



REPLY TO
ATTENTION OF

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH VA 22041-3258

March 25, 2005



Executive Office

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

Reference: Docket Number 1980N-0208, Proposed Rule and Proposed Order:
Bacterial Vaccines and Toxoids

Ladies and Gentlemen:

On behalf of the United States Army, I commend the Food and Drug Administration (FDA) for proposing the text for the Final Rule & Final Order Involving Bacterial Vaccines and Toxoids, as published on December 29, 2004, in the *Federal Register*. The U.S. Army serves as the executive agent within the Department of Defense (DoD) for biodefense vaccines. As a result, Army physicians and scientists and I have followed the science underlying anthrax vaccination for many years.

This comment pertains to section IV of the Proposed Rule and Proposed Order: Anthrax Vaccine Adsorbed – Proposed Order. FDA determinations regarding anthrax vaccine adsorbed are needed without delay as part of the urgent national program of strengthening medical bioterrorism countermeasures in both military and homeland security contexts.

In the American Revolutionary War, many of our troops died of smallpox, measles, diphtheria, and other now-preventable diseases. The Continental Army lost the Battle of Quebec due to a smallpox epidemic. In the 1800s, our troops died regularly of tetanus, typhoid fever, measles, mumps, and yellow fever. In the Spanish-American War, typhoid fever claimed more American lives than bullets did. Pandemic influenza devastated our forces in World War I. Tetanus, smallpox, typhoid, yellow fever and other vaccines proved highly successful in World War II, Korea, Vietnam, and the Persian Gulf Wars, as well as today's Global War on Terrorism. The DoD recognizes the extraordinary value of immunization in keeping individual members of the Armed Forces healthy. Further, the historical record shows that prominent among the proud achievements of military medicine have been our meaningful contributions to the science of immunology. My letter today provides an overview of the understandings of military medicine relating to the proposed order, and follows the sequence and style of the discussion presented in the Proposed Order.

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IV. Anthrax Vaccine Adsorbed--Proposed Order

A. The Panel Recommendation that Anthrax Vaccine Adsorbed be Placed in Category I (Safe, Effective, and Not Misbranded)

The proposed order noted that in the 1979 report of the Panel on Review of Bacterial Vaccines and Toxoids, the Panel found that Anthrax Vaccine Adsorbed (AVA), manufactured by Michigan Department of Public Health (MDPH, now BioPort) was safe and effective for its intended use and recommended that the vaccine be placed in Category I. In the December 1985 proposal, FDA agreed with the Panel's recommendation. During the comment period for the December 1985 proposal, FDA received no comments opposing the placement of AVA into Category I.

The proposed order further noted that the Panel based its evaluation of the safety and efficacy of AVA on two studies: A well-controlled field study conducted in the 1950s, "the Brachman study" and an open-label safety study conducted by the National Center for Disease Control (CDC, now the Centers for Disease Control and Prevention) (50 FR 51002 at 51058). The Panel also considered surveillance data on the occurrence of anthrax disease in the United States in at-risk industrial settings as supportive of the effectiveness of the vaccine (50 FR 51002 at 51059). In its proposed determination that the data support the safety and efficacy of AVA, FDA has identified points of disagreement with statements in the Panel report. However, FDA concludes that the data do support the safety and efficacy of the vaccine and, thus, FDA continues to accept the Panel's recommendation and proposes to place AVA in Category I. As discussed further below, the scientific evidence unequivocally supports this proposed action.

The proposed order also reviewed recent litigation relating to FDA's previous determinations, including a 2002 citizens petition response, that AVA is safe and effective for prevention of anthrax disease independent of the route of exposure, and the final rule and final order published January 5, 2004 (69 FR 255) that, among other things, placed AVA in Category I and formalized in a final order the same FDA determination. When an October 2004 Court order in this litigation vacated the January 2004 final rule and final order on the grounds that a new comment period was necessary, the FDA reissued with little change the January 2004 action, this time as a proposed rule and proposed order for public comment.

B. Efficacy of Anthrax Vaccine Adsorbed

The proposed order summarized that the Brachman study included 1,249 workers in four textile mills in the northeastern United States that processed imported goat hair. Of these 1,249 workers, 379 received anthrax vaccine, 414 received placebo, 116 received incomplete inoculations of either vaccine or placebo, and 340 received no treatment but were monitored for the occurrence of anthrax disease as an observational group. The Brachman study used an earlier version of the protective antigen-based anthrax vaccine administered subcutaneously at 0, 2, and 4 weeks and 6, 12, and 18 months. During the trial, 26 cases of anthrax were reported across the four mills: 5 inhalation and 21 cutaneous anthrax cases. Prior to vaccination, the yearly average number of human anthrax cases was 1.2 cases per 100 employees in these mills. Of the five inhalation anthrax cases (four of which were fatal), two received placebo and three were in the observational group. Of the 21 cutaneous anthrax cases, 15 received placebo, 3 were in the observational group, and 3 received anthrax vaccine. Of the three cases in the vaccine group, one case occurred just prior to administration of the third dose, one case occurred 13 months after the individual received the third of the six doses (but no subsequent doses), and one case occurred prior to receiving the fourth dose of vaccine.

The proposed order further explained that in its report, the Panel stated that the Brachman study results demonstrate "a 93 percent (lower 95 percent confidence limit = 65 percent) protection against cutaneous anthrax" and that "inhalation anthrax occurred too infrequently to assess the protective effect of vaccine against this form of the disease." (50 FR 51002 at 51058). On the latter point, FDA does not agree with the Panel report. Because the Brachman comparison of anthrax cases between the placebo and vaccine groups included both inhalation and cutaneous cases, FDA has determined that the calculated efficacy of the vaccine to prevent all types of anthrax disease combined was, in fact, 92.5 percent (lower 95 percent confidence interval = 65 percent). The efficacy analysis in the Brachman study includes all cases of anthrax disease regardless of the route of exposure or manifestation of disease. FDA agreed that the five cases of inhalation anthrax reported in the course of the Brachman study are too few to support an independent statistical analysis. However, of these cases, two occurred in the placebo group, three occurred in the observational group, and no cases occurred in the vaccine group. Therefore, FDA proposed the indication section of the labeling for AVA not specify the route of exposure, and the vaccine be indicated for active immunization against *Bacillus anthracis*, independent of the route of exposure.

The proposed rule went on to discuss the consideration by the Panel of epidemiological data--sometimes called surveillance data--on the occurrence of anthrax disease in at-risk industrial settings collected by the CDC and summarized for the years

1962-1974 as supportive of the effectiveness of AVA. In that time period, individuals received either vaccine produced by MDPH, now BioPort, or an earlier version of anthrax vaccine. Twenty-seven cases of anthrax disease were identified. Three cases were not mill employees but people who worked in or near mills; none of these cases had been vaccinated. Twenty-four cases were mill employees; three were partially immunized (one with one dose, two with two doses); the remainder (89 percent) were unvaccinated (50 FR 51002 at 51058). These data provide confirmation that the risk of disease still existed for those persons who were not vaccinated and that those persons who had not received the full vaccination series (six doses) were susceptible to anthrax infection, while no cases occurred in those who had received the full vaccination series.

The proposed order also discussed the 2002 report of the Institute of Medicine, stating that FDA agrees with the report's finding that certain studies in humans and animal models, including the Brachman study, the CDC surveillance data, and several published studies of vaccine efficacy in non-human primates, support the conclusion that AVA is effective against *B. anthracis* strains that are dependent upon the anthrax toxin as a mechanism of virulence, regardless of the route of exposure.

Because the January 2004 final order was for the purpose of concluding a regulatory action started in 1985, it emphasized information addressed in the 1985 proposed rule. This emphasis carried over to the substantively unchanged December 2004 proposed order. However, it is now appropriate to take full cognizance of all available scientific information, including more recent data.

The 2002 IOM report provides the best framework for this review of the scientific evidence on AVA efficacy. The IOM committee must be given special recognition because: the IOM review was chartered by the U.S. Congress specifically for the purpose of providing the best possible, comprehensive, independent scientific assessment of anthrax vaccine to resolve questions that had been raised concerning the Department of Defense program; it included an internal critique by a panel of distinguished experts; it was decidedly independent and considered the entire spectrum of views; and its conclusion reflects the consensus view among prominent independent reviews over several years (Martinez-Lopez 2005).

The IOM report's conclusion that "the available evidence from studies with humans and animals, coupled with reasonable assumptions of analogy, shows that AVA as licensed is an effective vaccine for the protection of humans against anthrax, including inhalation anthrax" is correct. The primary evidence is the Brachman study, a well-controlled, randomized field trial of a comparable, predecessor vaccine, which concluded that the calculated efficacy of the vaccine in preventing all forms of anthrax disease combined was 92.5% (lower 95 percent confidence interval = 65 percent),

including all cases of cutaneous or inhalational exposure in the vaccinated and placebo groups (Brachman 1962). The conclusion that the assessment of efficacy is applicable regardless of the route of exposure is corroborated by at least four other sources. First, the observational group of the Brachman study identified three additional cases of inhalation anthrax, all among unvaccinated individuals (Brachman 1962). Second, as noted by the Panel, the CDC surveillance data covering the period 1962-1974, identified 27 cases of anthrax disease, none among individuals fully vaccinated (Panel 1985). Third, the collective results of a series of studies of the efficacy of AVA in protecting macaque monkeys, an animal model for which the IOM notes the pathophysiology of anthrax is similar to that in humans, are that 95% of the vaccinated macaques survived inhalation challenges with dozens to a thousand times the median lethal dose, compared to 100% fatality among unvaccinated macaques (Fellows 2001; Friedlander 1999; Ivins 1996; Ivins 1998; Pitt 1996; Henchal 2005). Experimental challenge data in rabbits, another animal model the IOM considers appropriate for studying the human form of inhalation anthrax, are similar (Henchal 2005). A fourth form of corroboration is in the well-understood pathophysiological mechanism of the anthrax bacteria and the effect at the cellular level of antibodies that bind to the protective antigen (PA) portion of the toxins secreted by the bacteria after entry into the body. These antibodies, produced in response to the protective antigen component of anthrax vaccine, appear to prevent entry into the cell of the lethal factor protein of the toxin, thereby preventing the cellular damage and disease (IOM pp. 46-49, Brachman 2005; Friedlander 2005, Pittman 2005).

C. Safety of Anthrax Vaccine Adsorbed

The proposed order noted that CDC conducted an open-label study under an investigational new drug application (IND) between 1967 and 1971 in which approximately 7,000 persons, including textile employees, laboratory workers, and other at-risk individuals, were vaccinated with anthrax vaccine and monitored for adverse reactions to vaccination. The vaccine was administered in 0.5-mL doses according to a 0-, 2-, and 4-week initial dose schedule followed by additional doses at 6, 12, and 18 months with annual boosters thereafter. Several lots, approximately 15,000 doses, of AVA manufactured by MDPH were used in this study period. In its report, the Panel found that the CDC data "suggests that this product is fairly well tolerated with the majority of reactions consisting of local erythema and edema. Severe local reactions and systemic reactions are relatively rare" (50 FR 51002 at 51059).

The proposed order also summarized that subsequent to the publication of the Panel's recommendations, DoD conducted a small, randomized clinical study of the safety and immunogenicity of AVA, referenced in the product label. These more recent DoD data as well as post-licensure adverse event surveillance data available to FDA

from the Vaccine Adverse Event Reporting System (VAERS) further support the safety of AVA. These VAERS data are regularly reviewed by FDA, and provided the basis for a description of the types and severities of adverse events associated with administration of AVA included in labeling revisions approved by FDA in January 2002.

Again, the IOM report includes a thorough review of safety studies and data on AVA, which it summarized (on page 2 of the report) by characterizing AVA as "reasonably safe," by noting that: immediate reactions (i.e., local events such as redness, itching, swelling, or tenderness at the injection site and a smaller number of systemic events such as fever and malaise) and the rates at which they occur "are comparable to those observed with other vaccines regularly administered to adults;" no evidence was found of increased risk of life-threatening or permanently disabling conditions from AVA; and there was no convincing evidence in limited existing data that vaccine recipients face elevated risk of developing adverse health effects over the longer term.

A number of peer-reviewed studies published since the IOM report provide further support for the FDA proposal (Woofler 2005). These include cohort studies indicating no significant difference in hospitalization rates among all active-duty military personnel from 1998 to 2000 (4,187,000 person-years of experience) between vaccinated and unvaccinated people (Lange 2003); no significant difference in health conditions between Gulf War veterans whose vaccination records show anthrax vaccination received and an unvaccinated cohort (Mahan 2004); and no significant difference in rates of disability evaluations between 154,456 anthrax-vaccinated and 562,377 unvaccinated Army soldiers over 4.25 years (Sulsky 2004). Additionally, a report on VAERS data referred to in the IOM report and the proposed order documents that among 1,793 anthrax vaccine recipients described in 1,857 reports to the Vaccine Adverse Events Reporting System, no unexpected patterns of adverse events were detected (Sever 2002; Sever 2004). A review of all available data on the safety of AVA, including data published in peer-reviewed medical journals, affirm the proposed order.

It is important to note that some recipients of anthrax vaccine in the Armed Forces vaccination program suffered adverse events subsequent to vaccination. A number of these individuals submitted comments to FDA expressing concerns about the safety of AVA. In many of these cases, a cause-and-effect relationship between vaccination and subsequent adverse event cannot be conclusively proven or disproven (Winkenwerder 2005; Grabenstein 2005). The Department of Defense responsibility to utilize its Military Health System capabilities, including the Vaccine Healthcare Centers, and disability compensation system to provide the greatest possible assistance applies without regard to whether a condition, temporary or permanent, is attributable to vaccination or other known or unknown causes (Winkenwerder 2005).

D. The Panel's General Statement: Anthrax Vaccine, Adsorbed, Description of Product

The proposed rule noted that the Panel report states: "Anthrax vaccine is an aluminum hydroxide adsorbed, protective, proteinaceous, antigenic fraction prepared from a nonproteolytic, nonencapsulated mutant of the Vollum strain of *Bacillus anthracis*" (50 FR 51002 at 51058). FDA clarified that while the *B. anthracis* strain used in the manufacture of BioPort's AVA is the nonproteolytic, nonencapsulated strain identified in the Panel report, it is not a mutant of the Vollum strain but was derived from a *B. anthracis* culture originally isolated from a case of bovine anthrax in Florida.

E. The Panel's Specific Product Review: Anthrax Vaccine Adsorbed: Efficacy

The proposed order commented that the Panel report states:

3. Analysis--a. Efficacy--(2) Human. The vaccine manufactured by the Michigan Department of Public Health has not been employed in a controlled field trial. A similar vaccine prepared by Merck Sharp & Dohme for Fort Detrick was employed by Brachman in a placebo-controlled field trial in mills processing imported goat hair. The Michigan Department of Public Health vaccine is patterned after that of Merck Sharp & Dohme with various minor production changes (50 FR 51002 at 51059).

The proposed order continued with an explanation that FDA has found that contrary to the Panel's statement, the vaccine used in the Brachman study was not manufactured by Merck Sharp & Dohme, but instead this initial version was provided to Dr. Brachman by Dr. G. Wright of Fort Detrick, U.S. Army, DoD (Brachman 1962). The DoD version of the anthrax vaccine used in the Brachman study was manufactured using an aerobic culture method (Wright 1954; Wright 1962). Subsequent to the Brachman trial, DoD modified the vaccine's manufacturing process to, among other things, optimize production of a stable and immunogenic formulation of vaccine antigen and to increase the scale of manufacture. In the early 1960s, DoD entered into a contract with Merck Sharp & Dohme to standardize the manufacturing process for large-scale production of the anthrax vaccine and to produce anthrax vaccine using an anaerobic method. Thereafter, in the 1960s, DoD entered into a similar contract with MDPH to further standardize the manufacturing process and to scale up production for further clinical testing and immunization of persons at risk of exposure to anthrax spores. This DoD-MDPH contract resulted in the production of the anthrax vaccine that CDC used in the open-label safety study and that was licensed in 1970.

Further, the proposed order noted that while the Panel attributes the manufacture of the vaccine used in the Brachman study to Merck Sharp & Dohme, 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 until the vaccine was licensed to the State of Michigan provide a foundation for a determination that the MDPH anthrax vaccine is comparable to the original DoD vaccine. See *Berlex Laboratories, Inc. v. FDA*, 942 F. Supp. 19 (D.D.C. 1996). The comparability of the MDPH anthrax vaccine to the original DoD vaccine 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*. In addition, there are data comparing the safety and immunogenicity of the MDPH vaccine with the original 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 original DoD vaccine were similar with respect to peak antibody response and seroconversion.

F. The Panel's Specific Product Review: Anthrax Vaccine Adsorbed: Labeling

The proposed rule explained that the Panel report states: "3. Analysis--d. Labeling: The labeling seems generally adequate." There is a conflict, however, with additional standards for anthrax vaccine. Section 620.24 (a) (21 CFR 620.24(a)) defines a total primary immunizing dose as three single doses of 0.5 mL. The labeling defines primary immunization as six doses (0, 2, and 4 weeks plus 6, 12, and 18 months) (50 FR 51002 at 51059). The dosing schedule for AVA has always consisted of six doses, a 0.5-mL dose at 0, 2, and 4 weeks, and then at 6, 12, and 18 months, followed by a subsequent 0.5-mL dose at 1 year intervals to maintain immunity. Prelicensure labels described the vaccination schedule as three initial doses, followed by three additional doses, and yearly subsequent doses, which is consistent with the additional standards of AVA that were originally published in October 1970, immediately before the licensure of AVA. The 1979 labeling referred to "primary immunization" as consisting of six injections, with recommended yearly subsequent injections. The 1987 labeling of AVA, subsequent to the Panel's report, described the vaccination schedule as "primary immunization" consisting of three doses followed by three additional doses for a total of six doses followed by annual injections. The labeling is not inconsistent with Sec. 620.24(a) (21 CFR 620.24(a)) before it was revoked by FDA in 1996 as part of a regulatory streamlining final rule that revoked 21 CFR part 620 and other biologics regulations because they were obsolete or no longer necessary to include in the CFR (FDA 1996). Thus while use of the term "primary" has varied over time in reference to the AVA vaccination schedule, the licensed schedule itself has always consisted of six doses of 0.5 mL administered at 0, 2, and 4 weeks and 6, 12, and 18 months, followed by additional doses on an annual basis to maintain immunity.

The proposed order was correct in its discussion of the dosing schedule but failed to clarify its regulatory effect, particularly on public health programs. Section 620.24(a) called for "total primary immunizing doses of three single doses, each given at appropriate intervals." Although the best indicator of "appropriate intervals" is the dosing schedule recommended in the product labeling, a question has been raised whether, in cases in which circumstances compel longer-than-recommended intervals, the result is still, in the course of medical practice, an appropriate interval and still consistent with the labeled dosing schedule.

ACIP recommendations, both generally for vaccines and specifically for AVA, provide that longer-than-recommended intervals between doses do not reduce final antibody concentrations, although protection might not be attained until the recommended number of doses has been administered, and that an interruption in the vaccination schedule does not require restarting the entire series of a vaccine or toxoid or the addition of extra doses (ACIP 2000, 2002). These guidelines recognize the biological fact that the human immune system contains durable memory cells that remember previous vaccinations and permit deviations from the particular dosing schedules observed during clinical studies and field trials. Multiple studies and texts support the ACIP expert opinion, both in general (e.g., Salk 1984; Jilg 1985; McBean 1988; Hadler 1989; Marsano 1998; Wistrom 1999; Atkinson 2003), and specifically with respect to AVA (Pittman 2000, 2002a, 2002b). The FDA also received in January 2005 data from the CDC dose reduction and route of administration study under IND # 10031, which add to the fact base about the immune response to anthrax vaccination under a variety of dosing intervals.

The clearly established understanding of immunology has led the CDC and ACIP to establish guidelines for managing shortages of other vaccines, which have become quite frequent in recent years, by deferring immunizations for some groups, so that the available supply can be directed to those considered at higher risk for contracting vaccine-preventable diseases (GAO 2002, CDC 2004). The CDC has also established guidelines for dealing with the inevitable, day-by-day reality that patients and physicians and vaccine rarely all come together on a precise calendar schedule that exactly matches a labeled dosing schedule. These guidelines include catch-up schedules, minimum intervals between doses for children for whom immunizations were delayed, and the explicit guidance, endorsed by the American Academy of Family Physicians and the American Academy of Pediatrics, that: "There is no need to restart a vaccine series regardless of the time that has elapsed between doses" (ACIP 2005).

These CDC and ACIP guidelines are not mislabeling of the vaccines, and health care providers who follow them are not conducting experiments or violating the Food,

Drug, and Cosmetic Act. This is the regulatory issue more important than whether AVA doses 4, 5, and 6 are considered "primary" or "booster" doses. The scientifically-supported, ubiquitous clinical practice, essential for viable public health programs, is to treat the inevitable longer-than-recommended dosing intervals as appropriate intervals. Therefore, the Final Order should acknowledge that these appropriate intervals are consistent with the labeled dosing schedule.

Conclusion

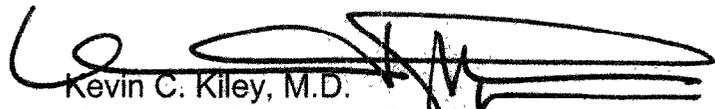
The scientific evidence clearly supports the FDA's proposed order concerning Anthrax Vaccine Adsorbed.

DoD has compiled clinical experience with more than 5.2 million doses of anthrax vaccine administered to more than 1.3 million people since March 1998. DoD has consistently shared that experience with independent panels of civilian physicians and scientists, both FDA and CDC, and published it in the peer-reviewed literature.

If we can provide you with any additional information about our clinical experience with anthrax vaccine, please feel free to contact Colonel Steve Jones or Colonel John Grabenstein, Military Vaccine Agency, at 703-681-5101.

On behalf of the United States Armed Forces, thank you for your continuing efforts to strengthen the Nation's protection against bioterrorism and biowarfare.

Sincerely,


Kevin C. Kiley, M.D.
Lieutenant General, US Army
The Surgeon General

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Enclosure 1. References

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