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ANTHRAX VACCINE

Safety and Efficacy Issues

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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 efficacy[1] of the anthrax vaccine. My testimony is based on previous studies[2] we have conducted to determine (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. Finally, I would like to discuss the effects of the anthrax vaccine on children, pregnant women or lactating women.

As you know, 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. For example, some active and reserve military personnel expressed concerns regarding the safety and efficacy of the anthrax vaccine after the FDA found problems during the inspection of the vaccine production facility. In addition, some Gulf War veterans are suffering from unexplained illnesses that they believe might have been caused by anthrax vaccinations received during the war.

The original anthrax vaccine was developed in the 1950s and was first produced on a large scale by the Merck Pharmaceutical Corporation. After a 1962 study on the vaccine's effect on mill workers, its manufacturing process was changed and the Michigan Department of Public Health took over as the vaccine's producer. This changed vaccine, which is the vaccine 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]Safety means relative freedom from harmful effects to persons affected directly or indirectly by a product that has been prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time. Efficacy 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.

[2]See *Medical Readiness: Issues Concerning the Anthrax Vaccine* (GAO/T-NSIAD-99-226, July 21, 1999) and *Medical Readiness: Safety and Efficacy of the Anthrax Vaccine* (GAO/T-NSIAD-99-148, April 29, 1999).

Summary

No studies have been done to determine the optimum number of doses of the anthrax vaccine. Although annual boosters are given, the need for a six-shot regimen and annual booster shots have not been evaluated.

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. Data on the prevalence and duration of short-term reactions to the vaccine are limited but suggest that women experience a higher rate of adverse reactions than do men. FDA's system for collecting data on adverse events associated with the vaccine, which DOD uses, relies on vaccine recipients or their health care providers to report adverse events.[3] Studies have shown that such systems may not accurately reflect the incidence of events due to underreporting. However, data from two recent DOD efforts to identify the prevalence of adverse events associated with anthrax vaccine show that a higher proportion of women reported both local and systemic reactions to the vaccine than their male counterparts. In addition, more than twice the proportion of women reported that they missed one or more duty shifts after their vaccinations than did males.

A study on the efficacy of the earlier vaccine concluded that it provided protection to humans against anthrax penetrating the skin but did not provide information to determine its effectiveness against inhalation anthrax. In the 1980's, DOD began testing the efficacy of the licensed vaccine in animals, focusing on its protection against inhalation anthrax. The studies showed that the vaccine protected some animals against inhalation anthrax. However, the level of protection varied for different species and the results cannot be extrapolated to humans. DOD recognizes that correlating the results of animal studies to humans is necessary and told us that it is planning research in this area. DOD also plans to develop a second generation anthrax vaccine and, as part of this effort, will need to address whether strains of deliberately engineered or naturally occurring anthrax can overcome the protective immunity of such a vaccine.

FDA's inspections of the vaccine production facility in 1997 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

[3]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.

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. The facility was shut down in early 1998. A new company, which purchased the facility in mid-1998, is addressing these issues.

Finally, you expressed concerns about the effects of the anthrax vaccine on children, pregnant women, or lactating women. The anthrax vaccine is not intended to be administered to children, pregnant women, or lactating women. No studies have been conducted on the vaccine's effects on these groups.

Background

In December 1997, the Secretary of Defense announced that all U.S. forces would be inoculated against the potential use of anthrax on the battlefield. 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. DOD has recognized that some of the concerns about using the current vaccine might be mitigated in the future through actions such as testing and research and adjustments to the program based on new data.

The inspection process for ensuring vaccine safety is more stringent and complex than for chemical drug because vaccines have three distinguishing features. First, either they have no clearly chemically defined composition, or chemical analysis is extremely difficult. Second, proper evaluation of vaccines generally requires measuring their effects in animals. 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.

From the 1970s until 1998, DOD had been procuring the anthrax vaccine from a facility owned by the State of Michigan, the only facility in the country licensed to produce the vaccine. In 1997 and 1998, FDA identified numerous manufacturing problems at the facility. In response to concerns about the potential loss of anthrax vaccine production, DOD began funding renovation of the facility. Production facilities were shut down in early 1998. In the summer of 1998, the State of Michigan sold the facility to the BioPort Corporation for $25 million. DOD contracts were then transferred to BioPort. BioPort is addressing manufacturing problems.

Data on the Need for Six Shots and Annual Boosters Are Not Available

No studies have been done to determine the optimum number of doses of the anthrax vaccine. The immunization schedule of three doses used for the earlier vaccine was based on a regimen developed using animals in the early 1950s. However, the number of doses was arbitrarily increased to six when three people (two at Fort Detrick and one in a private wool mill) who received three doses of the vaccine became infected after exposure to anthrax. In a study of the vaccine's human efficacy published in 1962, a six-dose schedule was used, and the researchers concluded that the vaccine provided protection against anthrax penetrating the skin. The study did not provide enough information to determine whether the vaccine was effective against inhalation anthrax. The license for the vaccine, which was granted in 1970, calls for the six-dose schedule and annual boosters used in the human efficacy study, and DOD has followed this regimen. In September 1998, the manufacturer submitted an Investigational New Drug application to FDA to determine whether the number of shots in the initial schedule could be reduced from six to five.

In November 1971, the Division of Biologics Standards, National Institutes of Health, noted an apparent increase in reports of adverse reactions after individuals received booster shots. The Division considered it advisable to reevaluate the need for annual boosters and possibly the amount of the booster dose. Although the record is unclear as to whether or not the Division requested the manufacturer to conduct a reevaluation, no such reevaluation has been done to date.

Vaccine Safety

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, data on the prevalence and duration of short-term reactions to the vaccine are limited but suggest that women experience a higher rate of adverse reactions than men. A study on the earlier vaccine's safety was done by Philip Brachman and published in 1962.[4] Brachman reported on 379 subjects that received this vaccine. The study concluded that individual reactions to the vaccine were relatively minor. About 35 percent had local reactions, a figure that varied during the

[4]P.S. Brachman et al., "Field Evaluation of a Human Anthrax Vaccine," *American Journal of Public Health,* vol. 52 (1962), pp. 632-645.

inoculation series. Some recipients developed more severe edema, or swelling, that extended to the mid-forearm or wrist. Two individuals had systemic reactions in addition to the edema. In addition to this study, some data was collected to support licensing of the vaccine but is of limited use because some participants had already received the earlier vaccine and it is not possible to identify who received which vaccine.

Post-licensing data 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 until 1990. This system, which DOD uses, alerts FDA and the Centers for Disease Control to increases in adverse events. 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.

Since DOD's mandatory inoculation program began in 1998, DOD has conducted two efforts to actively collect data on the short-term safety of the vaccine. These data also allow one to examine gender differences in adverse reactions after servicemembers have received the anthrax vaccine. The first effort, conducted in 1999 by a DOD physician stationed in Korea, was a survey given to service members when they reported for their initial six-dose schedule of shots; it asked questions about their reactions to the previous shot. Results from this effort reflect the researcher's preliminary analysis of the data. The second effort, conducted in 1998-99 at Tripler Army Medical Center, Hawaii, included a survey on adverse reactions to the first three shots when individuals reported for their fourth shot and later included a follow-up survey on adverse reactions to the fourth shot.

According to the data gathered in both efforts, a higher proportion of females reported reactions to the anthrax vaccine than did their male counterparts. Table 1 summarizes the rates of all reported reactions to the vaccine in Korea. The data show that a higher proportion of females reported reactions than males.

Table 1: Preliminary Data on Gender Differences in the Reported Rate of Adverse Reactions to the Anthrax Vaccine, From Korea Survey (1999)

Dose	Males Percent (number of doses)	Females Percent (number of doses)
First	42.1 (2036)	71.6 (495)
Second	44.4 (1953)	74.0 (474)

Note: This represents a preliminary analysis of the data by the researcher, and at the time of our review, data on reactions to the third shot were not available.

Source: DOD 1999.

The data gathered in Korea also show that after the first two shots, more than twice the proportion of women than men reported systemic reactions of fever, malaise, or chills than did men (see table 2).

Table 2: Preliminary Data on Gender Differences in Systemic Reactions, From Korea Survey (1999)

	Fever		Malaise		Chills	
Dose number	Male (percent)	Female (percent)	Male (percent)	Female (percent)	Male (percent)	Female (percent)
First	0.9	2.8	6.0	15.6	1.5	5.5
Second	1.7	4.8	7.1	15.4	1.9	4.0

Note: This represents a preliminary analysis of the data by the researcher, and at the time of our review, data on reactions to the third dose were not available.

Source: DOD.

The Tripler survey also demonstrates gender differences in reported reactions (see table 3). These data show that a higher proportion of women reported making an outpatient visit after a vaccination than their male counterparts. In addition, more than twice the proportion of women reported that they missed one or more duty shifts after their vaccinations than did males. In light of the fact no gender specific data were available from the pre-licensure studies, these findings underscore the need for monitoring to better understand the specific effects of this vaccine in different groups.

Table 3: Gender Differences in Reported Local Reactions, Outpatient Medical Visits, and Missed Duty, From Tripler Army Medical Center Survey (1998-99)

Reaction		Dose 1 (percent)	Dose 2 (percent)	Dose 3 (percent)	Dose 4 (percent)
Moderate to severe redness	(m)	17.5	20.4	17.2	31.6
	(f)	49.1	46.9	51.4	39.8
Swelling of lower arm	(m)	9.7	9.5	9.2	7.1
	(f)	13.4	13.5	13.0	8.4
Pain limiting motion of elbow	(m)	9.7	8.7	7.6	7.9
	(f)	17.1	13.5	11.7	8.6
Localized itching	(m)	25.2	25.7	24.5	27.7
	(f)	62.6	60.4	57.9	39.2
Lump or knot	(m)	63.9	64.4	60.5	65.5
	(f)	89.9	87.8	83.6	73.2
Muscle soreness	(m)	66.6	64.7	61.8	60.4
	(f)	79.7	76.4	70.8	61.6
Outpatient medical visit	(m)	5.3	2.0	2.7	[a]
	(f)	10.0	13.8	3.9	
Missed one or more shifts of duty	(m)	2.2	2.0	0.9	[a]
	(f)	5.0	5.1	3.9	

Note: Between 421 and 471 men and between 74 and 83 women responded to each question on the survey.

[a]Data were not available

Source: DOD.

Vaccine Efficacy

Studies on the efficacy of anthrax vaccine have been limited to a study of the efficacy of the earlier vaccine for humans, and studies of the efficacy of the licensed vaccine for animals. 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. There has been no specific study of the efficacy of the licensed vaccine in humans. Rather, its efficacy in 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.

Beginning in the late 1980s, 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 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.[5]

Research using monkeys showed for the first time that monkeys could be protected against aerosol exposure.[6] 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. A variation in virulence among anthrax strains and a variation in relative resistance to vaccine-induced immunity have been observed in experiments on animals. However, the reasons for the variation have not been scientifically proven.

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 consistent quality. 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. DOD conducted inspections, however, and identified deficiencies during a March 1992 inspection, including the absence of stability studies.

[5]P.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.

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

FDA's subsequent inspections of the production facility in 1997 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 and those of a generic nature that could compromise the safety and efficacy of any or all batches. The facility received warning letters from FDA, including one in March 1997 stating its intent to revoke the facility's license. In 1998, the manufacturer closed its plant, which is now being renovated. DOD has directed that supplemental testing for purity, potency, sterility and safety be done on the lots approved by FDA before the current vaccination program began.

Effects of the Vaccine on Children and Pregnant and Lactating Women

The anthrax vaccine is not intended to be administered to children, pregnant or lactating women, and consequently no studies have been conducted to determine the specific effects of administering the anthrax vaccine to these groups. Before approving vaccines or drugs for marketing, FDA currently requires the submission of clinical data broken down by (among other things) gender and age. FDA then evaluates these data to determine efficacy and safety for specific subgroups of the general population. In addition, depending on FDA's assessment of clinical data, specific labeling requirements pertaining to potential effects on pregnant women, nursing mothers and pediatric use may also be required. However, the Division of Biologics, National Institutes of Health, which licensed the vaccine in 1970, did not require the submission of data broken down this way.

Mr. Chairman, this concludes my statement. I will be happy to answer any questions you may have.

Contacts and Acknowledgments

For future contacts regarding this testimony, please contact Kwai-Cheung Chan at (202) 512-3652. Individuals making key contributions to this testimony included Sushil K. Sharma, Jonathan R. Tumin, and Howard Deshong.

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