance on self-reported immunization status is a leading cause bias well recognized by epidemiologists. Whatever the unanswered questions about anthrax vaccination and illnesses of ~ 150,000 Gulf War veterans given the US-manufactured anthrax vaccine, multiple safety studies among the 1,300,000 service members vaccinated since 1998 provide evidence for the lack of an association with unexplained illnesses or multisymptom syndromes (Lange et al., 2003; Sever et al., 2002; Sever et al., 2004; Sulsky et al., 2004).

Lot xxxxx had problems. No vial of anthrax vaccine adsorbed left the manufacturer without FDA's explicit permission. DoD did not use any lot of vaccine that FDA did not release as passing all applicable tests. Lot-to-lot comparisons in the various human safety studies performed to date found no meaningful differences based on lot (Sever et al., 2002; Sever et al., 2004; Sulsky et al., 2004).

Manufacturing quality. The Food & Drug Administrative gave full approval to manufacturing renovations at BioPort Corporation's Lansing facilities in January 2002. The process validation documentation for anthrax vaccine adsorbed amounts to thousands of pages to assure consistency from lot to lot. The official name of anthrax vaccine adsorbed is now designated with the "USP" suffix, reflecting the addition of a monograph for quality standards of anthrax vaccine manufacturing in the first supplement to the 27th revision of the United States Pharmacopeia (USP) in July 2003. Anthrax vaccine adsorbed, USP, also appears in the current 28th revision and will continue to appear in subsequent revisions. As FDA scientists know from their in-depth involvement with the USP review process, the US Pharmacopeia is acknowledged around the globe for setting quality standards for pharmaceutical manufacturing.

Antibiotics, superiority of, against anthrax: Anthrax attacks cannot be predicted, as postal workers know only too well. Early casualties can come without warning, and in large numbers. There is no better round-the-clock protection than anthrax vaccine adsorbed. Antibiotics can cure some cases of anthrax infection and may be useful in post-exposure prophylaxis of anthrax infection, but if antibiotics were used for prolonged pre-exposure prophylaxis unacceptable adverse effects would result. Antibiotics are effective against the germinated form of *Bacillus anthracis*, but are not effective against the spore form of the organism.

Over the years, a body of pseudo-scientific writings related to anthrax vaccine adsorbed has accumulated on various Internet sites and in other media. We are grateful for FDA's consistent reliance on objective, verifiable evidence as its standard for evaluating safety and effectiveness. We rely on the FDA's continued scientific excellence for the benefit of our healthcare beneficiaries in the Military Health System.

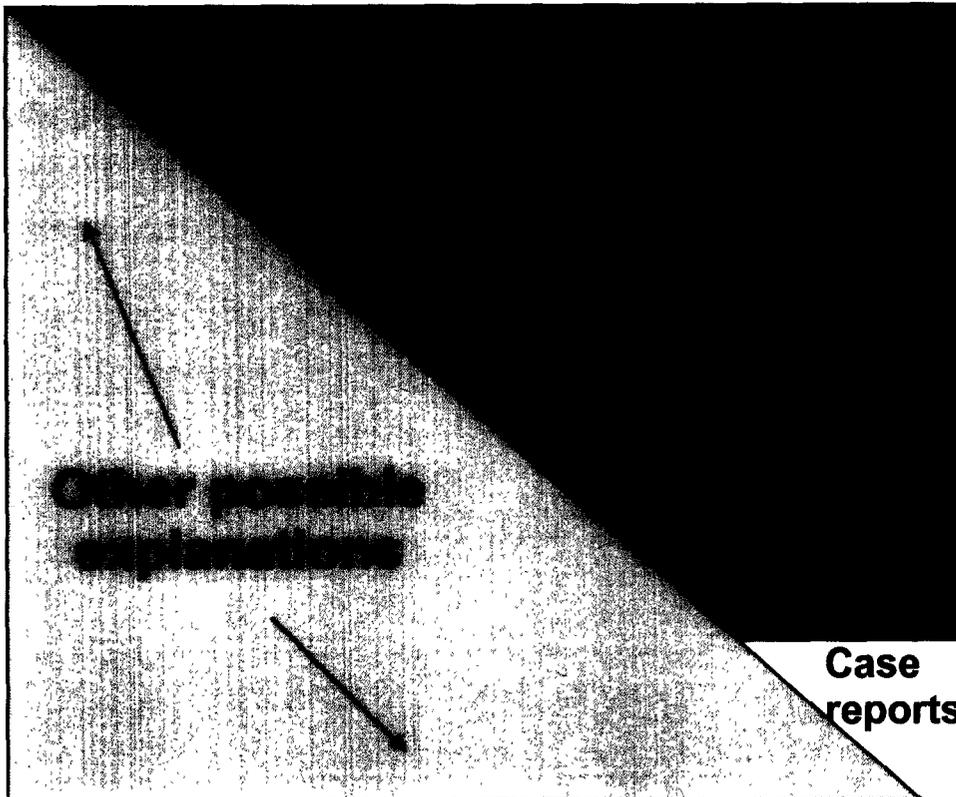
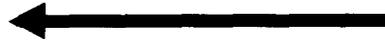
Thank you very much for your consideration.


Philip Volpe, MD
Colonel, United States Army
Assistant Surgeon General
for Force Projection

3 Enclosures

Enclosure 1. Hierarchy of Scientific Study Designs and Data Sources

**Value of Information,
Absence of Bias,
Scientific Objectivity**



**Scientific
Power**



Selection?
Peer review?
Replicated?
Et cetera



Enclosure 2. Bibliography

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Enclosure 3. Detailed Discussion of Squalene and Anti-Squalene Antibodies in Relation to Anthrax Vaccine

Content posted at www.anthrax.mil/squalene, 100 pages