

Comments and Questions regarding FDA's proposed rule and order to license Anthrax Vaccine Adsorbed

Re: DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration, 21 CFR Parts 201 and 610
[Docket No. 1980N-0208]
Biological Products; Bacterial Vaccines and Toxoids;
Implementation of Efficacy Review

ACTION: Proposed rule and proposed order, 29 Fed. Reg. 78281-78293
(Dec 29, 2004).¹

1. The lack of human efficacy trials precludes licensure.

In its proposed rule, the FDA claims that AVA is efficacious in humans for inhalation and other forms of anthrax, basing this determination on indirect pieces of evidence, because there exist no clinical trials documenting efficacy of AVA for any route of exposure in humans.

By so doing, FDA is flouting the existing statutory requirements² for licensure of a vaccine, which require valid human data from an adequate and well-controlled clinical trials that support both efficacy and safety.

In 1969 NIH asked that an IND study be undertaken "to determine human efficacy of the product."³ The manufacturer never complied with this recommendation.

2. The Animal Rule cannot be used to license anthrax vaccine adsorbed (AVA) without correlates of protection.

A second pathway for licensure of vaccines and drugs for bioterrorism, the so-called Animal Rule promulgated by FDA in 2002⁴, requires data obtained from at least two animal species, in conjunction with correlates of immunity that assure the animal data can be extrapolated to humans with absolute reliability. No such correlates of immunity (i.e., surrogate markers for survival following exposure to anthrax) have yet been established

¹ <http://www.fda.gov/cber/rules/bvactox.pdf>

² 21 CFR 601.25

³ Pittman M., Memorandum to S. Gibson, Assistant Director for Licenses and Inspections, NIH. February 10, 1969.

⁴ See Section 123, Public Law 107-188 ("Public Health Security and Bioterrorism Response Act of 2001"); and Fed. Reg. 2002; 67: 37988-37998.
<http://www.fda.gov/cber/rules/humeffic.pdf>.

for anthrax vaccine; therefore, AVA cannot be licensed using this pathway. Thus human data demonstrating safety and efficacy continue to be required in order to license this vaccine.

3. Data sources cited by FDA are inadequate to support safety and efficacy.

FDA cites six sources of information to justify AVA's safety and efficacy:

- 1) The Brachman study of the 1950s Defense Department vaccine;
- 2) The Centers for Disease Control (CDC) "Open-Label" study;
- 3) Surveillance data on the occurrence of anthrax in the general population between 1962 and 1974;
- 4) The March 2002 Institute of Medicine report titled "Anthrax Vaccine: Is it Safe? Does it Work?"
- 5) The VAERS data for anthrax vaccine; and
- 6) A 28-person subset of an army dose-reduction study.

We will review the limitations for each of these data sources to demonstrate that a) none of them provide acceptable evidence for efficacy or safety required by existing FDA regulations, and b) the conduct of some of these studies and their validity are open to question.

According to FDA, "the quality of data generated in clinical studies is of the utmost importance because safety and efficacy data from studies that do not or cannot meet regulatory requirements for adequate, well-controlled studies cannot lead to approval."⁵ We will demonstrate that these human studies do not and cannot meet FDA requirements for adequate, well-controlled studies, and therefore FDA must fail to approve a license for this vaccine.

In fact, the expert panel that reviewed AVA specifically addressed the importance of clinical trials in its "Generic Statement on Requirements for a Well-Controlled Field Trial":

"It has become generally understood that a successful and acceptable vaccine must be: (1) safe and (2) effective. Safety means that the preparation used must not cause the disease against which it is directed and that the occurrence of reactions, both local and general, must be within acceptable limits. Efficacy implies a useful degree of clinical protection...It is the clinical trial, however, which must provide the final critical assessment of the efficacy and safety of the new vaccine." See 50 Fed. Reg. 51005 (Dec. 13, 1985). (emphasis added)

⁵ Baylor N, Midthun K and Falk LA. The role of the FDA in vaccine testing and licensure. *In* New Generation Vaccines, 3d Edition. Ed. Levine MM et al. Marcel Dekker, New York. 2004. Pages 117-125.

Anthrax vaccine absorbed (AVA) has never met this standard, nor did the Brachman field trial of a different vaccine, nor does FDA's current proposed rule.

4. The 1950's Brachman field trial of a similar, but different anthrax vaccine⁶ fails to provide evidence for inhalation efficacy

The Brachman study^{7, 8} was conducted in four goat hair mills in the northeastern US in the late 1950s. All five inhalation anthrax cases occurred between August 27, 1957 and October 30, 1957 at Arms mill in Manchester, New Hampshire. No inhalation cases had previously occurred there. All other cases at the four mills were cutaneous. In 1960, Brachman et. al. wrote the following, indicating that he and his co-authors did not feel their study had established vaccine efficacy:

"The efficacy of the anthrax cell-free antigen as a vaccine was not fairly tested in this epidemic. Although none of the nine [cutaneous plus inhalation] cases occurred in vaccinated individuals, only approximately one fourth of the employees had received the vaccine. There was an apparent difference in attack rates between workers who received placebo inoculations and those who received vaccine, but analysis of their job categories suggested that the vaccinated group was not at as high a risk as the placebo or uninoculated control groups." (Brachman, 1960, p. 20)

In other words, randomization by job categories had not occurred, the placebo group was found to be at greater risk from anthrax than the vaccinated group, and therefore the apparent statistical evidence for efficacy was misleading. Brachman repeatedly made the point over the next 42 years that his study did not prove efficacy against the inhalation route of exposure, reiterating it as recently as 2002:

"Each participant was evaluated 24-48 hours after receipt of the vaccine or placebo, and a minimal number of significant reactions were noted. The results showed a 92.5% efficacy in preventing cutaneous anthrax. Although five cases of inhalational anthrax occurred in one of the field

⁶ In 1999, the Government Accountability Office (GAO) observed: "...MDPH was granted a license for a similar vaccine that differed from the original vaccine in three ways. First, the manufacturing process changed when MDPH took over. Second, the strain of anthrax that Merck used to grow the original vaccine was changed, and another strain was used to grow the MDPH vaccine. Finally, to increase the yield of the protective antigen (which is believed to be an important part of the vaccine's protective effects), the ingredients used to make vaccine were changed from the original vaccine. See GAO T-NSIAD-99-148, "Medical Readiness: Safety and Efficacy of the Anthrax Vaccine" (Apr 29, 1999). (<http://www.gao.gov/archive/1999/ns99148t.pdf>)

⁷ Brachman PS, Gold H, Plotkin SA et al. Field evaluation of a human anthrax vaccine. Am J Pub Health 1962;52: 632-45.

⁸ Brachman PS, Plotkin SA, Bumford FH et al. An Epidemic of Inhalation Anthrax: The First in the Twentieth Century. II. Epidemiology. Am J Hygiene 1960; 72: 6-23.

trial mills (two in placebo recipients and three among nonparticipants) the results were not statistically significant in view of the small number of events to address the efficacy of the vaccine in preventing inhalation anthrax.”⁹

According to FDA, “when the primary efficacy study is not prospective and randomized, additional supporting studies may be required.”¹⁰ This study was improperly randomized. It also used a different vaccine. Please explain the additional evidence for human efficacy FDA has obtained.

5. Brachman changed his position only when FDA’s licensure of the vaccine was under legal challenge due to the Doe v. Rumsfeld lawsuit.

Dr. Brachman submitted a letter to FDA’s anthrax vaccine docket on March 2, 2005, making erroneous claims to assert that his 1950’s study of a different vaccine demonstrated efficacy of the current AVA for all routes of anthrax exposure, declaring:

“In analyzing the data, we felt that since the pathophysiology of human anthrax is the same whether the organism gains entrance through the skin or through the lungs, and therefore, it was appropriate to combine the data from the field trial. The pathophysiology of anthrax is the result of a toxin produced by the organism causing local or systemic reactions regardless of the route by which the organisms entered the body. In our statistical analyses, we did omit cases of anthrax that occurred in employees that did not volunteer to participate in the study. However, if these cases are included in the analyses, the vaccine efficacy is not changed. Thus, I feel that the vaccine is appropriate for active immunization against Bacillus anthracis regardless of the route of exposure.”¹¹

The problem with this argument is threefold. First, the pathophysiology¹² of cutaneous anthrax is actually very different than that for inhalation anthrax, as noted earlier by Dr. Brachman himself.¹³ Second, even if the pathophysiology of the two forms of anthrax

⁹ Brachman PS. Bioterrorism: Update with a Focus on Anthrax. Am J Epidemiology 2002; 155: 981-987.

¹⁰ Anthony BF and Sutton A. The role of the FDA in vaccine testing and licensure. In New Generation Vaccines, 2nd Edition. Eds. Levine MM, Woodrow GC, Kaper JB et al. Marcel Dekker NYC.

¹¹ Brachman PS. Submission to FDA Docket 1980N-0208. March 2, 2005.

¹² Definition of pathophysiology: Altered functions in an individual or an organ due to disease. www.nhlbi.nih.gov/health/public/lung/other/bpd/glossary.htm

¹³ Brachman PS and Friedlander AM. Anthrax. In Vaccines, 2nd Edition. eds. Plotkin S. and Orenstein A. 1994. Saunders, Philadelphia. Pages 729-739. The different features of cutaneous and inhalational disease are discussed separately.

was identical, that would provide no proof that protection for different routes of exposure would be effective from one vaccine, as will be demonstrated with two examples later in this document (in point # 8). Third, the vaccine Brachman tested was very different than AVA, and so his study is inapplicable to the current vaccine. Brachman himself noted (in a series of editions of the textbook *Vaccines*) that there have been no controlled clinical trials in humans of the efficacy of the currently licensed U.S. vaccine.¹⁴ And in a submission to FDA in 1973 the manufacturer admitted that “it is not possible at this time to provide a quantitative estimate of the efficacy of the MDPH vaccine in conferring protection in man against either form of the disease.”¹⁵

Given these contradictions, the March 2, 2005 letter from Dr. Brachman to FDA should be considered less than reliable.

6. Apparent statistical support for vaccine efficacy is confounded by low worker participation in the study, and variability of exposure between vaccine and placebo groups: yet these facts have been omitted in FDA’s analysis of this study.

Brachman’s original study did not contain an “observational control group” as often claimed later. Fully 50% of the Manchester, New Hampshire mill (where all inhalation cases occurred) employees refused to participate in Brachman’s study. Brachman further acknowledged that the unimmunized employees tended to work in areas of higher anthrax contamination.

Yet, in order to make the vaccine appear to be efficacious, this variation in exposures was ignored by FDA in its discussion of this study in its proposed rule and order, and the employees who refused to be part of the study were later used by FDA in the efficacy analysis. Had they been left out of the analysis, as is normally done, only two inhalation cases would have occurred in the placebo group versus no cases in the vaccine group.

FDA’s analysis of the Brachman data is therefore unsound.

7. The vaccine tested by Brachman was different than AVA.

Even if Brachman’s study had demonstrated vaccine efficacy for inhalation anthrax, this would not support licensure of AVA. The reason is that the two vaccines are very different. Brachman tested a vaccine produced at Fort Detrick, using small-scale technology. The vaccine Brachman used was supplied by the Army Chemical Corps, which employed an anthrax strain derived from the Vollum strain, named R1-NP. It was grown in medium 599 under aerobic conditions. Aluminum potassium sulfate was the adjuvant. Mercury-containing thimerosal was a preservative. Systemic reactions

¹⁴ Ibid.

¹⁵ Michigan Department of Public Health submission to FDA expert panel. May 1, 1973.

occurred in 0.2% of recipients. George Wright, the vaccine's developer, claimed that there were no local reactions from the initial dose of the vaccine.¹⁶

Today's AVA is made using entirely different technology, including different fermenters, different filters, a different medium (1095), a different anthrax strain that was not derived from Vollum, anaerobic fermentation conditions, and a different adjuvant, aluminum hydroxide. It contains no thimerosal as a preservative. Four to six times as much antigen was elaborated at the time as a result of these changes,¹⁷ i.e., the 1970 version of AVA had an estimated five times as much active ingredient as the earlier vaccine.

Furthermore, the 2002 FDA-approved AVA label notes that the rate of systemic reactions is 5-35%, which is 25 to 175 times higher than reported by Brachman. It should be readily apparent that the two vaccines are very different. Had Brachman's vaccine produced acceptable safety and efficacy, there would have been no need to continue to develop newer and different anthrax vaccines.

8. Route of exposure a critical determinant of vaccine efficacy.

In order to specify an indication for a vaccine, according to statutory requirements for product labeling (21 CFR 201.56 and 21 CFR 201.57), there must be valid evidence of efficacy for that indication. FDA's proposed rule ignores the fact that vaccines have markedly different efficacy for different routes of disease exposure. Therefore FDA has no scientific justification for combining cutaneous and inhalation cases together in a single efficacy equation.

In its proposed rule, FDA has attempted to interpret Brachman's study as showing evidence for vaccine efficacy by lumping both cutaneous and inhalation cases together and claiming statistical significance for this approach. By doing so, FDA deviated from the recommendations of its 1985 panel, which observed:

*"No meaningful assessment of its value against inhalation anthrax is possible due to its low incidence."*¹⁸

Without providing a scientifically valid justification for this departure from its statement in the 1985 Proposed Rule, FDA cannot reasonably abrogate the finding of its own expert panel that a similar, but different anthrax vaccine proved efficacious only for cutaneous

¹⁶ Wright GG, Green TW and Kanode RG. Studies on Immunity in Anthrax: Immunizing Activity of Alum-Precipitated Protective Antigen. *J Immunology* 1954; 73: 387-91.

¹⁷ Wright GG, Puziss M and Neely WB. Studies on immunity in anthrax. IX. Effect of variations in cultural conditions on elaboration of protective antigen by strains of *Bacillus anthracis*. *J Bacteriology* 1962; 83: 515-522.

¹⁸ FDA Proposed Rule, 50 Fed. Reg. 51059 (Dec 13, 1985). The 1985 proposed rule was the result of recommendations submitted to FDA by an expert panel in August 1979, and first made available to the public by FDA in 1980. (See also 45 Fed. Reg. 77134, Nov. 21, 1980).

anthrax. FDA advisory committees are “asked to comment on the adequacy of the clinical data for safety and efficacy.”¹⁹ The committee did exactly this, telling FDA that the data for efficacy for inhalation anthrax were insufficient. The data are still insufficient. If FDA wants to change this finding, it will need to convene another expert panel to review the evidence and again comment on its adequacy.

Furthermore, according to FDA authors Anthony and Sutton, FDA does not ask the expert panel to decide on licensure, because FDA uses nonclinical as well as clinical information to make licensing decisions, “e.g., details of manufacture, consistency of manufacturing, lot-release testing, unresolved noncompliance with the CFR, questions of data integrity or other matters that are not appropriate for public discussion at an open advisory committee meeting.”²⁰ Thus FDA can use manufacturing issues to withhold a vaccine license, but should not dispute its advisory committee’s analysis of the safety and efficacy data.

In fact, in February 2004 Dr. Gene Stollerman, M.D., chair of the expert panel on which the 1985 proposed rule was based, confirmed that FDA was misrepresenting his panel’s conclusion.²¹

9. Both the FDA and the Army have recognized, with at least two other biodefense vaccines, that differences in route of exposure result in differences in efficacy.

Both the licensed plague vaccine²² and the unlicensed C-84 Venezuelan Equine Encephalitis (VEE) vaccine have been used to protect troops from potential biological warfare threats. However, after years of use, later studies showed that although both vaccines had some efficacy for disease acquired cutaneously (via insect bites), they were ineffective for inhaled disease, the form expected from biological warfare agents.²³ The

¹⁹ Anthony BF and Sutton A. The role of the FDA in vaccine testing and licensure. In *New Generation Vaccines*, 2nd Edition. Eds. Levine MM, Woodrow GC, Kaper JB et al. Marcel Dekker NYC.

²⁰ Ibid.

²¹ T. Ready, "US soldiers refuse to fall in line with anthrax vaccination scheme", *Nature Medicine*, February 2004, Vol. 10 No. 2, p. 112.

<http://www.nature.com/cgi-taf/DynaPage.taf?file=/nm/journal/v10/n2/index.html#nv>

"...But the new interpretation of the data is a matter of semantics, not science, argues Gene Stollerman, who chaired the 1973 panel. "I will defend our interpretation,"

Stollerman says, "Any other interpretation has to do with legal issues." "

²² Licensed and available in the US until 1999; used to protect Canadian forces during the 1991 Gulf War from a postulated threat of inhaled plague.

²³ CDC, "Prevention of Plague: Recommendations of the Advisory Committee on Immunization Practices (ACIP)", *MMWR Weekly*, Dec 13, 1996 / 45(RR-14);1-15

<http://www.cdc.gov/mmwr/preview/mmwrhtml/00044836.htm>

"...Although various modifications of killed plague vaccine have been available since World War II, its efficacy in protecting humans has not been adequately demonstrated. Pneumonic plague has developed in at least two persons despite

differences in efficacy due to route of exposure are widely acknowledged both by civilian and military medical experts.^{24 25 26 27}

In particular, Army researchers have acknowledged in published papers and official meetings that both the plague vaccine and the Venezuelan Equine Encephalitis (VEE) vaccine are known to work for cutaneous infection, but not for inhalation exposure in a biological warfare environment.^{28 29} Also noteworthy is that the plague vaccine was licensed, presumably based on demonstrated efficacy, and was once recommended by the CDC's Advisory Committee on Immunization Practices.³⁰ But this vaccine is now no longer produced. In a 1998 article, the Army's top anthrax vaccine researcher, Dr. Arthur Friedlander, explained the inability of the licensed plague vaccine to provide protection against inhalation exposure.³¹

vaccination, indicating that the vaccine may not be effective in the prevention of infection via inhalation of infectious respiratory droplets or other airborne materials."

²⁴ Morris GJ. *Yersinia Infections*. In Cecil Textbook of Medicine, 22nd Edition, 2004. Eds. Goldman L and Ausiello D. Saunders (Elsevier), Philadelphia, PA. pp 1865-8.

²⁵ Immunizations and Chemoprophylaxis. BUMEDINST 6230.15. Army Regulation 40-562. January 2005.

²⁶ Jahrling PB and Stephenson EH. Protective efficacies of live attenuated and formaldehyde-inactivated Venezuelan Equine Encephalitis virus vaccines against aerosol challenge in hamsters. *J Clin Microbiology* 1984; 19: 429-31.

²⁷ CDC. Prevention of Plague: recommendations of the advisory committee on immunization practices. *MMWR* 1996; 45 (RR-14): 1-15.

<http://www.cdc.gov/mmwr/preview/mmwrhtml/00044836.htm>

²⁸ LTC Gerard P. Andrews, Ph.D., Chief, Bacteriology Division USAMRIID, Fort Detrick, FDA Medical Defense Against Bioterrorism - Workshop (Dec 6-7, 2000)

<http://www.fda.gov/cber/summaries/120600bio09.htm>

²⁹ Dr. Richard Kenyon, project manager for the DoD Joint Vaccine Acquisition Program, stated during a May 1999 AVIP conference: "There are vaccines that have been developed such as the VEE vaccine which protects very nicely against mosquito bites but does not protect very well against aerosol. So, we have to show the FDA that these vaccines protect against an aerosol challenge. Aerosol, of course, is much more difficult to prove the efficacy than an aerosol against a parenteral [sic] challenge." See R. Kenyon, AVIP conference official transcript (May 25, 1999).

³⁰ CDC Morbidity and Mortality Weekly Report, *MMWR*: 1982 / 31(22);301-304.

<http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00041848.htm>.

"Plague vaccines have been used since the late 19th century, but their effectiveness has never been measured precisely. Field experience indicates that vaccination with plague vaccine reduces the incidence and severity of disease resulting from the bite of infected fleas. The degree of protection afforded against primary pneumonic [i.e. inhalation] infection is not known." [emphasis added]

³¹ Colonel Arthur Friedlander, M.D., USAMRIID, Fort Detrick, *Vaccines*, July 1998; 16 (11-12) 1131-7. The article abstract states: "The current human whole-cell vaccine is ineffective against pneumonic plague..." [i.e. inhalational plague].

These two examples – plague and VEE vaccines -- point up the fact that route of exposure can be critical in the determination of whether a vaccine will be effective against a particular pathogen. Despite this, FDA’s proposed rule not only ignores this important distinction, but also willfully conceals it in the agency’s treatment of plague vaccine.

10. FDA’s concurrent proposed rule conceals plague vaccine’s failure to protect against disease acquired via inhalation.

FDA’s proposed rule for anthrax vaccine also contains proposed rules for other bacterial vaccines, including plague vaccine.³²

The 1985 FDA proposed rule reviewed the plague vaccine dosage schedule and label; FDA responded to these panel recommendations in its new proposed rule. Yet no plague vaccine is available in the US because a) cutaneously-contracted plague is treated with antibiotics; and, b) the military ceased use of plague vaccine for biodefense due to the vaccine’s lack of inhalation efficacy. Once there was no military market for the vaccine the manufacturer stopped production in 1999.

So, no plague vaccine of this formulation is expected to be manufactured and both CDC and military websites report that no plague vaccine is currently available.³³ Yet, FDA has disingenuously addressed changes to the plague vaccine’s immunization schedule in its proposed rule as if the vaccine was in use, or might be used, in the future.

FDA does not want to recognize the plague vaccine’s current lack of use because to do so would be to acknowledge that the same efficacy limitations that pertain to plague vaccine also pertain to anthrax vaccine. So, FDA now proposes [the](#) detailed dosing and label change that was recommended by its expert panel in 1979, twenty years before [this](#) [obsolescent](#) vaccine ceased production.

FDA has carefully avoided explaining the irrelevance of this proposed change for plague vaccine in its proposed rule, and has curiously avoided recommending that the plague vaccine license be revoked.³⁴

³² 29 Fed. Reg. 78291 (Dec 29, 2004). Sec.U., “Plague Vaccine Immunization Schedule”

³³ See e.g., CDC, "Health Information for International Travel", 2001-2002

<http://www.cdc.gov/travel/yellowbk99.pdf>

"...Plague vaccine is no longer commercially available. Vaccination against plague is not required by any country as a condition for entry."

³⁴ The FDA proposed rule notes that licenses of other ineffective vaccines, including one licensed to the anthrax vaccine manufacturer, BioPort Corp. (previously the Michigan Department of Public Health), were revoked as part of its review. See. Table 2, 29 Fed. Reg. 78285 (Dec 29, 2004).

Apparently, FDA does not want to acknowledge that a second bacterial vaccine being reviewed concurrently with the anthrax vaccine also failed to protect against disease acquired by inhalation – and that that vaccine, logically, is no longer used.

11. Anthrax vaccines were never intended to protect against cutaneous anthrax.

There is no need for a vaccine for cutaneous anthrax. Cutaneous anthrax is easily treatable with common antibiotics, and is not contagious. Why would anyone go through a rigorous course of six initial inoculations, then yearly boosters, to prevent a disease that is effectively treated the same way as a strep throat, and for which there is only about one case yearly in the entire United States?

Therefore, it is time for FDA to stop pretending there is a role for this vaccine in the prevention of cutaneous anthrax. FDA's proposed rule acknowledges that even in the 1950's textile mills the incidence of anthrax infection was low.³⁵ So did Dr. Brachman in his report on the 1950's field study:

"One hundred and thirty-six cases of cutaneous anthrax, with one fatality, were reported from this mill during the period from January 1, 1941, to June 30, 1957. No cases of inhalation anthrax were observed during the same period."³⁶

CDC also noted the low incidence of infection in surveillance data collected in so-called at risk industrial settings between 1962 and 1974.³⁷ FDA has agreed with CDC in its proposed rule.³⁸

The historical low incidence of anthrax infection, even in at-risk settings, and the demonstrated efficacy of antibiotics, is the reason the CDC Advisory Committee on Immunization Practices recommends AVA for pre-exposure prophylaxis only for those "at risk for repeated exposure" and only in situations where a "quantifiable risk" of exposure exists.³⁹

³⁵ FDA proposed rule, "Prior to vaccination, the yearly average number of human anthrax cases was 1.2 cases per 100 employees in these mills." 29 Fed. Reg. 78286 (Dec 29, 2004).

³⁶ Brachman PS, et.al., American Journal of Hygiene (Dec 1960), Vol. 72, pp 6-23, at page 9.

³⁷ FDA proposed rule, 29 Fed. Reg. 78286 (Dec 29, 2004).

"...epidemiological data—sometimes called surveillance data—...in at-risk industrial settings collected by the CDC and summarized for the years 1962-1974....In that time period...Twenty-seven cases of anthrax disease were identified." 29 Fed. Reg. 78286 (Dec 29, 2004).

³⁸ FDA proposed rule, footnote 5, 29 Fed. Reg. 78286 (Dec 29, 2004).

"...and the low incidence and sporadic occurrence of anthrax disease also makes further adequate and well-controlled clinical studies of effectiveness not possible."

³⁹ Centers for Disease Control, "Use of Anthrax Vaccine in Response to Terrorism: Supplemental Recommendations of the Advisory Committee on Immunization

In short, the Defense Department (DoD) wants anthrax vaccine only for inhalation exposure.⁴⁰ FDA's proposed rule is an attempt to provide DoD with a licensed product, simply so the military can mandate its use without informed consent.

DoD made the true rationale for its use of anthrax vaccine clear in the 1996 investigational new drug (IND) application the Army prepared for the manufacturer. The IND application, submitted to FDA by the Michigan Biologic Products Institute on September 20, 1996, requested that inhalation anthrax be added as a specific indication to the vaccine label:⁴¹

“The indications defined in the current labeling for AVA do not specify the route(s) of exposure to B anthracis (i.e., oral, cutaneous, respiratory) against which the vaccine is effective. The Department of Defense is concerned with exposure of its personnel to B. anthracis via inhalation of spores and will use animal models to support the efficacy of the vaccine against that route of exposure in humans.”

Therefore, to justify licensure of this vaccine, efficacy must be established for the inhalation route of exposure, because that is the only route for which the vaccine will realistically ever be used. FDA appears to argue in its proposed rule that since performing clinical trials to establish efficacy in humans is logistically and ethically “not possible”, the vaccine should be licensed anyway.⁴² However, the Food Drug and Cosmetic Act does not allow the agency to abrogate the statute simply because its requirements are inconvenient.

Therefore, any decision by FDA to license AVA must provide a scientifically valid explanation of how FDA has assessed this vaccine's efficacy against inhalation anthrax in humans in the absence of an adequate and well-controlled clinical trial. (21 CFR 201.56 and 21 CFR 201.57). In the absence of such data, or unless FDA uses the “animal efficacy rule,” FDA cannot justify licensure of AVA as a Category I biologic.

12. Surveillance data are unreliable to assess inhalation efficacy

CDC surveillance data from 1962-1974 are said by FDA to support vaccine efficacy, because 27 cases of anthrax occurred in non-immunized or partially immunized persons, and none in fully vaccinated individuals.

Practices", Morbidity and Mortality Weekly Report/ 51(45);1024-1026, Nov 15, 2002.
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5145a4.htm>

⁴⁰ Judge Sullivan's October 27, 2004 ruling agreed, as did FDA's Department of Justice attorneys. See at Sullivan ruling p. 30, footnote 9.

<http://www.dcd.uscourts.gov/Opinions/2004/Sullivan/03-707c.pdf>

⁴¹ IND application for Anthrax Vaccine Adsorbed. #6847, Sep 20, 1996.

⁴² FDA proposed rule, footnote 5, 29 Fed. Reg. 78286 (Dec 29, 2004).

These CDC data do not support cutaneous efficacy for AVA because they represent the use of at least two other anthrax vaccines, and not the currently-produced AVA. The other vaccines include the Merck, Sharp and Dohme vaccine, an earlier version of AVA produced by the Michigan Department of Public Health, and possibly vaccine manufactured at Fort Detrick. Since the CDC surveillance data do not distinguish between these vaccines, and since these vaccines differed substantially from the current AVA, the CDC surveillance data cannot be extrapolated to support licensure of the current AVA.

Based on information provided in FDA's proposed rule, none of the 27 anthrax infection cases reported by CDC were inhalation anthrax. During the period 1962-1974 there were between zero and two inhalation anthrax cases reported in the United States.⁴³ Thus, even if one construed the CDC surveillance study as relevant to cutaneous exposure for AVA, these data still appear to provide no statistically significant support for protection against inhaled anthrax by vaccination during this period.

During pre-licensure monitoring of AVA use by CDC, this agency's failure to establish the risk of exposure to study subjects caused NIH to dismiss the use of surveillance data to justify licensure. Regarding the use of surveillance data to support licensure of AVA, in 1969 Dr. Margaret Pittman, chairman of the ad hoc committee on AVA licensure at NIH, stated :

*"The lack of cases of anthrax in an uncontrolled population of approximately 600 persons in the Talladega mill can hardly be accepted as scientific evidence for efficacy of the vaccine...without evidence of actual exposure in this mill during this time, and the apparently unpredictable incidence and distribution of anthrax in various mills -- "*⁴⁴
(end of sentence redacted by FDA)

Similarly, CDC never established how many of its 1962-1974 surveillance data set of vaccinated individuals were actually exposed to infectious doses of anthrax, making these data scientifically irrelevant.

Furthermore, it is uncertain whether CDC's anthrax case data are accurate and complete. William Patrick, former chief of product development at Fort Detrick, gave a lecture at Maxwell Air Force Base in 1999.⁴⁵ He discussed the case of a Fort Detrick researcher who was fully vaccinated, but opened his bio-hood, inhaled anthrax, and died 30 hours later despite treatment. This Army researcher's death does not appear to have been

⁴³ Brachman PS. Inhalation Anthrax. *In* Bacteria as agents of airborne contagion. Annals NY Acad Sci 1980. Pages 83-93.

⁴⁴ Pittman M., NIH Memorandum, Ref. No. 67-70. Feb 6, 1969.

⁴⁵ Patrick W. Video: Biological Warfare Briefing. Given at USAF Counterproliferation Center, Maxwell Air Force Base. Feb 23, 1999. *Copy available on request.*

counted by CDC. Patrick also noted that Fort Detrick experienced a total of 31 human anthrax infections before 1969. At least some of these would have been vaccinated. Were any of these cases reported to FDA, or included in the CDC surveillance data set?

The a) use of different vaccines by CDC in its surveillance study; b) lack of quantifiable exposure; and, c) lack of reliable case identification remain insurmountable obstacles to the use of these CDC surveillance data in establishing AVA efficacy.

13. Institute of Medicine report was tainted by vested interests and political concerns.

FDA's proposed rule cites (at footnote 4) the March 2002 report of an Institute of Medicine committee chaired by Dr. Brian Strom. This Institute of Medicine (IOM) report "Anthrax Vaccine: Is it Safe? Does it Work?"⁴⁶ was paid for by the Department of Defense, and conducted by the Medical Follow-Up Agency (MFUA) of the National Academy of Sciences, which is wholly funded by the Departments of Defense and Veterans Affairs. Therefore the MFUA has a strong vested interest in providing the Defense Department with reports that support Defense Department policies.⁴⁷

Additionally, the IOM report (at page viii) acknowledged that the committee was influenced by the post-9/11 anthrax letters attacks and rushed its investigation and report into print approximately seven months earlier than planned. Notably, the last six months of the IOM committee's deliberations, beginning immediately after September 11, 2001, were held in closed session.

The manner in which the IOM Committee conducted its meetings⁴⁸, and its acknowledged complete reliance⁴⁹ on FDA, CDC, DoD and their proxy vaccine

⁴⁶ Committee to Assess the Safety and Efficacy of the Anthrax Vaccine. Medical Follow-up Agency, Institute of Medicine. Anthrax Vaccine: Is it Safe? Does it Work? National Academy Press 2002; Washington, DC.

⁴⁷ The IOM report study director, Dr. Joellenbeck, has co-authored other IOM reports that were blanket endorsements of Army biodefense policies. See, for example, her 1999 IOM (MFUA) report with retired MGen Philip Russell, MD, former commander of Ft. Detrick: <http://books.nap.edu/catalog/9711.html>

⁴⁸ The IOM committee, in 13 days of meetings and conference calls, spent less than three hours hearing from those opposed to the vaccine. These opponents had to pay their own way to travel to Washington from all over the country. None of their concerns about the experimental and unapproved nature of the vaccine were included in the IOM report. In contrast, the committee gave unlimited access to BioPort, DoD, FDA and CDC to present their views, all directly or indirectly appearing at government expense.

⁴⁹ See Acknowledgments, IOM report, page ix. In particular, Army Colonel John Grabenstein, deputy director of the Military Vaccine Agency, is cited 31 times in the IOM report: "As our study contact with the Department of Defense, LTC John Grabenstein was very helpful and responsive in his efforts to provide information to the

manufacturer for data, undercut the proposed rule's characterization of the IOM committee's work as "an independent examination of AVA." (Proposed Rule at page 78286).

14. Two Institute of Medicine reports in conflict

An earlier IOM committee, chaired by Dr. Harold Sox, was also charged with investigating the safety of anthrax vaccine. This study was not conducted by the Medical Follow-Up Agency, but by the Division of Health Promotion and Disease Prevention at the National Academy of Sciences. The Sox IOM committee, issuing its report in September 2000 (18 months before the later Strom IOM committee's report) reviewed all published, peer-reviewed literature available and concluded there was no evidence establishing long-term safety of anthrax vaccine:

*"The committee concludes that in the peer-reviewed literature there is inadequate/insufficient evidence to determine whether an association does or does not exist between anthrax vaccination and long-term adverse health outcomes."*⁵⁰

The first (Sox) IOM committee used the IOM's traditional methodology for reviewing vaccine research, termed a weight of evidence approach. However, the later (Strom) IOM committee, cited in FDA's proposed rule, chose at the onset not to use that approach.⁵¹ Yet, having discarded this standard method, they did not provide a discussion of the methodology, if any, that they used, and the rationale for choosing a different approach for evaluating data from many sources.

The second (Strom) IOM committee cited in FDA's proposed rule reviewed the same extensive literature on the vaccine, reviewed additional unpublished information, and heard a number of presentations about the vaccine from FDA, DOD and others. The committee also reviewed hospitalization data provided by the Defense Medical Surveillance System (DMSS) comparing soldiers post-vaccination to their own pre-vaccination status and to soldiers never vaccinated with AVA. Some of this data comprises the report's Appendix G. This committee ignored the extensive evidence for a

committee." Colonel Grabenstein has made numerous published false and inaccurate statements about anthrax vaccine that will inevitably be used to challenge FDA's reliance on the IOM report as an unbiased, "independent" source on which to base its licensure decision.

⁵⁰ Institute of Medicine. Gulf War and Health: Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide, and Vaccines 1999. National Academies Press, Washington DC. Page 313.

⁵¹ Committee to Assess the Safety and Efficacy of the Anthrax Vaccine. Medical Follow-up Agency, Institute of Medicine. Anthrax Vaccine: Is it Safe? Does it Work? National Academy Press 2002; Washington, DC. Page 40 or 52 (online) <http://books.nap.edu/books/0309083095/html/52.html#pagetop>

role for anthrax vaccine in the etiology of Gulf War Syndrome in the peer-reviewed scientific literature, and cited only army studies, most unpublished and pre-peer review, to claim AVA was “sufficiently safe.”

Sufficiently for whom? FDA’s proposed rule fails to answer this question by providing a statement on risk-benefit ratio, as was done in the 1985 proposed rule, which stated:

“This vaccine is recommended for a limited high-risk of exposure population along with other industrial safety measures designed to minimize contact with potentially contaminated material. The benefit-to-risk assessment is satisfactory under the prevailing circumstances of use.” (50 Fed.Reg. 51059, Dec. 13, 1985)

Please provide an explanation why FDA did not address risk-benefit ratio in its proposed rule and why the agency offered no explanation for omitting the statement made in the 1985 proposed rule.

15. Institute of Medicine Report valued methodologically suspect research.

The March 2002 IOM committee’s conclusions contained significant errors of fact and interpretation. Having discarded the IOM’s usual approach of weighting the data by its reliability, the Strom IOM committee gave significant weight to a series of mostly unpublished army studies of the vaccine, even though the January 2002 FDA-approved vaccine label dismissed these studies due to a large number of methodological problems:

*“Post Licensure Survey Studies In addition to the VAERS data, adverse events following anthrax vaccination have been assessed in survey studies conducted by the Department of Defense in the context of their anthrax vaccination program. These survey studies are subject to several methodological limitations, e.g., sample size, the limited ability to detect adverse events, observational bias, loss to follow-up, exemption of vaccine recipients with previous adverse events and the absence of unvaccinated control groups.”*⁵²

16. Institute of Medicine claim of efficacy unsupported by entire body of scientific literature

The IOM report cited in FDA’s proposed rule claimed that AVA “should be effective against anthrax toxicity from all known strains” even though vast experimental evidence from anthrax studies performed around the world, using five animal species, has repeatedly shown that many anthrax strains defeat this vaccine.^{53 54 55} In fact, in animal

⁵² Anthrax vaccine label, page 6: <http://www.fda.gov/cber/label/biopava0131022LB.pdf>

⁵³ Nass M. Anthrax Vaccine: Model of a response to the biologic warfare threat. *Inf Dis Clinics North America* 1999; 13: 187-208. <http://www.anthraxvaccine.org/AVmodel.htm>

⁵⁴ Turnbull PCB. Anthrax vaccines: past, present and future. *Vaccine*. 1991 Aug; 9 (8): 533-9. Review.

models AVA is less effective than the US animal vaccine and both Russian and British human vaccines.

17. Institute of Medicine supports animal model that has not been scientifically extrapolated to humans

The IOM report cited in FDA's proposed rule supported rabbits as a ~~good~~ valid animal model to demonstrate human efficacy for anthrax, even though the disease in rabbits is not identical to human disease, and no correlates of immunity have been established between rabbits and humans. FDA has also supported the rabbit as an animal model that could be used if the "animal efficacy rule" were invoked to license new anthrax vaccines.

It has been known for many years that rabbits develop an exceptionally strong immune response to vaccination against anthrax, stronger than all other rodents.⁵⁶ Thus they are usually protected against anthrax no matter which vaccine they receive. By using rabbits as their animal model, scientists can make it appear that whatever anthrax vaccine they test has excellent efficacy. However, without established surrogate endpoints, the rabbit data cannot be translated to humans; and after all, it is humans we are trying to protect, not rabbits.

Please explain FDA's justification for relying on animal data in three of the five efficacy studies cited in the Proposed Rule (see footnote 5 (Refs. 3, 4, and 5), 29 Fed. Reg. 78286 (Dec 29, 2004))

18. Institute of Medicine conclusions ignored serious reported adverse events

The IOM report's text did identify some "signals" from the DMSS database of a statistical association between immunization with anthrax vaccine and later hospitalizations for diabetes, breast cancer, asthma, regional enteritis, thyroid cancer and multiple sclerosis. However, in a turnaround, the IOM report then claimed, citing only the methodologically suspect army studies and no independent research, that there is "no convincing evidence at this time of elevated risks of later-onset health events among personnel who have received AVA."⁵⁷ Then the report's conclusions recommended *against* additional follow-up of these signals for anthrax vaccine.

Appendix G of the IOM report lists additional disorders for which hospitalizations were at least two times as common following anthrax vaccination as prior to vaccination.

⁵⁵ Turnbull PC. Current status of immunization against anthrax: old vaccines may be here to stay for a while. *Curr Opin Infect Dis.* 2000 Apr;13 (2):113-120. Review.

⁵⁶ Zaucha GM, Pitt LM, Estep J et al. The Pathology of Experimental Anthrax in Rabbits Exposed by Inhalation and Subcutaneous Inoculation. *Arch Pathol Lab Med* 1998; 122: 982-992.

⁵⁷ Committee to Assess the Safety and Efficacy of the Anthrax Vaccine. *Medical Follow-up Agency, Institute of Medicine. Anthrax Vaccine: Is it Safe? Does it Work?* National Academy Press 2002; Washington, DC. page 128.

Has FDA requested focused studies to address any of these signals *identified in the IOM report* of potential vaccine-associated illnesses? If not, please explain why FDA has not required either BioPort or the de facto⁵⁸ manufacturer, DoD, to conduct such studies?

19. What authority does the Institute of Medicine report have?

Both Meryl Nass, M.D.⁵⁹ and Walter Schumm, Ph.D.⁶⁰ have written extensive critiques of the IOM report after it was issued in 2002, and we ask the FDA to review these comments before giving any weight to the report.

An earlier Final Rule⁶¹ for anthrax vaccine issued by FDA on December 30, 2003 appeared to rely on the findings of the IOM as the arbiter of the science associated with anthrax vaccine.

However, FDA's expert panel had responsibility for reviewing the scientific evidence for vaccine licensure and drawing conclusions as to the reliability and completeness of that evidence. FDA may not cede any regulatory authority to the Institute of Medicine; nor can it depend upon this IOM report ~~very highly~~ due to the many key scientific and analytic errors it contains.

Further, the IOM committee, by finding that AVA "as licensed"⁶² is effective for inhalation anthrax, exceeded the scope of its Congressionally-directed "Statement of Task"⁶³ which was solely to analyze the "technical aspects regarding the anthrax vaccine" – and not to make a legal finding that is only within FDA's authority to make.

Please justify how the FDA has used this IOM report to draw conclusions on vaccine safety and efficacy, when the IOM committee was never considered an expert panel operating under the auspices of the Food Drug and Cosmetic Act.

20. Multiple problems with the Centers for Disease Control 1966-72 safety study

⁵⁸ Based on FDA's arguments in the proposed rule, the *Doe v. Rumsfeld* lawsuit, and the FDA's Aug 28, 2002 response to a Citizen Petition on anthrax vaccine.

⁵⁹ Nass M. Trampling on the Science. Published on website Red Flags Daily:
http://www.redflagsweekly.com/nass/2002_march11.html

⁶⁰ Schumm W, Webb FJ, Jurich AP et al. Comments on the Institute of Medicine's 2000 Report on the safety of anthrax vaccine. *Psychol Rep* 2002;91:187-91.

⁶¹ 69 Fed. Reg. 255 (Jan. 5, 2004)

<http://www.fda.gov/OHRMS/DOCKETS/98fr/03-32255.pdf>

⁶² IOM report at 2, 10, 22, and 77.

⁶³ See IOM report, Appendix A.

<http://books.nap.edu/books/0309083095/html/213.html#pagetop>

The unpublished CDC ‘Open Label’ safety study⁶⁴ involved providing 14 physicians at different sites with anthrax vaccine, which was administered to lab workers at Fort Detrick, to goat hair mill employees and to some other individuals. The physicians were asked to check for reactions 48 hours after each vaccine dose was administered. Approximately 7,000 subjects received a total of 15,000 vaccine doses, or an average of two per study subject. The study began in 1966, not 1967 as reported by FDA.

Although FDA states that doses were administered according to the approved schedule of six doses over 18 months with yearly boosters, this was the case only for the Fort Detrick employees who were vaccinated. In 1967 alone, 1,983 inoculations were administered at Fort Detrick. The majority of the other vaccinees received, on average, only one dose of vaccine.

The following comprise important limitations of this study:

a) The study used early lots of AVA that were produced using a different production method than is used today and were, due to manufacturing changes in the early 1990’s, significantly less potent than today’s AVA. The Government Accountability Office reported in 2001 on an Army study that found the current AVA could be up to 100 times more potent than the AVA that was licensed in 1970.⁶⁵

b) Most study subjects received only one dose of vaccine. Yet the bulk of serious reactions to the vaccine probably result from excess immune stimulation and generally occur after multiple doses prime the immune system. Much higher antibody levels are achieved after later doses than after the first vaccine dose. Therefore, having a majority of subjects in a safety study who received only one dose is entirely inadequate to assess safety, particularly since the usual regimen calls for six initial doses over 18 months and then yearly boosters. In fact, if the study subjects were truly “at risk of” anthrax, as the study report states, why did they receive inadequate doses of vaccine?

c) The report reveals that booster injection doses (used in at least 1,666 subjects) contained only half the volume of vaccine prescribed in the label and used currently; therefore, the relevance to safety of these even less potent doses is questionable.

d) The only vaccine lots used in the study from 1966 until October 15, 1970 were lots 2 (manufactured in 1966) and lot 7 (manufactured in 1968). The report states,

⁶⁴ Centers for Disease Control. Observational study of anthrax vaccine, 1966-72. Report and raw data obtained by FOIA to CDC, August 21, 2000.

⁶⁵ GAO-02-181T, Anthrax Vaccine: Changes to the Manufacturing Process, Oct 23, 2001, at p. 5: “First, in an unpublished study performed in 1990, the Department of Defense (DOD) found up to a hundredfold increase in the protective antigen levels in lots produced after the filter change that year.” See: <http://www.gao.gov/cgi-bin/getrpt?gao-02-181t>

“Lot 2 was distributed only from August 1, 1969 to October 1, 1969, and then was withdrawn from further use since it did not meet potency standards.” There is no evidence that Lot 2 was recalled or that investigators participating in the CDC study who were given vials from Lot 2 were notified to cease using it. Ninety-four inoculations using Lot 2 in 1971 were later documented. On October 2, 1970 the Michigan Department of Public Health notified CDC that Lot 7 had lost potency after two years in storage and recommended replacing it with Lot 8. This provides further confirmation that most study subjects appear to have received vaccine of limited potency, undermining the study’s relevance to the safety of the current AVA.

e) Investigators who were given vaccine to administer completed a form delineating vaccine reactions occurring up to 48 hours post-vaccination. The form asked for local reactions to be classified as “none,” “mild,” “moderate” or “severe.” The CDC form then asked, “If a mild systemic reaction occurs, describe below.” There was no specified follow-up of reactions after 48 hours unless the investigator chose to do so, and the report includes no tabulation of any late follow-up for any reactions. Thus any persistent reactions or late-appearing reactions were missed in this study. Severe systemic reactions, if they occurred, may have been presumed to be due to another cause, since the report form strongly implies that only mild systemic reactions are expected to occur from this vaccine. No severe systemic reactions appear to have been recorded. Although it is useful to collect data on local reactions, virtually all local reactions resolve. Capturing systemic reactions, especially those that persist, is what is crucial to an assessment of long-term safety, and this is the type of data that FDA should require prior to considering the current AVA for licensure.

f) During this CDC study, for the 5,556 vaccine doses for which reaction data are available to me, 92% of the subjects had no local or systemic reaction, and 7% had a mild local reaction, leaving less than 1% who had a moderate or severe local reaction to the vaccine. However, today the local reaction rates for AVA are generally acknowledged to be greater than 50% and have been as high as 80% in recent studies. This suggests the vaccine used in the CDC study was very different from the current AVA, further negating the applicability of the CDC study data to assessment of the safety of present-day AVA.

g) In a report from the Michigan Department of Public Health describing work done under contract DA-18-064-404-CML-498, provided as part of the CDC study report, is found the following quote:

“Sterility tests showed Lots 5 and 7 to be contaminated during filtration or final processing. These were treated with excess formalin (the brand name for formaldehyde) until sterile and the excess formalin neutralized with sodium bisulfite as described under the Records for Lots 5 and 7 in Appendix 1. Subsequent to this treatment, Lot No. 5 was still effective in immunizing rabbits and Lot No. 7 was no worse than before treatment. However, suitability of the treated vaccine for human use is not known.”

Yet this reprocessed and questionable vaccine was subsequently used in thousands of volunteers in the CDC study, which calls into question both its safety and efficacy (based on adulteration with formaldehyde, a carcinogen) and the ethical conduct of the study.

h) The safety test performed on each vaccine lot by the manufacturer, and accepted as evidence of safety by FDA, consisted of injecting vaccine subcutaneously into 3 white mice and 2 guinea pigs.

*“The animals are observed for a period of 7 days. The symptoms looked for include local reaction at injection site, loss of weight and any illness. If all the animals survive the observation period and remain in good health, the test is satisfactory. **Retesting is permitted** and is conducted as in the original test.”* (emphasis added)

This procedure may or may not be able to predict safety problems in humans, but allowing the test to be repeated with new animals if the lot fails the safety test negates its usefulness at identifying problem lots.

i) Some study results reveal problems with accuracy of the data. For example, arithmetic miscalculations caused reaction rates in one May 1967 Reactogenicity table to be reported as only one tenth as high as they really were.

j) This Reactogenicity table also reveals that old vaccine manufactured by Merck, Sharp and Dohme was used in some subjects, and vaccine from Michigan Department of Public Health in other subjects. Yet the FDA does not distinguish between these two vaccines in its use of this CDC study to assert vaccine safety of AVA. How can study conclusions apply to AVA when some study results were obtained using a different vaccine?

k) In 1971, out of a total of 1,427 injections administered at a mill in Talladega, Alabama as part of the CDC study, there were reports of local reactions in 309 recipients. Most reactions (266) were listed as mild, with 40 moderate and 3 severe. Yet there was concern at CDC, and as a result the textile mill doctor wrote to CDC that the plant nurse had been “overzealous in reporting instances of minor significances” though there had “been a few cases where an employee reported general malaise with a very low grade fever for a day or two.” Dr. Kokko at CDC then wrote to the Division of Biologic Standards at NIH, the licensing agency, with the mill doctor’s response, but incorrectly reported that, “No systemic reactions occurred.”

This points up the fact that no attempt was made to obtain a confirmatory assessment of adverse events from anyone other than the administering physicians. Thus there was no standardization in the identification and grading of adverse events between the fourteen clinics, leading to additional questions about the reliability of the data.

l) Both the Fort Detrick employees and some mill employees were required to be vaccinated as a condition of employment. Thus they may have had reason to

minimize adverse reactions to the vaccine, because if they had reactions preventing them from receiving further doses they might lose their job. Furthermore, they did not provide free informed consent to participate in the study because they were compelled to be vaccinated. Fort Detrick employees did not sign informed consent documents for the study. Thus the trial did not comply with FDA requirements for “the assurance of informed consent” and “full compliance with accepted ethical principles for the participation of human subjects in clinical studies.”⁶⁶ In fact, FDA’s expert panel on anthrax vaccine made this exact point in the 1985 proposed rule.⁶⁷

Please explain FDA’s policy on the use of data from trials in which subjects did not give informed consent.

m) The points above demonstrate that the “CDC Observational Study,” in which CDC gave vaccine to fourteen investigators to use at goat hair mills, research laboratories (especially Fort Detrick) and other situations was entirely inadequate to determine the safety of Anthrax Vaccine Adsorbed, and there exist a number of questions about the ethical conduct of the study.

21. Problems with the 1996-1999 DoD study of vaccine safety and efficacy.

To support vaccine safety, the FDA’s proposed rule states that since the 1985 panel review, “DoD conducted a small, randomized clinical study of the safety and immunogenicity of AVA” but cites only the AVA label as its data source, failing to provide an accurate reference to this study.

Since the January 2002 FDA-approved package insert (at pages 2, 3 and 5) refers to a study conducted between 1996 and 1999 that had 173 subjects, 28 of whom received AVA according to the standard schedule of doses and route of administration, we can only deduce that this is the study to which the current proposed rule refers. Therefore, the analysis that follows addresses that army study.

The Army’s “Comparative Study to Determine the Best Two-Dose Schedule and Route of Administration of Human Anthrax Vaccine” conducted by Col. Phillip Pittman, MD during that time period fits the description of the study in the product label. Our discussion of this study is based on a review of the 1996 IND application discussing this

⁶⁶ Anthony BF and Sutton A. The role of the FDA in vaccine testing and licensure. In *New Generation Vaccines*, 2nd Edition. Eds. Levine MM, Woodrow GC, Kaper JB et al. Marcel Dekker NYC.

⁶⁷ “Also no longer acceptable are comparisons of the frequencies of disease in those who do and do not volunteer for a vaccine study. The fallacy of this approach is that volunteers differ from non-volunteers in many important aspects....” See 50 Fed. Reg. 51012-51013 (Dec. 13, 1985).

proposed research,⁶⁸ the May 6, 1998 “Preliminary Report to the U.S. Food and Drug Administration. BB – IND 6847. LOG A-7281 Protocol: Comparative Study to Determine the Best Two Dose Schedule and Route of Administration of Human Anthrax Vaccine” obtained via FOIA to FDA, and the version of the study published in the journal *Vaccine* in 2002.⁶⁹ We attended the presentation Dr. Pittman made regarding this study to the Institute of Medicine in 2001. The following comprise important limitations of this study:

a) -FDA does not refer to this “assessment of safety” conducted by Colonel Pittman as a controlled clinical trial because it was uncontrolled; there was no unvaccinated control group. All of the subjects received anthrax vaccine, though the schedules and route of administration varied. Furthermore, the trial used an “open label” rather than a “double blind” format, which means that both the investigators and subjects knew each subject received anthrax vaccine and not a placebo. This is well known to introduce bias in the collection and analysis of study results.

b) In Pittman’s study, a total of 173 subjects were vaccinated with AVA, but only 28 subjects received AVA using the standard 0-2-4 week schedule and the subcutaneous route, two of whom dropped out during the study. Although it is reasonable to limit a study of the standard regimen’s efficacy to this subgroup, 173 people received AVA and all were entered into a safety study. Why were 145 subjects dropped from the safety analysis cited by FDA? This is epidemiologically unacceptable, casting doubt on the validity of this subgroup analysis, and it also significantly decreases the power of the study to identify adverse effects.

c) Subjects were evaluated 6 times during the first 30 days post-vaccination for safety. At least 14% of the total number of subjects (24 of 173 vaccinees) had a systemic adverse event after the first dose, and at least 12% had a systemic adverse event after the second vaccination. Twelve subjects did not complete the study after being vaccinated. One person stopped vaccinations due to developing a rash, and another subject committed auto theft and was dropped from the study. Pittman stated in the 1996 study proposal that if subjects had significant reactions they would not be given additional vaccine doses.⁷⁰ The reasons why ten other individuals dropped out during the study were not provided. This is an important omission, because a major reason for dropouts is the occurrence of adverse reactions that result in a contraindication for additional drug or vaccine doses.

d) This Army study began in October 1996, and the 6- and 12-month (4th and 5th) vaccine doses should have already been administered when this preliminary report was provided to FDA in May 1998. However, neither the 1998 preliminary report, nor the

⁶⁸ IND application for AVA September 20, 1996 PI Dr. Phillip Pittman. Sponsor Robert C Myers D.V.M., Michigan Biologic Products Institute.

⁶⁹ Pittman PR, et.al. "Anthrax vaccine: immunogenicity and safety of a dose-reduction, route-change comparison study in humans," *Vaccine*. 2002 Jan 31; 20 (9-10): 1412-20.

⁷⁰ IND application, Ibid.

2002 published report, provide any information on adverse reactions to doses administered after the first month (i.e. after the first three doses). In fact, in each of these reports, adverse reactions are presented only for the first month of the study. While reactions occurring 30 minutes post-vaccination are discussed, for other adverse reactions the period of time after vaccination and duration of the reaction are not given, nor is there any indication of long-term follow-up, even though the study lasted for 18 months, and was not published until three years after it concluded.

The study protocol makes clear that the Army had the ability to collect more detailed information on adverse reactions. Subjects had blood drawn 23 times during the first year of the study, at a minimum once each month, to determine antibody titers. However, adverse event data were collected only during the first thirty days each subject participated in the study. Given this continued monitoring of the subjects for efficacy, and FDA's recommendation for active adverse event follow-up at the time of blood draws in IND studies,⁷¹ why did the collection of safety data suddenly end at 30 days?

The adverse events most essential to an assessment of vaccine safety are those that persist long-term, and historically more severe reactions occur after multiple doses have been given. Thus this report of reactions occurring only through the first month of vaccinations falls far short of what is required to study a vaccine for which six initial doses are required, and for which long-lasting adverse reactions have been widely reported, including on the label.

Although the study collected data on 173 subjects' systemic as well as local reactions to AVA for up to 30 days following vaccination, the Army's report of the study provided to FDA in 1998 and published in 2002 omits any discussion of persistent reactions. Thus, this study as reported is entirely inadequate to determine the safety of Anthrax Vaccine Adsorbed. Why did FDA approve this IND research proposal without asking that safety be evaluated at each visit in which blood was collected?

e) The May 1998 Pittman preliminary report to FDA states,

"This report covers data analyzed up to and including 24 weeks. The Final Report will include data for the control group (sic) at 6, 12 and 18 months and subsequent analyses."

The "control group" referenced in the Pittman interim report apparently was the 28-person cohort receiving the standard dosing schedule and route of administration.

However, the 2002 published report provides no additional information regarding reactions following the three later doses, as had been promised. Why not? Has FDA sought out this information?

⁷¹ Ball LK, Ball R and Gellin BG. Developing safe vaccines. *In* New Generation Vaccines, 3d Edition. ed. Levine MM et al. Marcel Dekker NYC. 2004. Pp 127-144.

f) The published report also appears to omit substantive information related to the safety of the vaccine used in the Pittman study. The May 1998 preliminary report states that Lots 016 and 032 were used, with the 12- and 18-month doses coming from Lot 016. However, the published report states that only Lot 032 was used. Notably, FDA quarantined Lot 016 shortly after the preliminary study was sent to FDA because of particulates in the vials. There is no reason given in the published report why this adulterated vaccine was used or why any mention of Lot 016 was omitted.

g) The Army preliminary report of this study for the FDA, dated May 6, 1998, provides this final paragraph as the study's conclusion, which acknowledges it was only a "small study for safety" and therefore no conclusions at all are stated regarding systemic adverse reactions:

"19.0 CONCLUSION. Based on antibody response, this study provides evidence supporting the non-inferiority of a two-dose primary vaccination schedule of Anthrax Vaccine, Adsorbed, compared with the standard three-dose primary vaccination schedule. Although a small study for safety, data show the IM [intramuscular] route to be less reactogenic than SQ [subcutaneous] route of administration of AVA."

h) In summary, the Pittman study cited by FDA is neither an adequate nor a controlled clinical trial; there is no reporting of adverse reactions after one month despite frequent serology follow-up for more than a year; safety data for 145 of the study participants have been omitted from consideration; there is no reporting of the presence or absence of persistent reactions; the 2002 published study omitted substantive facts that raise questions about the ethical conduct of the study and the possibility that adulterated vaccine may have caused unreported adverse reactions. Further, an expert panel has never reviewed this study. Taken together, these issues undermine the validity of the Pittman study in general, and its current use by FDA to assert AVA's safety in particular.⁷²

22. FDA makes two specious arguments regarding comparability of MDPH and prototype DoD vaccines

The proposed rule argues:

"In addition, there are data comparing the safety and immunogenicity of the MDPH vaccine with the DoD vaccine. These data, while limited in the number of vaccines and samples evaluated, reveal that the serological responses to the MDPH vaccine and the DoD vaccine were similar with respect to peak antibody response and seroconversion."

⁷² FDA has also attempted to use this army study in its recent "emergency use authorization" (EUA). See 70 Fed. Reg. 5454 (Feb 2, 2005).
<http://www.fda.gov/cber/vaccine/eua013105.pdf>

Probably FDA has chosen to use the name MDPH vaccine, rather than AVA, because it is referring to data obtained from vaccine produced at the Michigan Department of Public Health prior to vaccine licensure, given that the name AVA was approved in 1970.

Because the anthrax vaccine produced in Michigan has undergone a series of manufacturing changes, which have resulted in a materially altered product that is much more concentrated than the original MDPH vaccine,⁷³ we fail to see how comparisons of two older and very different anthrax vaccines have any bearing on licensure of the current version of AVA.

The first US human anthrax vaccine, termed the DoD vaccine by FDA, was developed at the army's biological weapons facility in the early 1950s by George Wright. It was intended to protect workers in the bioweapons program,⁷⁴ two of whom (one scientist and one electrician) are acknowledged to have died from anthrax infections. The vaccine underwent several modifications, was used in Dr. Brachman's clinical trial, and at least ten pilot lots were manufactured at Merck Sharp and Dohme.

Further changes were then made to develop a more potent vaccine that could be manufactured in industrial quantities. The original AVA, described earlier in this paper, was created in the 1960s. It had an estimated six times as much active ingredient, known as Protective Antigen or PA, as the vaccine used by Brachman.⁷⁵ Army studies done by Bruce Ivins before 1988 revealed that there was an enormous degree of variability between vaccine lots, with some lots having 40 times as much active ingredient (PA) as other lots.⁷⁶

Though this vaccine too was developed (and patented) by the army, the Defense Department contracted with the Michigan Department of Public Health (MDPH) in the late 1960s to manufacture and then license the new vaccine. The license was granted in November 1970 by the then-licensing authority for vaccines, the National Institute of Health's Division of Biologics Standards. The customer for anthrax vaccine was the DoD, which used it to protect anthrax researchers in the army's biodefense program, as well as selected troops who might be exposed to anthrax in the field. (The army's offensive bioweapons program ended in the early 1970s with US ratification of the Biological Weapons Convention, which came into force in 1975.)

The Michigan Department of Public Health continued to make improvements to the anthrax vaccine. Substantial changes, especially in the fermenters and filters, were made

⁷³ GAO-02-181T Anthrax Vaccine: Changes to the Manufacturing Process, See: <http://www.gao.gov/new.items/d02181t.pdf>.

⁷⁴ Huxsoll DL, Patrick WC 3rd, Parrott CD. Veterinary services in biological disasters. *J Am Vet Med Assoc.* 1987 Mar 15;190(6):714-22.

⁷⁵ Ivins BE, Fellows PF and Nelson GO. Efficacy of a standard human anthrax vaccine against *Bacillus anthracis* spore challenge in guinea pigs. *Vaccine* 1994; 12:872.

⁷⁶ Ivins BE and Welkos SE. Recent advances in the development of an improved, human anthrax vaccine. *Eur J Epidemiol* 1988;4:12.

in the early 1990s. Perhaps because MDPH did not market the vaccine commercially, the manufacturer did not seek FDA approval for some changes in the vaccine's manufacturing process.⁷⁷ This contravened existing FDA regulations.⁷⁸

Unpublished army studies of the 1990's vaccine then revealed that the newer vaccine lots had up to *one hundred times* the content of Protective Antigen as the earlier MDPH lots.⁷⁹

Since the mandatory Anthrax Vaccine Immunization Program began in 1998, all vaccine used to immunize troops has come from these later, highly concentrated lots. Thus, although the original MDPH vaccine was said to have only six times as much PA as the earlier DoD vaccine, later versions of AVA (administered to 1.3 million people over the past seven years) may have had several hundred times as much PA as the original DoD vaccine.

Consequently, comparing the 1950's DoD vaccine to the 1960's-1970's MDPH vaccine may be of historical interest, but it tells us very little that is relevant to the currently available and much stronger version of AVA, now renamed Biothrax.

If one compares the safety data for the DoD vaccine and the current form of AVA (Biothrax), as was discussed earlier, they are clearly very different. The current AVA vaccine has 25 to 175 times the rate of systemic reactions as the DoD vaccine was reported to induce, based on a comparison of the current package insert's adverse event rates with the Brachman trial data. Furthermore, the current AVA is associated with a number of serious adverse events, listed in the package insert and in the FDA's own recent submission to the anthrax vaccine docket⁸⁰ that were not reported for the earlier vaccine.

The claim that both vaccines stimulate seroconversion and similar peak antibody responses is questionable, since there existed no ELISA assay to quantify anti-PA antibody responses when the DoD vaccine was in use, and the older Ouchterlony test, in use at the time, provides no precise quantification of antibody. Furthermore, antibody levels cannot be used as a surrogate marker for efficacy, as acknowledged by all experts in the field.^{81 82 83 84 85} Because they do not predict survival to anthrax exposure,

⁷⁷ GAO-02-181T Anthrax Vaccine: Changes to the Manufacturing Process, See: <http://www.gao.gov/new.items/d02181t.pdf>.

⁷⁸ *ibid* and Letter from Clifford JCM (FDA) to Joellenbeck L (IOM). March 27, 2001.

⁷⁹ *ibid.* and Pitt article cited in GAO report

⁸⁰ Ball R et al. FDA VAERS submission to the anthrax vaccine docket: Adverse Events Following Anthrax Vaccine Reported to the Vaccine Adverse Event Reporting System 12/22/2004.

<http://www.fda.gov/ohrms/dockets/dockets/80n0208/80n-0208-cr00001-02-vol1128.pdf>

⁸¹ Turnbull PCB, Quinn CP, Hewson R et al. Protection conferred by microbially-supplemented UK and purified PA vaccines. *Salisbury Medical Journal special supplement* January 1990; (68): 89-91.

antibody levels and/or seroconversion do not provide acceptable evidence of vaccine efficacy or similarity. Finally, since seroconversion is defined as “the development of antibodies to a particular antigen”⁸⁶ FDA’s use of the term in the proposed rule (at page 78287) is redundant.

The FDA proposed rule then provides a specious argument to claim that the current version of AVA is comparable to the original DOD anthrax vaccine of the 1950s, stating:

“FDA has reviewed the historical development of AVA and concluded that DoD’s continuous involvement with, and intimate knowledge of, the formulation and manufacturing processes of all of these versions of the anthrax vaccine provide a foundation for a determination that the MDPH anthrax vaccine is comparable to the original DoD vaccine.”

Here is an analogy that demonstrates the flaws in FDA’s logic: Dr. Maurice Hilleman, in charge of vaccine development at Merck for decades, was continuously involved and had intimate knowledge of the formulation and manufacturing processes of Merck’s different measles vaccines.⁸⁷ Merck’s first measles vaccine, a killed virus vaccine, showed no evidence of protective efficacy. A second vaccine used the same virus in a live product. It had excessive side effects, but these were reduced if it was given with a dose of gamma globulin. After performing quality control studies on the vaccine, it was found that the chick embryo cell cultures in which the measles virus was grown contained avian leucosis (chicken leukemia) virus, a potential human carcinogen. A third vaccine, *Rubeovax*, was made by growing the same virus in uncontaminated cells. A fourth vaccine, *Attenuvax*, passaged the virus forty additional times, reducing reactogenicity. The fourth vaccine did not require gamma globulin.

The last two vaccines were licensed, but each had to go through separate licensing procedures, because they were acknowledged to be different. Even though *Attenuvax* was developed from *Rubeovax*, and used the same initial virus, it was licensed separately. Although Dr. Hilleman and Merck were intimately and continuously involved with and supervised development of all these vaccines, that did not make them comparable to each

⁸² Welkos SL and Friedlander AM. Comparative safety and efficacy against *Bacillus anthracis* of protective antigen and live vaccines in mice. *Microbial Pathogenesis* 1988; 5: 127-139.

⁸³ Leppla SH. Anthrax Toxin. *Methods Enzymology* 1988; 165.

⁸⁴ Hambleton P, Carman JA and Melling J. Anthrax: The disease in relation to vaccines. *Vaccine* 1984; 2: 125-132.

⁸⁵ Ivins BE, Ezzell JW, Jemski J et al. Immunization studies with attenuated strains of *Bacillus anthracis*. *Infect Immunity* 1986; 52: 454-458.

⁸⁶ See glossary of terms at NIH website:

<http://www.niaid.nih.gov/factsheets/GLOSSARY.htm>

⁸⁷ Galambos L and Sewell JE. *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895-1995*. Cambridge University Press 1995, Cambridge UK. Pages 89-99.

other.

Further, Dr. Hilleman was also intimately and continuously involved in developing vaccines for rubella, mumps, and animal diseases. That did not make all these different vaccines comparable to each other, either. Nor did it allow these different vaccines to be licensed without separate clinical trials for each. .

So, beyond FDA's rhetorical suggestion of "comparability" based on the army's "continuous involvement," please provide scientifically valid evidence of comparability between the pre-licensure prototype anthrax vaccines and the current AVA, as modified since 1991.

23. Potency data have historically been unreliable.

FDA's proposed rule states,

"The comparability of the MDPH anthrax vaccine to the DoD vaccine [the vaccine tested by Brachman] has been verified through potency data that demonstrate the ability of all three versions of the vaccine to protect guinea pigs and rabbits against challenge with virulent B. anthracis."

The historical record reveals that the potency test for anthrax vaccine has gone through a number of changes since licensure, because it is unreliable and irreproducible. The small animals receive human-size vaccine doses. Finally, the manufacturer is allowed to repeat the test if the lot fails.

Twenty-two vaccine lots were manufactured between 1990 and 1997, were initially released by FDA, and were to have been used in the Anthrax Vaccine Immunization Program. The manufacturer had reported satisfactory potency results for each lot. Seventeen of the twenty-two were later discovered by FDA or through DoD's so-called "supplemental testing"⁸⁸ beginning in 1998 to have failed potency testing. (These

⁸⁸ "Supplemental testing" is an extra-regulatory procedure implemented by DoD after FDA inspected the manufacturer in February 1998 and concluded: "the anthrax vaccine manufacturing process is not validated." The same manufacturer (MBPI.BioPort) that was in violation of statutory cGMP standards performed all supplemental testing; it was simply overseen by a DoD contractor. The Government Accountability Office (GAO) questioned the validity of DoD's supplemental testing in an April 1999 report to Congress, yet FDA allowed the "supplemental testing" to continue as if it were a valid test of vaccine safety and efficacy. See:

GAO, T-NSIAD-99-148, "Medical Readiness: Safety and Efficacy of the Anthrax Vaccine", April 29, 1999. <http://www.gao.gov/archive/1999/ns99148t.pdf>

"Finally, quality cannot be guaranteed from final tests on random samples but only from a combination of in-process tests, end-product tests, and strict controls of the entire manufacturing process."

included lots 009, 010, 011, 012, 013, 018, 021, 022, 023, 024, 025, 028, 029, 032, 035, 037 and 039.)

A 1991 DoD information paper on the potency test made the following comments:

- *“There have been historical problems with this potency test.”*
- *“If a lot of vaccine “fails” the potency test, it is generally not a failure of the vaccine.”*
- *“Continue to work with FDA to evaluate possibility of another reliable test, such as the ELISA test for protective antigen content in the vaccine.”⁸⁹*

Thus FDA is using potency data that it knows are unreliable to assert the comparability of two different anthrax vaccines. Even if the potency data were reliable, this would only establish comparable animal efficacy for the two vaccines, and fail to establish human efficacy, human safety and the comparability of the vaccines for humans.

Do other data indicate that the three vaccines provide comparable protection to guinea pigs and rabbits against anthrax challenge? We really do not know, as there are no data in which animals vaccinated with the different vaccines were exposed to the same anthrax challenge strains and same inoculum sizes. Furthermore, old vaccine is no longer available so comparisons can no longer be performed. Even if these data were available, they would only provide information on animal protection, not human protection. Therefore, they could only be used to support vaccine licensure using the “animal efficacy rule.”

When FDA issued a biologics license amendment for BioPort’s anthrax vaccine in January 2002, how did it solve the problem of the potency test (and several other lot release tests) having a known, high level of unreliability?

24. Can a proper dose be calculated?

Paracelsus made an important point 500 years ago:

“All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.”

The amount of active ingredient in anthrax vaccine has been increased several times by changes in manufacture. Lots made today can be hundreds of times stronger than the original DOD vaccine used in the only human efficacy trial of a killed anthrax vaccine. Did the modifications in manufacturing procedures turn AVA from a remedy to a poison?

How have FDA and the manufacturer calculated the proper dose for each AVA

⁸⁹ Johnson-Winegar A. Information Paper. Subject: Guinea Pig Potency Testing for Anthrax Vaccine. SGRD-PLA. 7 Jan 1991.

inoculation when there exist no human efficacy tests, the potency test is unreliable and inapplicable to humans, and antibody titres and other immune tests fail as surrogate markers of protection from death or disease?

Studies that have injected human-sized volumes of vaccine into rabbits, mice and guinea pigs do nothing to reveal the appropriate human dose.

Significantly, both the Army's IND #6847 submitted to FDA on September 20, 1996, and the current CDC IND #10031 submitted to FDA on August 15, 2001, have sought a means of dose reduction as well as an alternate means of administration. If the Army and CDC cannot validate a different dose schedule after eight years, using modern testing protocols, then how can the FDA consider the original dosing schedule valid when it was little more than an educated guess?

If neither the Army, nor CDC, can scientifically ascertain an appropriate dose of anthrax vaccine, and FDA has previously ignored multiple manufacturing changes that have altered the strength of the product since licensure, how can FDA now provide licensed dosage instructions for use of the product?

Please explain how FDA has validated the current dose and inoculation schedule.

25. Variability in strength of product should preclude license

Two important problems relating to vaccine manufacture must be demonstrated to be resolved before any license can be approved for AVA.

First, the marked variability between different vaccine lots should not be acceptable. FDA is supposed to insure consistency of biologic products. FDA's recent report on manufacturing cGMPs notes that reducing product variability is a key step in quality improvement.⁹⁰ AVA has had an acknowledged forty-fold difference in the concentration of PA between lots in 1988. If FDA claims that this variability has been resolved, has an amendment authorizing changes in vaccine production processes that resolved this problem been submitted to FDA and approved?

Second, the one hundred-fold increase in levels of Protective Antigen, the main immunizing ingredient, occurred due to changes in vaccine manufacture since 1990. How has FDA ruled out this tremendous increase in vaccine concentration as the cause of the high levels of adverse reactions now being reported?

Please describe how FDA has demonstrated that current dosage levels, which are extraordinarily higher than earlier levels, are not the cause of the current vaccine's high rate of serious adverse effects.

⁹⁰ FDA. Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach. Final Report, Fall 2004. http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm#

As FDA has noted, “a particularly important question is whether the product to be licensed is the same as or comparable to the product used in the Phase 3 studies for safety and efficacy. If there have been significant manufacturing changes, ‘bridging’ data may be required.”⁹¹ We have shown that the Brachman and CDC studies used much different and weaker versions of AVA than what is now being manufactured.

What “bridging studies” has FDA used to fulfill this requirement in order to enable licensure of the current AVA?

26. How can the VAERS data be used to determine links between vaccination and disease?

In a December 22, 2004 FDA VAERS summary submitted as a comment to the AVA docket, the agency asserts that the VAERS data support the long-term safety of anthrax vaccine.⁹² This is surprising, since FDA generally argues that VAERS data, for which the reporting rates are generally unknown, are only good for identifying “signals” that would then justify a focused study using cases and controls to determine whether or not there is a vaccine safety problem.

In fact, FDA’s submission to the anthrax vaccine docket on the VAERS data makes this exact point.⁹³ Said another way, “reports to VAERS are essentially non-controlled clinical case reports or case series, useful for generating hypotheses but not for testing them.”⁹⁴

FDA has listed⁹⁵ four criteria by which an adverse event can be linked causally to a vaccine.⁹⁶ These include:

- a) the event conforms to a specific clinical syndrome whose association with vaccinations has strong biological plausibility,

⁹¹ Anthony BF and Sutton A. Ibid.

⁹² FDA submission can be found at:

<http://www.fda.gov/ohrms/dockets/dockets/80n0208/80n-0208-cr00001-02-vol1128.pdf>

⁹³ Ibid.

⁹⁴ Chen RT, Rastogi SC, Mullen JR et al. The VaccineAdverse Event Reporting System (VAERS). *Vaccine* 1994; 12: 542-60.

⁹⁵ Ellenberg S and Chen R. The complicated task of monitoring vaccine safety. *Public Health Reports* 1997; 112: 10-20.

⁹⁶ See also Chen RT, Lane JM, Commentary, *Lancet*. 2003 Oct 25;362(9393):1345-6. CDC's Immunization Safety Branch, National Immunization Program has more recently suggested a more rigorous and more inclusive set of criteria, which include:
1) strength of association; 2) consistency of reporting of the event; 3) the adverse reaction appears to be relatively specific; 4) a temporal relation between vaccination and the adverse event; 5) there is biological coherence; 6) there is biological plausibility and analogy with previous findings.

- b) a laboratory result confirms the association,
- c) the event recurs on re-administration of the vaccine, or
- d) a controlled clinical trial or carefully designed epidemiologic study shows greater risk of adverse events among vaccinated than control groups.

However, FDA acknowledges that “few of the adverse events reported to VAERS meet any of the first three criteria, and clinical trials are almost always too small to provide useful information on serious rare adverse events.”⁹⁷ FDA further admits that “most of these [serious reactions] tend to be of a type known to occur in the absence of vaccines as well, so in an individual case it is almost never possible to definitively assess the role of the vaccine”⁹⁸ and “the greatest limitation of VAERS, however, is its general inability to determine whether a vaccine actually caused the reported adverse event.”⁹⁹

Thus it is almost impossible to meet the FDA’s causality criteria to demonstrate that a vaccine caused a specific reaction. The cards are stacked against the injured parties.

The CDC’s National Immunization Program (which co-administers the VAERS system) acknowledges serious deficiencies with VAERS:¹⁰⁰

- *Reporting of adverse events appears to depend on a number of factors, such as clinical seriousness, temporal proximity to vaccination, and health care workers’ awareness of and obligation to report particular adverse events.*
- *Outcomes with delayed onset after vaccination or outcomes not generally recognized to be associated with vaccination often have significantly lower reporting sensitivities.*
- *Many adverse events are poorly defined clinical syndromes. Clinical information reported is often difficult to categorize and encode.*
- *Less than 1% of cases of thrombocytopenia were reported following MMR vaccination, and less than 1% of cases of hytonic-hyporesponsive episodes were reported following DPT vaccination.*

Another group of CDC and FDA authors noted that “the sensitivity of VAERS is influenced by the likelihood that an adverse event is both suspected as being associated

⁹⁷ Ellenberg S, Ibid.

⁹⁸ Ellenberg S, Ibid.

⁹⁹ Ellenberg S, Ibid.

¹⁰⁰ Rosenthal S and Chen R. The reporting sensitivities of two passive surveillance systems for vaccine adverse effects. *Am J Pub Hlth* 1995; 85: 1706-9.

with vaccine receipt and reported to VAERS.”¹⁰¹ What this means is that until reporting entities discover that the adverse event may be due to the vaccine, the likelihood that the reaction will be reported to VAERS is extremely low. This is why vaccine labels should include all major reported events, in order to stimulate additional reporting from which causality signals can be derived and studied.

For all these reason, the VAERS reports should be only one starting point from which to gather impressions about potential relationships between diseases and vaccines. Then, targeted surveillance of large vaccinated and comparison unvaccinated groups by independent scientists is essential to adequately assess serious adverse effects of vaccination. The generation of hypotheses from the VAERS data, and epidemiologic testing of these hypotheses is critical to finally determine which adverse events are in fact causally related to vaccination.¹⁰² But FDA has not performed any such targeted studies for anthrax vaccine nor required the manufacturer to do so. Is this a case of avoiding the collection of necessary data because FDA knows what it does not want to find?

There are actually many signals one can extract from the anthrax VAERS data. Two published studies of the anthrax VAERS reports have found that joint¹⁰³ and gastrointestinal disorders¹⁰⁴ are reported more commonly following anthrax vaccine than following other vaccines. There are over five hundreds reports of fatigue (coded as asthenia) and neurological problems in the VAERS database. The DMSS database and even the seriously flawed (Strom) IOM report of 2002 revealed evidence of many illnesses that occur more commonly after anthrax vaccinations. The FDA-approved vaccine label lists a number of serious conditions that have been reported following anthrax vaccinations.

Please explain how anthrax vaccine can be licensed as a Category I biologic when FDA has failed to direct the manufacturer, BioPort, and the de facto manufacturer, DoD, to conduct studies of sentinel events reflected in the VAERS data, especially when they relate to conditions already described in the FDA-approved package insert.

27. Military vaccine healthcare centers (VHCs) were established to treat anthrax vaccine-associated illnesses and have a wealth of clinical experience with the adverse reactions.

The Vaccine Healthcare Center Network, four clinics established by DoD at the behest of Congress to care for servicemembers with vaccine-associated illnesses, have performed

¹⁰¹ Singleton JA, Lloyd JC, Mootrey GT et al. An overview of the vaccine adverse event reporting system (VAERS) as a surveillance system. *Vaccine* 1999; 17: 2908-2917.

¹⁰² *Ibid.*

¹⁰³ Geier DA, Geier MR. Anthrax vaccination and joint related adverse reactions in light of biological warfare scenarios. *Clin Exp Rheumatol.* 2002 Mar-Apr;20(2):217-20

¹⁰⁴ Geier MR, Geier DA. Gastrointestinal adverse reactions following anthrax vaccination: an analysis of the Vaccine Adverse Events Reporting System (VAERS) database. *Hepatology.* 2004 May-Jun;51(57):762-7

detailed case evaluations on over 1,000 patients with anthrax vaccine-associated disorders since being established in 2001. They have made presentations,¹⁰⁵ developed evaluation and treatment algorithms,¹⁰⁶ and have more clinical experience than any other institution in caring for those affected by anthrax vaccine.

Why has FDA not used the vast clinical experience of the VHCs, especially the oldest VHC, located at Walter Reed Army Medical Center, as an important data source in its licensing recommendation in the proposed rule?

28. Is impaired cognition/memory loss an anthrax vaccine adverse event?

Three studies have now shown that although US and UK Gulf War I veterans are less likely to die from disease than the general population (believed to be due to the “healthy warrior” effect), they are significantly more likely to die from accidents, especially motor vehicle accidents.¹⁰⁷ In the UK, nearly all Gulf War I soldiers received at least one dose of anthrax vaccine; it is uncertain what percentage of US soldiers did. For women, the association with accidental death is stronger than for men. Women also have approximately twice the rate of systemic adverse reactions to anthrax vaccination as men.

It is noted that in the FDA’s report of anthrax VAERS reports submitted to the anthrax vaccine docket, 347 of the adverse event reports were designated as serious. In these 347 serious reports, a total of 430 neurologic adverse events have been reported. Unfortunately, the docket submission does not go into more detail about what the adverse reactions were. However, an earlier review of the first 1,600 anthrax vaccine VAERS reports performed by Meryl Nass, M.D. and reporter Thomas D. Williams of the Hartford Courant noted that 10% met the CDC criteria for Gulf War Syndrome (GWS). One of the three CDC criteria for GWS is cognitive or emotional disorder. Because many of the anthrax VAERS reports meet the CDC’s definition of GWS,¹⁰⁸ FDA included this definition as a reported adverse reaction to anthrax vaccine in the vaccine’s 2002 label. Yet FDA omitted mention of the fact that the syndrome definition it provided was the definition of Gulf War Syndrome.

Does FDA plan to correct this omission in a revised package insert? Having acknowledged that anthrax vaccine is linked to Gulf War syndrome, why has FDA

¹⁰⁵ Martin BL, Nelson MR, Labutta R et al. Anthrax vaccine temporally associated systemic adverse events referred to a tertiary medical center. *J Allergy Clin Immunol* 2002; 109: S78. Poster presented at 58th annual meeting of the American Academy of Allergy Asthma and Immunology, March 1-6, 2002.

¹⁰⁶ www.vhcinfo.org/downloads/cpguidelines_tables.pdf

¹⁰⁷ Kang HK, Bullman TA, Macfarlane GJ et al. Mortality among US and UK veterans of the Persian Gulf War: a review. *Occup Environmental Med* 2002; 59: 794-799. <http://oem.bmjournals.com/cgi/content/full/59/12/794>

¹⁰⁸ The CDC paper that defines Gulf War Syndrome: Fukuda K, Nisenbaum R, Stewart G et al. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *JAMA* 1998; 280: 981-8.

ignored all the Gulf War Illness literature in its proposed rule?

Because increased motor vehicle deaths could be the consequence of an increased rate of cognitive problems in veterans, and because cognitive problems following anthrax vaccine are frequently reported to VAERS and to the Vaccine Healthcare Centers, a study that evaluated neuropsychological function in vaccinees and unvaccinated controls would be very useful.

Has FDA performed or called for the manufacturer(s), BioPort and DoD, to carry out such a study?

29. How does the reporting rate for reactions from anthrax vaccine compare to the rates for other vaccines?

The Defense Department formally limited reporting of anthrax vaccine reactions to the Vaccine Adverse Event Reporting System (VAERS) during 1998 and at least the first half of 1999 with the following instruction to health care providers:

*“Report all adverse vaccine reactions resulting in hospitalizations or time lost from duty (more than 21 hours), using the Health and Human Services Vaccine Adverse Events form. Other reactions **will not be reported** unless contamination of lots is suspected.”¹⁰⁹ (emphasis added)*

Military medical providers have minimized or denied anthrax vaccine adverse reactions, according to GAO testimony to Congress¹¹⁰ and many reports forwarded to our organizations by servicemembers. In fact, we continue to hear of military medical providers refusing to file VAERS reports for military servicemembers who report post-vaccination symptoms or illnesses listed as possible vaccine sequelae in the FDA-approved package insert.

Without an understanding of how military reporting rates for anthrax vaccine compare to military reporting rates for other vaccines for which such instructions were not issued, and compare to civilian reporting rates, FDA will have difficulty assessing the significance of those military adverse event reports it has received.

Please state how FDA has investigated the underreporting of reporting of anthrax vaccine reactions to VAERS by military medical practitioners?

30. Published case reports of anthrax vaccination adverse events support systemic autoimmune risks

There exist in the world’s medical literature a number of other studies, independent

¹⁰⁹ SECNAVINST 6230.4. APRIL 29, 1998. ANNEX C TO ENCLOSURE (1). PAGE C-5.

¹¹⁰ <http://www.gao.gov/cgi-bin/getrpt?GAO-02-445>

reviews of the anthrax VAERS reports and individual case reports that are relevant to consideration of the safety of anthrax vaccine. The case reports have linked aplastic anemia,¹¹¹ Stevens-Johnson Syndrome,¹¹² chorioretinopathy,¹¹³ recurrent urticaria and erythema multiforme,¹¹⁴ pemphigus vulgaris,¹¹⁵ lymphocytic vasculitis,¹¹⁶ hypersensitivity pneumonitis,¹¹⁷¹¹⁸ gastroparesis,¹¹⁹ optic neuritis,¹²⁰ and delayed anaphylaxis to anthrax vaccine.¹²¹

While individually of no statistical significance, FDA should take into account that all of these published, peer-reviewed reports documented autoimmune disorders. Given these reports, and the signals from the DMSS database of several autoimmune disorders that may occur more commonly in those who received anthrax vaccine, FDA should obtain and review valid longitudinal data to determine if autoimmune disorders do occur more commonly following anthrax vaccination.

Does FDA plan to investigate systemic autoimmune risks from AVA prior to making a licensure decision? If not, please explain why.

31. Studies of anthrax vaccine adverse events from other countries

Evidence from other countries indicates problems with anthrax vaccine. Studies of Gulf

¹¹¹ Shah C, Lemke S, Singh V, Gentile T. Case reports of aplastic anemia after vaccine administration. *Am J Hematol.* 2004 Oct; 77(2):204

¹¹² Chopra A, Drage LA, Hanson EM, Touchet NL. Stevens-Johnson syndrome after immunization with smallpox, anthrax, and tetanus vaccines. *Mayo Clin Proc.* 2004 Sep;79(9):1193-6.

¹¹³ Foster BS, Agahigian DD. Central serous chorioretinopathy associated with anthrax vaccination. *Retina.* 2004 Aug;24(4):624-5.

¹¹⁴ Gilson RT, Schissel DJ. Recurrent, localized urticaria and erythema multiforme: a review and management of cutaneous anthrax vaccine-related events. *Cutis.* 2004 May; 73 (5): 319-25.

¹¹⁵ Muellenhoff M, Cukrowski T, Morgan M, Dorton D. Oral pemphigus vulgaris after anthrax vaccine administration: association or coincidence? *J Am Acad Dermatol.* 2004 Jan;50(1):136-9.

¹¹⁶ Muniz AE. Lymphocytic vasculitis associated with the anthrax vaccine: case report and review of anthrax vaccination. *J Emerg Med.* 2003 Oct;25(3):271-6.

¹¹⁷ Timmer SJ, Amundson DE, Malone JD. Hypersensitivity pneumonitis following anthrax vaccination. *Chest.* 2002 Aug;122(2):741-5.

¹¹⁸ Schuyler M. Link between anthrax immunization and hypersensitivity pneumonitis? *Chest.* 2003 May;123(5):1769; Author reply 1769-70.

¹¹⁹ Pande H, Lacy BE, Crowell MD. Inflammatory causes of gastroparesis: report of five cases. *Dig Dis Sci.* 2002 Dec;47(12):2664-8.

¹²⁰ Kerrison JB, Lounsbury D, Thirkill CE, Lane RG, Schatz MP, Engler RM. Optic neuritis after anthrax vaccination. *Ophthalmology.* 2002 Jan;109(1):99-104.

¹²¹ Swanson-Biearman B, Krenzlok EP. Delayed life-threatening reaction to anthrax vaccine. *J Toxicol Clin Toxicol.* 2001;39(1):81-4.

War veterans from Canada,¹²² the UK^{123 124 125} and Australia¹²⁶ suggest that anthrax vaccine is a contributor to Gulf War Syndrome. French veterans were not vaccinated, and have a much lower rate of Gulf War Syndrome than US, UK and other vaccinated veterans of the first Gulf War. A suggestion was made that those few French veterans who developed Gulf War Syndrome might have been vaccinated with US and UK troops while serving in liaison positions,¹²⁷ but this issue has not been resolved.

Regarding the adverse effects of recent anthrax vaccinations in the United Kingdom, two small studies have been done of soldiers vaccinated before their recent Gulf deployment. The (voluntary) UK vaccine is given as a four dose series over one year, with yearly boosters; the (mandatory) US vaccine is given in six doses over 18 months, with yearly boosters.

In the first paper by Hayes and World, 129 soldiers working in a military field hospital were offered vaccine, and 76% (98 soldiers) accepted and began the series.¹²⁸ Initially, 63% had adverse reactions, and the authors noted, “forty-five percent of these caused incapacity.” Approximately 22% of reactors had arm pain that prevented lifting or driving for 48 hours. Twenty-one percent of reactions were designated severe. Only 27 of the 98 soldiers who began the vaccinations completed the four dose series. The authors concluded, “Although the old vaccine is considered safe, the number of adverse reactions and incapacity reported by a military medical unit was unexpected.”

The second paper looked at vaccine acceptance and adverse reactions in personnel at five Royal Air Force (RAF) bases.¹²⁹ According to the study, “Those completing the [vaccine] course as a percentage of those starting it varied from 22% at base 2 to 3.7% at base 4.” Yet these authors reported that only 11% of vaccinees had side effects, and that these were mild.

¹²² Goss-Gilroy. Study of Canadian Gulf War Veterans. Never published except on the DND website. http://www.dnd.ca/menu/press/Reports/Health/health_study_eng_1.htm (could not be accessed March 15, 2004) This study linked chronic fatigue, a cardinal feature of Gulf War Syndrome, to receipt of anthrax and plague vaccines

¹²³ Unwin C et al. Health of UK servicemen who served in the Persian Gulf War. *The Lancet* 1999; 353:169-178.

¹²⁴ Hotopf M. Reanalysis of Gulf war vaccination data does not contradict findings. *BMJ*. 2000 Sep 23;321(7263):761-2

¹²⁵ See letters to the *BMJ* at <http://bmj.bmjournals.com/cgi/eletters/320/7246/1363#8241>

¹²⁶ Kelsall HL, Sim MR, Forbes AB, McKenzie DP, Glass DC, Ikin JF, Ittak P, Abramson MJ. Symptoms and medical conditions in Australian veterans of the 1991 Gulf War: relation to immunisations and other Gulf War exposures. *Occup Environ Med*. 2004 Dec; 61(12):1006-13.

¹²⁷ French to check liaison officers for Gulf Syndrome. *Reuters* (Paris) Sept. 14, 2000.

¹²⁸ Hayes SC and World MJ. Adverse reactions to anthrax immunisation in a military field hospital. *J R Army Med Corps*. 2000 Oct;146(3):191-5.

¹²⁹ Enstone JE, Wale MCJ, Nguyen-Van-Tam JS et al. Adverse medical events in British service personnel following anthrax vaccination. *Vaccine* 2003; 21:1348-54.

Neither set of authors was able to explain the remarkable dropoff in vaccine uptake. The UK Ministry of Defense supported both studies.

How does FDA account for this strong body of evidence from three other nations that anthrax vaccines a) are linked to chronic illness, including Gulf War Syndrome, and b) resulted in between 70 and 96 per cent of volunteer vaccinees at six UK bases stopping vaccinations before completing the primary four dose series?

32. FDA needs to craft a more accurate and complete label reflecting reported adverse events

In designing the revised label for anthrax vaccine in January 2002, FDA took note of a still-unpublished Navy study of women who had received anthrax vaccine during the first trimester of pregnancy,¹³⁰ and changed the pregnancy warning category for the vaccine from a 'C' to a 'D'.

FDA also took note of the much higher rate of reported adverse reactions than was stated in the old label, and changed these in the new label. FDA furthermore included a list of chronic illnesses that had been reported to develop after vaccination; and the new label mentioned six reported deaths. This showed that even in a period of crisis following the anthrax letter attacks FDA had concerns about the safety of the vaccine, and wished to provide meaningful adverse event information to medical practitioners and vaccine recipients while making the vaccine available. However, the adverse event information (and available data) fell far short of what is standard for the labels of other licensed vaccines.

More than three years have passed since that label was written, and an additional 700,000 Americans have received anthrax vaccinations since then. Yet FDA has to date made no label alterations reflecting this enhanced clinical experience with the vaccine.

Please explain FDA's plans to publish in the vaccine label the types and rates of adverse reactions reported to VAERS, identified by the DMSS database,¹³¹ and compiled by the military Vaccine Healthcare Centers¹³² and the Military Vaccine Education Center¹³³

¹³⁰ MMWR 127 vol 51 No. 6. "Notice to Readers: Status of US Department of Defense preliminary evaluation of the association of anthrax vaccination and congenital anomalies." <http://www.cdc.gov/mmwr/PDF/wk/mm5106.pdf>

¹³¹ Rubertone MV, Brundage JF. The Defense Medical Surveillance System and the Department of Defense serum repository: glimpses of the future of public health surveillance. Am J Public Health. 2002 Dec; 92(12):1900-4.

¹³² www.vhcinfor.org

¹³³ The Military Vaccine Education Center is a 501(c)3 non-profit organization that assists servicemembers who become ill following immunization with anthrax (and other) military vaccines. MVEC has compiled a searchable online database based on anecdotal reports from servicemembers and others who received anthrax vaccine.

since then?

33. Two recent expert committee reports suggest role of anthrax vaccine in Gulf War Syndrome

In the fall of 2004, both the U.S. Department of Veterans Affairs' Research Advisory Committee on Gulf War Veterans' Illnesses and the U.K. Independent Public Inquiry on Gulf War Illnesses issued reports on Gulf War Syndrome. Among the Research Advisory Committee recommendations are the following:

- *“That VA work with federal agencies involved in conducting vaccine trials that include administration of anthrax vaccine adsorbed to ensure these trials include follow-up assessment of study subjects a minimum of five years after inoculation. Such studies should utilize methods and instruments capable of capturing chronic symptoms and cognitive difficulties similar to those experienced by Gulf War veterans.*
- *That VA conduct a retrospective cohort study that compares chronic symptoms and diagnosed conditions experienced by veterans who received AVA as part of the military's mandatory anthrax vaccination program to those of a comparable group of veterans who did not receive this vaccine.”¹³⁴*

The UK report, when discussing the cause or causes of the illnesses, noted that:

“A third strong candidate must be the multiple vaccinations, especially the combination of anthrax and pertussis. This would be the best explanation for those few [who developed Gulf War Syndrome] who received the vaccines but were never deployed to the Gulf.”¹³⁵

How has FDA taken these expert panel reviews into account in its assessment of vaccine safety?

34. Pending House bill (HR 514) directs the Secretary of Veterans Affairs to carry out a research program to determine causal relationships between adverse health effects and anthrax vaccine:

The Secretary of Veterans Affairs shall— (1) carry out an ongoing assessment of the adverse health effects being reported by members and former members of the Armed Forces with respect to the smallpox and anthrax vaccines administered by

<http://www.milvacs.org/Sick/AdverseReactions.cfm>

¹³⁴ Research Advisory Committee on Gulf War Veterans Illness. Scientific Progress in Understanding Gulf War Veterans' Illnesses: Report and Recommendations. September 2004.

¹³⁵ Lord Lloyd of Berwick, Jones N and Davies M. Report: Independent Public Inquiry on Gulf War Illnesses.

the Department of Defense; (2) carry out a research program to determine causal relationships (if any) between such effects and those vaccines; and (3) prepare an estimate of the future cost to the Department of Veterans Affairs to treat those adverse health effects, if determined to be service-connected¹³⁶.

Why must the Congress write legislation to mandate research that FDA should have reviewed prior to issuing a license for anthrax vaccine? Why hasn't FDA required such research to be performed before considering licensure?

35. Why have there been no reliable safety trials despite mass vaccine use?

The FDA's expert panel on bacterial vaccines met during the 1970s and the FDA responded to the panel recommendations in its proposed final rule in 1985. At that time only several thousand people had received AVA, and nearly all of these were workers at goat hair mills or Fort Detrick. The mass use of the vaccine did not begin until 1990, when a reported, but undocumented, 150,000 troops received the vaccine for deployment in the first Gulf War. Between 1991 and 1998 (after the Gulf War but before the Anthrax Vaccine Immunization Program (AVIP) began) over 475,000 doses were administered by DoD, according to FDA's report to the Institute of Medicine.¹³⁷ Since 1998, 1,300,000 military service members and military contractors have received anthrax vaccine through the Anthrax Vaccine Immunization Program (AVIP).

FDA and its expert panel had little evidence from clinical use of the vaccine to go on when they made their recommendations twenty years ago. The panel specified that this lack of evidence was acceptable given "prevailing circumstances of use" in that anthrax was a limited use vaccine.

Since then at least 1,500,000 Americans have received anthrax vaccine, but the quality of the data relating to its human use is only marginally better than in 1985. Anthrax is no longer a "limited use" vaccine, and FDA can no longer be excused for accepting marginal evidence to support wide use of this vaccine, particularly in a situation where, if licensed for inhalation, the vaccine will again be part of a mandatory program of mass inoculations. The mandatory use of anthrax vaccine by DoD takes away medical decision-making from military medical providers, who, from a practical standpoint, have not even been allowed to give medical waivers for this vaccine. Thus the "learned intermediary" has been prevented from making a risk/benefit judgment regarding vaccination for his/her patient.

Therefore, the licensure of AVA is a situation in which *extra* evidence of safety and efficacy should be required, not less than has been required for other licensed vaccines

¹³⁶ <http://www.theorator.com/bills109/hr514.html>

¹³⁷ Clifford J., Presentation to the Institute of Medicine Committee on anthrax vaccine safety and efficacy, October 3, 2000. Dr. Clifford's briefing slide stated: "1991-98: >1,200,000 doses, mostly DOD (>475,000 doses administered by DOD)."

used in civilians.¹³⁸

Please explain why, despite the hundred-fold increase in AVA use since the original licensure, FDA has not required independent clinical trial evidence of safety, since these data were not available in 1970?

36. DoD appears to have suppressed relevant reports on AVA safety

Two important sources of information on AVA safety appear to have been suppressed.

First, the U.S. Navy study of AVA administration in the first trimester of pregnancy, performed by Cdr. Megan Ryan, M.D., has never been published. Preliminary findings from this study were released in late 2001. FDA changed the label's pregnancy warning from a C to a D in January 2002, apparently based on this extensive study.

The preliminary report of this study, published in the MMWR in December 2001, cannot be found in the National Library of Medicine online database, and has been removed from the CDC's MMWR website. However, a follow-on MMWR article of February 15, 2002 informed readers that because of "important limitations in computerized medical records" used in this study, that original paper medical records were being sought, and the "evaluation will require several months."¹³⁹ It has never appeared.

Second, a completed 1999 RAND study of anthrax vaccine and Gulf War Syndrome, sponsored by the Defense Department and written by Dr. Beatrice Golomb, has never been released.¹⁴⁰

Has FDA investigated this suppressed information?

37. Anthrax vaccines (and other untested drugs for bioterrorism) are being readied for U.S. civilians

¹³⁸ Paytash CA. The learned intermediary doctrine and patient package inserts: a balanced approach to preventing drug-related injury. *Stanford Law Rev.* 1999 May;51(5):1343-71.

¹³⁹ MMWR 127 vol 51 No. 6. "Notice to Readers: Status of US Department of Defense preliminary evaluation of the association of anthrax vaccination and congenital anomalies." <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5106a5.htm>

¹⁴⁰ Beatrice Alexandra Golomb, "Volume 3: Immunizations", "A Review of the Scientific Literature as It Pertains to Gulf War Illnesses (Series)", RAND.

<http://www.rand.org/multi/gulfwar/publications.html>

In 1999, Dr. Beatrice A. Golomb, MD, PhD, a RAND contract researcher, completed a report on immunizations given during the Gulf War. That report, as is evident from the RAND study website, has never been published because DoD has not allowed it to be released.

In 2004 the Department of Health and Human Services contracted to purchase and stockpile 80 million doses of anthrax vaccines for American civilians, to include AVA and a yet-to-be fully tested recombinant anthrax vaccine, termed rPA102.¹⁴¹

The American taxpayer is therefore investing approximately one billion dollars to stockpile unproven and possibly dangerous anthrax vaccines for civilian use. The American taxpayer may pay again when the vaccines are administered in response to a real or manufactured anthrax “threat,” and many citizens may subsequently develop chronic illnesses.

The director and deputy director of CBER’s Office of Biostatistics and Epidemiology note that “benefit to risk considerations are needed to support informed public health policy decisions and personal choices regarding vaccinations.”¹⁴² However, personal choice may be a thing of the past for biodefense vaccines, since the 2004 adoption of the Project Bioshield Act (Public Law 108-276) and related legislation. Under an Emergency Use Authorization, untested and unlicensed vaccines and drugs can be used on civilians as well as military servicemembers. Without full disclosure of clinical trial data (that are proprietary and confidential and may not be sufficient to assess safety and efficacy in any event) citizens will be in no position to make an informed choice regarding use of these products.

Furthermore, the Model Emergency Health Powers Act¹⁴³ or similar legislation has been enacted in 33 states; it removes freedom of choice from citizens, who will not be allowed to refuse untested drugs and vaccines in a designated emergency.

This is especially worrisome because an emergency use authorization under PL 108-276 has already been issued for the use of anthrax vaccine by the military. Yet lawyers for the Defense Department admitted in court that the so-called “emergency” they are addressing has been extant for at least the past seven years, since the start of the force-wide anthrax vaccination program. The Bioshield legislation does not require a true emergency, but only the potential for an emergency, in order to invoke an emergency use authorization. Government lawyers have argued that the predicate facts supporting these ‘emergencies’ are “unreviewable by anyone.”¹⁴⁴

When will FDA perform its regulatory function of assuring that anthrax vaccines (and other bioterrorism drugs) are safe and effective prior to their use by millions of civilians?

38. Lessons from those exposed to anthrax in 2001

¹⁴¹ Kaufman Marc. U.S. awards anthrax vaccine deal: Under Project Bioshield, firm will make doses for stockpile. Washington Post; November 5, 2004: page A04.

¹⁴² Foulkes MA and Ellenberg SS. Vaccine safety and efficacy evaluation. *In* The Jordan Report: Accelerated development of vaccines 2002. Produced by DHHS and NIH’s NIAID. <http://www.niaid.nih.gov/dmid/vaccines/jordan20/>

¹⁴³ <http://www.publichealthlaw.net/Resources/Modellaws.htm>

¹⁴⁴ Doe v. Rumsfeld, court transcript, Feb 14, 2005 at p. 18-19.

At the time of the anthrax letter attacks in 2001, at least 10,000 people¹⁴⁵ who were thought to have been exposed to anthrax were given 60 days of antibiotics for post-exposure prophylaxis, before clinical disease developed. Though probably many in this group had minimal exposure to anthrax spores, it is known that others had high levels of exposure.

Approximately 44% of those receiving antibiotics stopped using them prior to sixty days.¹⁴⁶ None of the prophylactic antibiotic recipients developed an anthrax infection, demonstrating that even short courses of antibiotics were highly effective at preventing disease, and that at least in the case of the anthrax letters, vaccination was unnecessary as a component of post-exposure prophylaxis. The efficacy of this antibiotic therapy raises serious questions about whether the “emergency” asserted by the EUA is warranted to effect a resumption of anthrax vaccinations in the military.

Later, after 60 days of antibiotics, about two hundred of these 10,000 exposed but asymptomatic individuals chose to receive anthrax vaccine. CDC and NIH were reticent about recommending AVA for post-exposure prophylaxis because of the known safety risks from the anthrax vaccine, and the unknown efficacy. These risks were publicly acknowledged by Dr. Anthony Fauci,¹⁴⁷ director of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, but are now being ignored by FDA in their proposed rule.

Because no late cases of anthrax occurred, even in the unvaccinated group, there was no additional benefit conferred by vaccinations following the anthrax letter attacks.

¹⁴⁵ The 10,000 postal workers and Congressional staff who were offered antibiotics were chosen because of known workplace exposure. Yet tens of thousands more Americans were exposed to anthrax when they received mail that had been processed at contaminated postal centers in New Jersey, Connecticut, and the District of Columbia. There was no CDC recommendation for prophylactic antibiotics for this larger population of mail recipients. Two anthrax deaths were from the much larger universe of Americans exposed through the mail, and represent a very small mortality rate, however tragic.

¹⁴⁶ Shepard CW, et al. Antimicrobial postexposure prophylaxis for anthrax: adverse events and adherence. *Emerg Infect Dis*; 2002 Oct;8.

<http://www.cdc.gov/ncidod/EID/vol8no10/02-0349.htm>

¹⁴⁷ Dr. Anthony Fauci, NIH, PBS News Hour, Dec 19, 2001.

http://www.pbs.org/newshour/bb/health/july-dec01/fauci_12-19.html

Dr. Fauci: "...since there are toxicities associated with the vaccine, and importantly the vaccine has never been used in a context like this, that's the reason why you need informed consent and you need a decision on the part of the individual themselves....The number one potential risk is the risk associated with taking any vaccine -- namely toxic side effects."

Military doctrine also requires that vaccinated soldiers receive antibiotics following an exposure to anthrax, since vaccine efficacy cannot be assured. But since antibiotics have been completely effective, is there even a role for pre-exposure vaccination?

The CDC Advisory Committee on Immunization Practices (ACIP) has considered the risk-to-benefit equation for the anthrax vaccine license and concluded that the vaccine should only be given pre-exposure to those at risk for “repeated exposure” to anthrax, and only when a “quantifiable risk” can be established. Otherwise, the ACIP recommends post-exposure antimicrobial (antibiotic) prophylaxis and consideration of post-exposure immunization.

Please state why FDA, in failing to include a risk-to-benefit statement in its proposed rule, has ignored the ACIP recommendations and statements by the director of the National Institute of Allergy and Infectious Diseases and thereby effectively endorsed indiscriminate DoD use of the vaccine in the absence of a validated threat, or a quantifiable risk of exposure?

Conclusions

According to the newest FDA standards,¹⁴⁸

“The Agency must ensure that science-based policies and standards form the foundation upon which product quality is based. Because the American public is the ultimate customer of pharmaceutical manufacturing and because the public is often unable to judge the quality of a product, the goal of our regulatory system is to make sure that patients do not have to worry about the quality of their medicines.”

This submission to FDA simply asks one thing of the agency: use valid science to assure safety and efficacy before approving the anthrax vaccine license. Unfortunately, FDA has shown a bias toward ignoring the science in its vaccine regulatory decisions.¹⁴⁹

“Vaccines are held to the highest standards of safety because they are usually given to healthy individuals to prevent an infectious disease to which they might be exposed in the future rather than treat an established disease or condition.”¹⁵⁰

¹⁴⁸ Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach. Final Report, Fall 2004.

http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm#_Toc84065735

¹⁴⁹ FDA allowed millions of doses of Chiron’s flu vaccine to be shipped from the UK to the United States for the 2004-2005 flu season, despite known bacterial contamination. Americans’ use of this vaccine was only stopped when the British Medicines Control Agency stepped in and pulled the vaccine license, preventing local distribution. FDA knew of the contamination, which had been an ongoing problem at the vaccine plant, but decided to look the other way and hope for the best.

“In the past, FDA regulation was usually strengthened only after a major disaster occurred. Public authorities acted only after disasters to identify the causes of the problem, to look for new and improved quality control methodologies, and to revise regulation and norms.”¹⁵¹

FDA’s history of regulatory malfeasance with respect to anthrax vaccine, combined with the emergency use provision of the 2004 BioShield Act, create the scenario for an anthrax vaccine disaster that affects a much larger segment of the U.S. population, and not just the military.

As is abundantly demonstrated in this submission, the science base does not support licensure of the anthrax vaccine as a Category I biologic. We urge FDA to act responsibly and to enforce the statutory licensure requirements in its decision on the proposed rule.

Signed,

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¹⁵⁰ Ball LK, Ball R and Gellin BG. Developing Safe Vaccines. *In* New Generation Vaccines, 3d Edition. Ed. Levine MM et al. Marcel Dekker, New York. 2004.

¹⁵¹ Homma A. Regulation of vaccines: strengthening the science base by Julie Milstien. *J Pub Health Policy* 2004; 25: 190-196.