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MEDICAL READINESS

Safety and Efficacy of the Anthrax Vaccine

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Mr. Chairman and Members of the Subcommittee:

We are pleased to be here today to discuss the results of our ongoing examination of the safety and efficacy¹ of the anthrax vaccine, which is being done at your request. My testimony presents preliminary findings on (1) the short- and long-term safety of the vaccine, (2) the efficacy of the vaccine, and (3) problems the Food and Drug Administration (FDA) found in the vaccine production facility in Michigan that could compromise the safety, efficacy, and quality of the vaccine. We plan to issue the final report on our review this fall.

As you know, concerns have been raised about the Department of Defense's (DOD) anthrax immunization program since the Department began vaccinating the first of 2.4 million active duty and reserve members. For example, some Gulf War veterans are suffering from unexplained illnesses that they believe might have been caused by anthrax vaccines that they received during the war. Also, some active duty military personnel expressed concerns regarding the safety and efficacy of the anthrax vaccine after the FDA found problems during the inspection of the facility that was manufacturing the anthrax vaccine. With this background, I will discuss our results.

Results in Brief

The anthrax vaccine being given to U.S. military personnel was licensed in 1970. Before the vaccine was licensed, the vaccine and the manufacturing process were changed, creating a similar vaccine, produced by the Michigan Department of Public Health (MDPH), which was the one eventually licensed.² The safety study conducted before licensing used both the original vaccine and MDPH vaccine. Knowledge to date about the safety of the vaccine includes the results of the original study and a 1998 DOD study of 500 vaccine recipients. While these studies identified varying

¹Safety means relative freedom from harmful effects to persons affected directly or indirectly by a product that has been prudently administered, taking into considerations the character of the product in relation to the condition of the recipient at the time. Efficacy is not an absolute term. It is a measure of a product's ability to produce a given response. An effective vaccine will provide a certain degree of protection for a certain period of time.

²The original license for the production of anthrax vaccine was issued to MDPH. In 1995, the facility changed its name to the Michigan Biologic Products Institute. In 1998, the facility was sold, and its name was change to BioPort. The term MDPH will be used to refer to the licensed facility throughout this testimony.

rates of adverse reactions, they did not question the safety of the vaccine. The long-term safety of the vaccine has not yet been studied.

Prior to the time of licensing, no human efficacy testing of the MDPH vaccine was performed. However, a study was done on the efficacy of the original vaccine. This study concluded that the vaccine provided protection to humans against anthrax penetrating the skin. In the 1980s, DOD began testing the efficacy of the licensed vaccine on animals, focusing on its protection against inhalation anthrax. DOD recognizes that correlating the results of animal studies to humans is necessary and told us that it is planning research in this area.

Careful control of the manufacturing process is essential to ensure the quality of the product. The FDA inspections of the facility where the licensed vaccine was manufactured uncovered numerous problems. The facility received warning letters from FDA, including one in March 1997 stating its intent to revoke the facility's license. The facility closed its plant in 1998 and is now being renovated. FDA requires the manufacturer to meet specifications for sterility, stability, purity, and potency. In addition to the lot release testing required by FDA, DOD is conducting supplemental testing of each lot from this plant before distributing the vaccine.

Background

The nature and magnitude of the military threat of biological warfare (BW) has not changed since 1990, both in terms of the number of countries suspected of developing BW capability, the types of BW agents they possess, and their ability to weaponize and deliver those BW agents. Inhalation anthrax is considered by DOD to be the primary BW threat because of its lethality, ease of production, and weaponization.

The original anthrax vaccine was developed by George Wright in the 1950s and first produced on a large scale by Merck. After a 1962 study on the vaccine's effects in mill workers, its manufacturing process was changed, and MDPH took over as the vaccine's producer. This changed vaccine was licensed in 1970 by the Division of Biologics, National Institute of Health, to be manufactured by MDPH.

Vaccines have three distinguishing features that contrast with those of chemical drugs. First, either they have no clearly chemically defined composition, or simple chemical analysis is insufficient for effective characterization. Second, proper evaluation of them (qualitatively or quantitatively) is usually done by measuring their effects *in vivo* (in the

living organism). 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.

Vaccine Safety

Studies have been performed to examine the safety of both the original vaccine and the licensed vaccine. These two vaccines were made using different processes and have different data to support their safety. While these studies identified varying rates of adverse reactions, they did not question the safety of the vaccine. The long-term safety of the vaccine has not yet been studied.

Data on Safety of the Original Vaccine

A study on the original vaccine's safety was done by Philip Brachman and published in 1962.³ Brachman reported on 379 subjects that received this vaccine. About 35 percent had local reactions, a figure that varied during the inoculation series. Some recipients developed more severe edema that extended to the mid-forearm or wrist. Two individuals had systemic reactions in addition to the edema. The researchers actively collected data on adverse reactions to the vaccine, and the study concluded that individual reactions to the vaccine were relatively minor.

Data on Safety of the Licensed Vaccine

After the original vaccine was developed, 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.

Four safety studies have been done that include the licensed vaccine. The results of those studies are presented in table 1. The Center for Disease Control collected data on the Investigational New Drug (IND) study, DOD collected data for both the Pittman study and the Tripler Army Medical Center (TAMC) Anthrax Survey, and DOD is currently collecting reports on

³P.S. Brachman et al., Field evaluation of a human anthrax vaccine, *American Journal of Public Health*, vol. 52 (1962), pp. 632-645.

adverse events. The number of adverse reactions appears to depend, in part, upon whether the mechanism for monitoring reactions is active or passive. (Active monitoring means that the vaccine recipients are contacted to ascertain any adverse reactions after vaccine administration; passive monitoring means that the onus is on the vaccine recipients to report any adverse reactions after vaccine administration.) None of the studies questioned the vaccine's safety.

Table 1: Reactions to Licensed Anthrax Vaccine Reported in Various Studies

Study	Type of reporting	Number vaccinated (or doses)	Local reactions (percent)		Systemic reactions (percent)	
			Mild	Moderate/severe	Mild	Moderate/severe
IND	Active/passive	3,984 ^a	6 – 20 ^b	1 – 10 ^b	None ^b	.05 ^b
Pittman (1997)	Active	508	16	5	29 ^c	14
TAMC (1998)	Active	536	Not addressed	Not addressed	43 ^d	5
DOD (Current monitoring)	Passive	223,000 ^e	e	e	e	e

^aThis number represents the number of study participants who received the first dose of the licensed vaccine.

^bThese figures represent the percentage of people who experienced this type of reaction during the study, even if they had previously been inoculated with the Merck vaccine.

^cThis figure also includes persons who had reactions of "unknown" severity.

^dThis figure represents the frequency of the most common side effect, myalgia.

^eDOD testified that as of March 16, 1999, more than 223,000 servicemember have been immunized. There had been 42 reports on adverse effects submitted to the FDA and CDC. Only seven servicemembers required hospitalization or experienced loss of duty for more than 24 hours.

Vaccine Efficacy

Studies on the efficacy of the original and the licensed vaccines have been limited to a study of the efficacy of the original vaccine for humans, and studies of the efficacy of the licensed vaccine for animals. The study on the original vaccine concluded that the vaccine offered protection against anthrax penetrating human skin. The studies on the licensed vaccine focused on the efficacy of the vaccine in protecting animals against inhalation of anthrax. These studies, while showing some positive results, may not be extrapolated to humans. DOD is planning to conduct such correlating studies.

Human Efficacy Study

The only study of the efficacy of the vaccine for humans was performed by Brachman, using the original vaccine. The Brachman study claimed that the vaccine gave 93 percent (and a lower confidence limit of 65 percent) protection against anthrax penetrating the skin. It found that the number of individuals who contracted anthrax by inhalation was too low to assess the efficacy of the vaccine against this form.

Because the vaccine used in the Brachman study was different from the licensed vaccine, additional data were submitted to the Division of Biologics, Department of Health, Education, and Welfare (HEW), to support the license application for the MDPH vaccine. In a February 1969 memorandum, an HEW committee concluded that based on the data, the assumption of efficacy appeared speculative. Similarly, a 1991 Army document noted that “it would be scientifically incorrect to assume that this (*licensed*) vaccine would be totally efficacious under different circumstances, that is, beyond the parameters of the study design.” Thus, assuming that the epidemiological evidence from the original vaccine is applicable to the licensed vaccine, we can conclude that the licensed vaccine is efficacious against cutaneous exposure but that testing still needs to be conducted on inhalation anthrax. In the absence of a specific study, efficacy of the licensed vaccine for humans has been inferred from other data, including a reduction in the incidence of anthrax following immunization of at-risk individuals and from animal experiments.

Animal Efficacy Studies of Licensed Vaccines

Beginning in the late 1980s, DOD began studying the efficacy of vaccines on animals, using guinea pigs, rabbits, and monkeys. All of these studies support the view that in these animals, the licensed vaccine can protect against exposure to some strains of anthrax either by inoculation or inhalation. It is clear, however, that animal species differ in their susceptibility. Studies of guinea pigs show that some anthrax strains are more or less resistant to vaccines for humans (both the U.S. and U.K. versions) but are protected by the live spore veterinary vaccine.⁴

⁴P.C.B Turnbull, et al., Development of antibodies to protective antigen and lethal factor components in humans and guinea pigs and their relevance to protective immunity, *Infectious Immunology*, vol. 52 (1988) pp. 356-363.

Research using monkeys showed for the first time that monkeys could be protected against aerosol exposure.⁵ However, in both the guinea pig and monkey studies, protection did not correlate with levels of antibodies to a protective antigen. Several studies have shown no direct comparison of immunity in humans to that in monkeys. Study findings suggest that “the importance of various specific immune mechanisms against inhalation anthrax may vary in different animal species or . . . the ability of the licensed human vaccine to stimulate cell-mediated immunity may be greater in some species than others.” A 1998 study comes to the same conclusion and emphasizes the need for further studies. In animals, the lack of correlation of protection with antibodies to protective antigen has some important consequences.

DOD recognizes the importance of establishing a correlate of immunity in humans. Recently, it has sought to develop a serologic correlate of immunity in an animal model to use for humans.

Vaccine Manufacturing Process

The quality of a vaccine is closely linked to its manufacturing process, which must be rigorously controlled to ensure that batches of vaccines produced on different occasions are of reproducible and consistent quality. In general, quality is achieved by applying the current good manufacturing practice. This process is not static but involves manufacturers and regulators in a continuing process of assessment and upgrades as scientific progress, technical development, and experience help to identify deficiencies and make improvements possible. Such principles also apply to the facilities and equipment in which products are manufactured.

Accordingly, vaccine production is very highly regulated to ensure that the products are of consistent quality and safe and effective for the purpose(s) for which regulatory approval was granted. Until 1993, FDA inspectors did not inspect the MDPH facility where the anthrax vaccine was made. According to FDA, access was not granted because its inspectors had not been vaccinated against anthrax.

FDA’s inspections of the MDPH facility found a number of deficiencies. The deficiencies that FDA identified in its February 1998 inspection fall

⁵B.E. Ivins, et al., Efficacy of a standard human anthrax vaccine against *Bacillus anthracis* aerosol challenge in rhesus monkeys, in “Proceedings of the International Workshop on Anthrax, [Salisbury Medical Bulletin](#), Special Supplement no. 87 (1996) pp. 125-126.

broadly into two categories: those that, although serious, might affect only one or a limited number of batches that were produced when the deficiency was extent and those of a generic nature that could compromise the safety and efficacy of any or all batches. DOD had also identified deficiencies during a March 1992 inspection, including the absence of stability studies. In 1998, MDPH closed its plant, which is now being renovated. DOD has directed that supplemental testing be done on the lots of vaccine in the current inventory.

Mr. Chairman, this concludes my statement. I will be happy to answer any questions you or members of the Subcommittee may have.

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