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The Honorable Steve Buyer
Chairman, Subcommittee on Military Personnel
Committee on Armed Services
House of Representatives

Subject: Summary of GAO's Findings on the Safety and Efficacy of the Anthrax Vaccine

Dear Mr. Chairman:

Concerns have been raised about the Department of Defense's (DOD) anthrax immunization program since DOD began vaccinating its 2.4 million active duty and reserve members in 1998. At your request, we are providing you with information we have previously reported concerning (1) the need for a six-shot regimen and annual booster shots, (2) the long- and short-term safety of the vaccine, (3) the efficacy of the vaccine and (4) the extent to which problems the Food and Drug Administration (FDA) found in the vaccine production facility in Michigan could compromise the safety, efficacy, and quality of the vaccine.[1] We are also providing for you the three testimonies that are the source of the information we are providing you today.

BACKGROUND

The original anthrax vaccine was developed in the 1950s and was first produced on a large scale by the Merck Pharmaceutical Corporation. In 1962, a study was published on the safety and efficacy of the Merck vaccine against cutaneous anthrax in wool mill workers. Later, the Michigan Department of Public Health took over as the vaccine's producer but the manufacturing process, the strain, and the ingredients differed from the Merck vaccine. This changed vaccine, which is the vaccine currently being given to U.S. military personnel, was licensed in 1970 by the Division of Biologics Standards, National Institutes of Health. FDA is currently responsible for licensing new vaccines and ensuring vaccine safety.

[1] *Medical Readiness: Safety and Efficacy of the Anthrax Vaccine* (GAO/T-NSIAD-99-148, Apr. 29, 1999); *Medical Readiness: Issues Concerning Anthrax Vaccine* (GAO/T-NSIAD-99-226, July 21, 1999); and *Anthrax Vaccine: Safety and Efficacy Issues* (GAO/T-NSIAD-00-48, Oct. 12, 1999).

As of July 1999, more than 315,000 service members had received at least one dose of the vaccine. Initial immunization consists of three shots given at 0, 2, and 4 weeks followed by three additional shots given at 6, 12, and 18 months.

SUMMARY OF OUR KEY FINDINGS

Our work has identified that data on the current immunization schedule and the vaccine's safety and efficacy is limited in some areas. Moreover, FDA has identified some deficiencies concerning the manufacturer's controls over the vaccine's quality. DOD and the company that purchased the vaccine production facility in 1998 have several efforts planned or underway to address these issues.

Data on the Need For Six Shots and Annual Boosters Are Unavailable

No studies have been done to determine the optimum number of doses of the anthrax vaccine. A three-dose regimen was used initially for the original vaccine based on a regimen developed using animals in the early 1950s. However, the number of doses was increased to six after three people who received three doses of the vaccine became infected. The licensed vaccine adopted this schedule and DOD has followed this regimen. Although annual boosters are required, the need for annual booster shots has not been evaluated.

Long-term and Short-term Safety of the Vaccine

The long-term safety of the licensed vaccine has not been studied. However, DOD is designing studies to examine the vaccine's long-term effects.

With regard to short-term safety, according to FDA officials, data from two studies conducted prior to licensing of the current anthrax vaccine are difficult to interpret since one study used the original vaccine, and part of the study population in the other study had already received the original vaccine.

Post-licensing data on safety are limited because only a limited number of doses—about 68,000—were distributed by the manufacturer from 1974 through 1989. Also FDA did not establish its Vaccine Adverse Event Reporting System (VAERS) until 1990. This system, which DOD uses, alerts FDA and the Centers for Disease Control to increases in adverse events.[2] However, it is a passive surveillance system, which means that FDA and the Centers for Disease Control must rely on vaccine recipients or their health care providers to report any adverse events after receiving the vaccine. Studies show that adverse events are reported significantly less frequently with passive surveillance systems than they would be in an active system where vaccine recipients are monitored to find out if they had any adverse effects.

[2]Clinical events reported to a passive surveillance system such as FDA's are usually termed adverse events rather than adverse reactions because there is usually insufficient evidence that the vaccine, rather than other health conditions, caused the reported events.

DOD has recently conducted two studies using active monitoring where DOD personnel contacted the vaccine recipients directly to find out if they had any adverse reactions. Data from these studies, conducted in 1998 and 1999, showed that a higher proportion of women reported both local and systemic reactions to the vaccine than their male counterparts. In addition, data from one of the studies showed that more than twice the proportion of women reported that they missed one or more duty shifts after their vaccinations than did males.

Vaccine Efficacy

A study on the efficacy of the original vaccine concluded that it provided protection to humans against anthrax penetrating the skin but did not provide sufficient data to determine its effectiveness against anthrax that was inhaled. Beginning in the late 1980's, DOD began studying the efficacy of the licensed anthrax vaccine 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 but not all 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 but are protected by the live spore veterinary vaccine.

Research using monkeys showed for the first time that monkeys could be protected against aerosol exposure. However, several studies have shown no direct comparison of immunity in humans to that in monkeys. DOD officials recognize that correlating the results of animal studies to humans is necessary and told us that DOD is planning research in this area. DOD also plans to develop a second generation anthrax vaccine, and as part of this effort, it will need to address whether strains of deliberately engineered or naturally occurring anthrax can overcome the protective immunity of such a vaccine.

Problems with the Vaccine Manufacturing Process

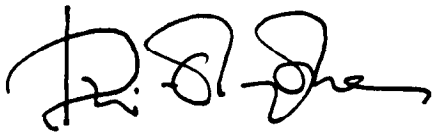
With regard to the manufacturing process, it is important to note that the quality of a vaccine is closely linked to its manufacturing process, which must be rigorously controlled to ensure that batches of vaccines produced on different occasions are of consistent quality. Accordingly, vaccine production is 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 Michigan Department of Public Health facility where the anthrax vaccine was made. According to FDA, access was not granted because its inspectors had not been vaccinated against anthrax. DOD conducted inspections, however, and identified deficiencies during a March 1992 inspection.

FDA's inspections of the vaccine production facility in 1996 and 1998 found a number of deficiencies. The deficiencies that FDA identified in its February 1998 inspection fall broadly into two categories: those that might affect only one or a limited number of batches that were produced and those that could compromise the

safety and efficacy of any or all batches. In 1998, the manufacturer shut down the facility for renovation. A new company, which purchased the facility in mid-1998, is addressing the issues identified by FDA.

If you need additional information on these issues, please call me on (202) 512-3652 or Dr. Sushil Sharma, Assistant Director, on (202) 512-3460.

Sincerely yours,



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