WRITTEN STATEMENT FOR THE RECORD

BY

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

COMMITTEE ON ARMED SERVICES

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INTRODUCTION

Mr. Chairman and Members of the Committee, thank you for the opportunity to submit a statement for the record. The statement of the Food and Drug Administration (FDA or the Agency) will describe vaccine licensing generally and specifically, the safety and efficacy of the anthrax vaccine, currently manufactured by BioPort Corporation. We will begin with a brief overview of the process for a vaccine to be licensed.

BACKGROUND

The Center for Biologics Evaluation and Research (CBER) is responsible for evaluating the safety, purity, efficacy and potency of the products we regulate. These products include biological products such as vaccines, products derived from

human blood, and many products produced by recent advances in biotechnology. The scope of regulatory responsibility extends to both licensed or approved products and unlicensed products under investigation.

From a regulatory perspective, there are four stages in vaccine development:

1) the pre-clinical stage (before the product is used in people);
2) the investigational new drug (IND) stage (where human use occurs under limited study conditions);
3) the license application stage for vaccines (where FDA reviews the results of the clinical studies and the manufacturing process); and
4) the post-licensure stage (following approval of the product for marketing).

Before a new vaccine can be studied in people, a sponsor must submit an IND application to FDA (sponsors may be individual physicians, a university, a hospital, or a commercial firm, as well as Government agencies, such as the Department of Defense or one of the Institutes of the National Institutes of Health [NIH]). In the application, the sponsor:

1) describes the composition, source, and method of manufacture of the product and the methods used in testing its safety, purity, and potency;
2) provides a summary of all laboratory and pre-clinical (animal testing) performed; and
3) provides a description of the proposed clinical study and the names and qualifications of each clinical investigator.

Once the sponsor submits the IND, FDA has 30 days to review the application to determine whether or not the study may proceed. FDA may prohibit a sponsor from conducting a study for a number of reasons, including when the study volunteers will be exposed to unwarranted risks, by putting the IND on "clinical hold".

The IND process generally is described as having three phases prior to product approval; however, the distinctions between these phases are not absolute. Phase I trials are focused on basic safety and, for vaccines, Phase I trials also usually evaluate the immune response elicited by the vaccine. These trials are usually small - generally between 20 and 100 subjects - and they frequently are done in healthy "normal volunteers" and may last just several months. Phase II

trials often include several hundred subjects, are often randomized, and last anywhere from several months to several years. These trials usually include individuals who are at high risk for the infectious disease of interest. Unless severe reactions or a lack of effectiveness surface during the first two Phases, the sponsor may decide to perform one or more Phase III studies that can include up to several thousands of people. These Phase III trials are intended to provide the definitive measure of effectiveness, as well as continue the evaluation of the product's safety. The size of the efficacy trial will be affected by the expected incidence of disease that the vaccine is intended to prevent. If at the end of Phase III trials the manufacturer believes there are adequate data to show the vaccine is safe and effective for its intended use, the manufacturer submits a license application to the Agency.

Licensing a new vaccine is only one stage of FDA's oversight of vaccine safety. Following issuance of the license, there is continued postmarketing surveillance of the product by monitoring adverse events, e.g., the Vaccine Adverse Events Reporting System (VAERS), and of the manufacturer's production activities, including compliance with good manufacturing practices. Manufacturers generally submit samples of each licensed vaccine lot and the results if their own tests for potency, safety, and sterility to the Agency

before release of each lot of the licensed product, because of the complex manufacturing processes for most biological products. In addition, licensed establishments are inspected regularly by FDA.

Let us now turn to anthrax.

ANTHRAX DISEASE

Anthrax is a highly infectious disease caused by spores of a bacterium known as *Bacillus anthracis.* These spores resist destruction and may be present in the soil for decades, occasionally infecting grazing animals that ingest the spores. Goats, sheep and cattle are examples of animals that may become infected. Human infection may occur by three routes of exposure to anthrax spores: cutaneous, gastrointestinal, and pulmonary (inhalation). Skin contact with live infected animals, or with the hide, hair or bones of an infected animal may lead to infection of a person's skin, known as cutaneous anthrax infection. This is the most common manifestation of anthrax in humans, accounting for more than 95 percent of cases. Untreated cutaneous anthrax infection is associated with a death rate estimated to be

approximately 20 percent. Eating undercooked or raw, infected meat can cause gastrointestinal anthrax infection. Breathing in airborne spores may lead to inhalation anthrax. Experience has shown that inhalation anthrax has a very high mortality rate, with estimates ranging from 80 percent to 90 percent or higher.

Inhalation anthrax infection has two phases. During the first phase, which occurs within one to five days after inhalation of the spores, the patient has influenza-like symptoms, such as a cough, malaise, fatigue and mild fever. Several days later these symptoms may subside, but are rapidly followed by the second, more severe stage of disease. During the second phase, the patient experiences sudden onset of severe respiratory distress, and sometimes chest pain accompanied by fever. Chest x-rays may show fluid in the lung. Within a day, septic shock and death will likely occur. Treatment of cutaneous anthrax infection involves administration of antibiotics. In the case of pulmonary anthrax infection, therapy has been of limited benefit, except when given immediately after exposure. Prior to use of the anthrax vaccine, cases of human anthrax infection in

the United States were much more prevalent.

The only known effective prevention against anthrax is the anthrax vaccine. According to data from the Centers for Disease Control and Prevention (CDC), there were approximately 130 reported cases of anthrax infection per year at the start of this century. In the past decade, there have been no confirmed reports of human anthrax in the United States. It is difficult to assess exactly how much of this dramatic reduction is due to the vaccine, but immunization with the anthrax vaccine of people at risk, along with vaccination of animals against anthrax, have likely contributed to this favorable decline. Elsewhere in the world, human anthrax cases continue to be reported, especially in countries with predominately agricultural economies.

HISTORY OF THE ANTHRAX VACCINE

Philip S. Brachman et al. conducted clinical trials on the anthrax vaccine during the 1950s. This controlled field study involved workers in four mills in the Northeastern United States that processed imported animal hides. This selected population was at risk because the mill workers routinely handled anthrax-infected animal materials. Prior to vaccination, the yearly average number of human anthrax

infection was 1.2 cases per 100 employees in these mills.

For this trial, employees who had not previously contracted anthrax were selected and divided into two groups. The groups were balanced with regard to their age, length of employment, department at the mill, and the particular job they performed. The trial was a single-blinded study, in which the participants were not told whether they received the vaccine or placebo. Individuals who did not participate in the controlled study (because they were ineligible [i.e., had a history of prior anthrax] or chose not to receive the injections) were also monitored for anthrax. These individuals who did not receive vaccine or placebo were referred to as the observational group.

During the trial, 26 cases of anthrax infection were reported at the mills - five inhalation and 21 cutaneous. Of the five inhalation cases, two individuals had received the placebo, while three individuals were in the observational group. Four of the five people who developed inhalation anthrax died. No cases of inhalation anthrax occurred in anthrax vaccine recipients. Of the 21 cutaneous cases, 15 individuals had received the placebo, three individuals were in the observational group, two individuals were partially immunized and one individual was fully immunized. Based upon

a comparison between the populations completely vaccinated versus the populations receiving placebo, the authors calculated a vaccine efficacy level of 92.5 percent.

On April 14, 1966, CDC submitted an IND for the anthrax vaccine to the Division of Biologics Standards, which was then part of NIH, later transferred to FDA. The method of preparing this vaccine was similar, but not identical, to the vaccine used in the Brachman et al. study. The vaccines in both studies were based on the immunity induced by the protective antigen (PA). Persons receiving the vaccine made by the two different methods demonstrated similar peak immune responses (antibody concentration) following the initial three doses. Textile employees and laboratory workers were immunized under this IND. A number of lots of investigational vaccine used by CDC under this IND were manufactured by the Michigan Department Public Health (MDPH), the original manufacturer of the anthrax vaccine, which eventually became known as BioPort.

The data submitted to the Division of Biologic Standards described CDC’s experience with approximately 16,000 doses of anthrax. This vaccine was administered to approximately 7,000 study participants. Reported local reactions at the immunization site ranged between three percent to 36 percent

of the initial series of doses, and three percent to 33 percent of the booster doses, depending on the lot. Reported mild reactions were three percent to 20 percent of all doses. Reported moderate local reactions were one percent to three percent of doses. Severe reactions were reported for less than one percent of doses. Systemic reactions were reported in four cases during the five-year reporting period. These reactions included fever, chills, nausea and general body aches, and were reported to have been transient.

The Division of Biologics Standards determined that the data submitted by CDC supported licensure of the vaccine. On November 10, 1970, the Division of Biologics Standards issued a product license to MDPH to manufacture anthrax vaccine.

Approved labeling for the anthrax vaccine states that immunization with this product is recommended for individuals who may come in contact with animal products that may be contaminated with *Bacillus anthracis* spores, and for individuals engaged in diagnostic or investigational activities which may bring them in contact with *Bacillus anthracis* spores. It is also recommended for persons at high risk, such as veterinarians and others handling potentially infected animals.

The approved labeling also states that anthrax vaccine is to

be administered subcutaneously (injected under the skin). After the initial dose of 0.5ml, further doses of 0.5ml are administered at two weeks, four weeks, six months, 12 months and 18 months, thereafter, with yearly boosters.

THE PANEL REVIEW

The Public Health Service Act, under which biologics such as vaccines were licensed, required evidence of safety, purity and potency. After the Division of Biologic Standards was transferred from NIH to FDA, expert panels were assigned to review information on biological products, including vaccines that had been on the market prior to the transfer. The review was initiated in order to verify whether existing data supported the safety and efficacy of marketed biological products.

Biological products were divided into one of six categories. FDA assigned responsibility for initial review and

recommendation for all products in these six categories to separate independent advisory panels of outside scientific experts, collectively known as the Advisory Review Panel. The Advisory Review Panel also was charged with advising FDA, in the form of a report, on classification of these products into one of the following categories: Category I - safe, effective and not misbranded; Category II - unsafe, ineffective or misbranded; Category III - insufficient information, further testing required.

Based upon their review of available data, the Advisory Review Panel recommended that the anthrax vaccine manufactured by MDPH be classified as a Category I product and that appropriate licenses be continued based upon substantial evidence of safety and effectiveness of this product. The safety data from the CDC trials and the efficacy data from the Brachman et al. trials were the basis for these findings. These findings were published in the Federal Register on December 13, 1985.

Today, it would be difficult to repeat the efficacy studies. This is because there are no evident populations in the United States where prophylactic vaccine protection against natural exposure to anthrax could be evaluated in a clinical field trial, such as was done in the Brachman et al. study.

Specifically, the incidence of naturally occurring anthrax in humans is low and sporadic in occurrence, making identification of a trial target population difficult. Likewise, it would be unethical to perform challenge/protection studies in humans. In addition, human immunogenicity and safety data would be required. The safety database obtained by CDC under the IND would be considered a reasonable pre-licensure database for evaluating a safety study today.

POST-MARKETING EXPERIENCE

Since licensure in November 1970, livestock workers, veterinarians, lab workers and researchers who are at risk for infection have used the anthrax vaccine. The manufacturer provided FDA the following information regarding distribution. From 1974 to 1989, approximately 68,000 doses were distributed. In 1990, approximately 268,000 doses were distributed. Between 1991 and April 1999, we understand that approximately 1,200,000 doses were distributed.

It is not possible to give a precise number of persons who received the vaccine prior to use in Operation Desert Shield and Operation Desert Storm. We estimate that approximately

7,000 subjects received approximately 16,000 doses of the vaccine during clinical trials conducted by CDC. In addition, between 1974 and 1989, our files show approximately 68,000 doses were distributed. This is sufficient to vaccinate about 11,000 people with the full six-dose regimen of the currently approved anthrax vaccine. It is possible that some doses distributed were not used, or that some individuals did not receive the full course of the vaccine or that some doses were used for annual boosters. Thus, it is

not possible to accurately report the precise number of people vaccinated between 1974 and 1989.

According to CDC, from 1962 to 1974, 27 cases of anthrax occurred in the “at-risk” populations in the United States. Of those, 24 cases occurred in unvaccinated individuals, one case after the person had been partially immunized with one dose of the vaccine and two cases after individuals had been partially immunized with two doses of the vaccine. No documented cases of anthrax were reported for individuals who had received the recommended six doses of the vaccine.

VACCINE ADVERSE EVENT REPORTING (VAERS)- ANTHRAX

With regard to safety data, FDA and CDC jointly operate the VAERS. FDA uses this system to track adverse events possibly associated with licensed vaccines. Reporting of adverse events associated with the use of anthrax vaccine is voluntary for individual healthcare providers. The vaccine manufacturer, however, must report to FDA all reports of adverse events of which they are aware.

The report of an adverse event to VAERS is not documentation that a vaccine caused the event, only that the event occurred soon after the vaccine was administered. Doctors and other healthcare providers are encouraged to report serious or unexpected adverse events following vaccination, whether or not they believe that the vaccination was the cause of the adverse event. Since it is difficult to distinguish a coincidental event from one truly caused by a vaccine, the VAERS database contains events of both types.

It should be emphasized that adverse event reports can be made by a healthcare professional, a patient or anybody else. If a patient’s physician does not file a VAERS report, the patient can do so. FDA encourages individuals to report to VAERS any clinically significant adverse event occurring after the administration of any vaccine licensed in the

United States. Reports to VAERS may be made in writing or by calling a toll-free number, 1-800-822-7967. Reporting instructions are available on the Internet at www.fda.gov/cber/vaers.html.

While the data gathered from the VAERS system can serve as a useful tool in identifying potential problems, the reports on anthrax vaccine received thus far do not raise any specific concerns about the safety of the vaccine. As more people receive the vaccine, the numbers of adverse events reported will increase. FDA continues to view the anthrax vaccine as safe and effective for individuals at risk of exposure to anthrax.

LOT RELEASE

As mentioned above, because of the complex manufacturing processes for most biological products, each product lot undergoes thorough testing for purity, potency, identity, and sterility. The anthrax vaccine is subject to lot release. FDA reviews the lot release protocols showing results of applicable tests and lot samples are submitted for possible testing by FDA. The manufacturer may not distribute a lot of the product until CBER releases it. The lot release program

is part of our multi-part strategy that helps assure product safety by providing a quality control check on product specifications.

FDA’s CONSULTATION WITH THE DEPARTMENT OF DEFENSE (DOD) REGARDING THE ANTHRAX VACCINE IMMUNIZATION PROGRAM

FDA has not had an official role in the development or operation of the Department of Defense’s Anthrax Vaccine Immunization Program (AVIP), including the AVIP tracking system or the program’s adverse event reporting system. In March 1997, DOD briefed FDA about their draft plan for the possible use of the anthrax vaccine to inoculate United States military personnel according to FDA approved labeling for six doses administered on a specified schedule over eighteen months. Subsequently, FDA learned that the DOD plan had been adopted.

In July 1998, DOD requested that CDC, in conjunction with the

Health Resources and Services Administration, National Vaccine Injury Compensation Program (VICP), organize and coordinate a program to evaluate VAERS reports for the anthrax vaccine. In response to the request by DOD, a group of non-government medical experts was convened by the VICP in the fall of 1998 as the Anthrax Vaccine Expert Committee (AVEC). These experts have been reviewing all VAERS reports for the anthrax vaccine. Representatives of VICP, FDA, CDC and DOD have attended meetings, and FDA has provided information to assist the committee in its deliberations. AVEC is unique in that it provides an independent civilian expert assessment of adverse events reported for the anthrax vaccine.

CONCLUSION

Mr. Chairman, we believe the anthrax vaccine is a safe and effective vaccine for the prevention of anthrax disease - an often-fatal disease - when used according to FDA approved label. Our confidence in this vaccine, like all vaccines, is based upon four components: first - the review of manufacturing and clinical trials and subsequent clinical laboratory experience with the vaccine; second - ongoing inspections of the manufacturing facility; third - our lot release requirements; and fourth - our ongoing collection and

analysis of adverse event reports. So far, the data gathered from VAERS reports on anthrax vaccine do not signal concerns about the safety of the vaccine. The Agency will continue to closely monitor and investigate reports of serious adverse events received on all vaccines, including anthrax, to assure that only safe products are on the market.

We appreciate the Committee’s interest in this very important topic.