



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH INSTITUTE OF INFECTIOUS DISEASES
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REPLY TO
ATTENTION OF:

March 25, 2005

Office of the Commander

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

Ladies and Gentlemen:

I'm writing in response to Docket Number 1980N-0208, Final Rule and Final Order Involving Bacterial Vaccines and Toxoids.

Human experience provides evidence that anthrax vaccine adsorbed (AVA) protects against disease caused by anthrax spores. This experience includes a placebo-controlled human field trial, as reported by Brachman et al. (*Am J Public Health*. 1962;52:632-645). In that study of mill workers who were occupationally exposed to anthrax spores, the vaccine, a less potent precursor of the current licensed anthrax vaccine, was 93% effective in preventing anthrax. There was one case of cutaneous anthrax in the vaccinated group compared to 13 cases of cutaneous and 2 of inhalational anthrax in the placebo-controls. Thus there was evidence of protection against both forms of anthrax. Of significance, there were 3 additional cases of inhalational anthrax that occurred in workers who were unvaccinated but did not participate in the trial. Thus, the vast majority of cases of cutaneous anthrax and all cases of inhalational anthrax occurred in individuals who were not vaccinated. In addition, there is a large body of evidence showing that AVA is highly efficacious against inhalational anthrax in the non-human primate, the best animal model of the human disease (*JAMA*. 1999;282:2104-2106).

Our knowledge of the mechanism of protection induced by the licensed anthrax vaccine based on experiments in animals suggests that AVA works by inducing antibodies to the protective antigen (PA) component of the toxins that the organism uses to cause disease. This is consistent with the views expressed in the 2002 report of the Institute of Medicine of the National Academy of Sciences that stated: "The efficacy of AVA against a broad spectrum of *B. anthracis* strains is consistent with the critical role of PA in the pathogenesis of anthrax." (*The Anthrax Vaccine*, National Academy Press, 2002, p. 71); and "Finally, the available data indicate that immunity to anthrax is associated with the presence of antibody to PA, such as those stimulated by anthrax vaccine." (*Ibid.*, p. 77)

A critical point in addressing how the vaccine works rests on our knowledge of the pathogenesis of anthrax. Regardless of the route of infection, the toxins are absolutely essential for the anthrax organism to cause disease. Whether the spore enters the skin,

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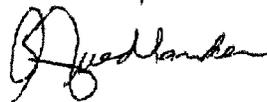
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gastrointestinal or respiratory tract, it only begins making toxin once it germinates into the bacillus and we believe this is the point where antibodies induced by AVA are acting. This is indicated by our current understanding of how the toxin works as depicted in the diagram in the Institute of Medicine report (Ibid., p. 47). Antibodies induced by AVA block the binding of toxin to the infected person's cells thereby protecting them from the destructive effects of the toxins. Thus the protective anti-toxin antibodies induced by AVA vaccination would be effective in any form of anthrax.

It is my interpretation that the indication section of the labeling for AVA does not specify the route of exposure. It is my opinion that the vaccine is indicated for protection against infection with *Bacillus anthracis*, including both cutaneous and inhalational forms of the disease. Again, this is consistent with the conclusions as stated in the Institute of Medicine report: "The committee finds 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 inhalational anthrax, caused by known or plausible engineered strains of *B. anthracis*." (Ibid., p. 77)

I offer the comments above based upon my studies on anthrax over many years. If I can offer you any further information or assistance please do not hesitate to contact me. I can be reached at 301-619-7343.

Sincerely,



Arthur M. Friedlander, MD
Senior Scientist