STATEMENT

OF

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INTRODUCTION

Mr. Chairman and Members of the Committee, I am Kathryn Zoon, Ph.D., Director, Center for Biologics Evaluation and Review (CBER), Food and Drug Administration (FDA or the Agency). I appreciate the Committee's interest in the anthrax vaccine and the opportunity for FDA to explain our role in the pre-market review and post-market surveillance of regulated products, and more specifically explain our role with respect to the regulation of the Anthrax Vaccine, Adsorbed. In a previous written statement submitted to this Committee on April 13, 2000, we provided a background on anthrax disease, the licensing process for vaccines, and a general explanation of the stages of clinical trials. Let me assure you, as I did in the previous written statement, that we will continue to help ensure that only safe and effective products are marketed and that these products meet high standards of quality in the manufacturing process.

FDA's responsibilities can be divided into pre-approval activities and post-approval activities. With respect to the former, we must help assure that clinical trials are conducted with the utmost regard for protection of human subjects.

Clinical trials conducted under investigational new drug applications (IND) must be properly designed to ensure the safety of human subjects and to generate meaningful safety and efficacy data used as the basis of FDA's decision on whether to allow product marketing. Products also must be manufactured under conditions that help assure that biologics are safe, pure and potent. FDA makes these determinations during the review of product applications and through on-site inspections.

Once FDA approves a product, we continue to monitor that marketed product to help assure continued safety and effectiveness. For vaccines, this is accomplished though ongoing review of adverse events reported though the Vaccine Adverse Event Reporting System (VAERS), routine inspections and other post-marketing activities. FDA performs routine inspections to verify that manufacturers are following current good manufacturing practices (GMPs) and may perform targeted inspections when there are changes to the manufacturing processes, facility or equipment.

These pre- and post-licensure activities, as they relate to Anthrax Vaccine, Adsorbed and BioPort Corporation (BioPort), are described below.

CLINICAL TRIALS / ANTHRAX VACCINE

The clinical trials on the anthrax vaccine were conducted by Philip S. Brachman et al. during the 1950's[1] and the Centers for Disease Control (CDC) in the 1960's. The controlled field study by Philip S. Brachman et al. involved workers in four textile 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, where 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) also were

[1] Philip S. Brachman, M.D., Herman Gold, M.D., Stanley A. Plotkin, M.D., F. Robert Fekety, M.D., Milton Werrin, D.V.M., F.A.P.H.A., and Norman Ingraham, M.D., F.A.P.H.A., Field Evaluation of a Human Anthrax Vaccine, AJPH Vol. 52,632-645, 1962.

monitored for anthrax. These individuals 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 anthrax vaccine to the Division of Biologics Standards, which was then part of the National Institutes of Health (NIH) and later transferred to FDA (now CBER). Textile employees and laboratory workers were immunized under this IND. 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. Persons receiving the vaccine made by the two different methods demonstrated similar peak immune responses (antibody concentration) following the initial three doses. A number of lots of investigational vaccine used by CDC under this IND were manufactured by the Michigan Department of Public Health (MDPH), now manufactured by BioPort.

The data submitted to the Division of Biologic Standards described CDC's experience with approximately 16,000 doses of anthrax vaccine from four lots manufactured at MDPH. These MDPH lots were administered to approximately 7,000 study participants. 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.

There are also relevant non-human primate efficacy data. Previously, data had been provided to FDA indicating that anthrax vaccine protects non-human primates against a high challenge dose of inhalation anthrax with the Ames Strain (which is non-homologous, or dissimilar, to the vaccine strain). More recent data on animal efficacy was published in summary form by Arthur Friedlander, M.D, et al. in the Journal of the American Medical Association on December 8, 1999. This publication noted that non-human primates had a high level of protection against two more non-homologous strains, in addition to the Ames Strain. All three of these strains have been considered by some to be "vaccine resistant." The Department of Defense (DoD) has committed to submit the new data to FDA under an existing IND.

THE PANEL REVIEW

The Public Health Service Act (PHS), under which biologicals such as vaccines are licensed, requires 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. This external 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 perform an efficacy study because there are no evident populations 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 this regard, an FDA proposed rule was published in the Federal Register that would allow the use of animal data to provide efficacy data to support FDA approval when scientifically reasonable (Proposed Rule: New Drug and Biological Drug Products; Evidence Needed to Demonstrate Efficacy of New Drugs for Use Against Lethal of Permanently Disabling Toxic Substances When Efficacy Studies in Humans

Ethically Cannot Be Conducted, Federal Register Volume 64 53960-70, 1999). Under this proposed rule, human immunogenicity and safety data would still be required. Comments on this proposed rule are under review by FDA.

INSPECTIONS

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, FDA is charged with, among other things, helping to assure that drugs marketed in the United States are safe and effective, and are manufactured in accordance with GMPs. The FD&C Act applies to any human drug for which marketing is sought or which currently is marketed. FDA also is responsible for implementing the provisions of the PHS Act applicable to biological products including vaccines.

FDA conducts “pre-approval inspections” for drugs or “pre-license inspections” for biologics of manufacturing facilities prior to product approval or licensure, and conducts “surveillance inspections” or “GMP inspections” periodically after approval or licensure. For domestic drug manufacturers, the FD&C Act requires registration and surveillance inspections. Inspections may also be performed prior to approval of

supplements for major manufacturing changes, on a “for-cause” basis or as part of our bioresearch-monitoring program.

SURVEILLANCE OR GMP INSPECTIONS

Licensed vaccines are regulated under both the FD&C Act and the PHS Act. Vaccines meet the definition of a drug under the FD&C Act, and, therefore, must be manufactured in accordance with the GMP regulations in Title 21, Code of Federal Regulations (CFR) Parts 210 and 211. As vaccines are also biologics, manufacturers must also comply with applicable regulations in 21 CFR Parts 600 through 680.

Surveillance inspections, also known as GMP inspections, are generally performed every two years and are more comprehensive in nature, in that multiple products and processes are covered. Once a product is approved or licensed by FDA, ongoing surveillance is needed to determine if the product continues to be manufactured in the manner approved in the application. Surveillance inspections focus on licensed products, as opposed to unlicensed products. In the case of vaccines, one or more of a specialized cadre of FDA’s Office of Regulatory Affairs investigators and CBER’s product specialists known collectively as “Team Biologics” perform these inspections. Team Biologics

assumed responsibility for surveillance inspections of vaccines as of October 1, 1999.

The possible outcomes of a surveillance inspection can be much different than a pre-approval inspection. If FDA discovers manufacturing deficiencies while conducting a pre-approval inspection, a possible outcome is that the application or manufacturing supplement may not be approved. If FDA conducts a surveillance inspection and finds deficiencies in the manufacture of products that are currently being marketed, there is a whole range of potential regulatory actions that may occur. These actions include issuing a warning letter or a notice of intent to revoke a license, suspending or revoking a license, filing an injunction against the firm or seizure of product.

There is currently only one FDA-licensed facility for the production of the anthrax vaccine. The MDPH originally operated the facility. In 1996, the facility became known as the Michigan Biologics Products Institute (MBPI), an entity controlled by the State Government of Michigan. Currently, the facility is operated by BioPort based upon the September 1998, transfer of ownership by MPBI to BioPort. In addition to manufacturing Anthrax Vaccine, Adsorbed, the facility is licensed to manufacture blood derivatives and other vaccines.

FDA has inspected this facility on many occasions during the past decade, identifying a number of deficiencies requiring correction. In particular, FDA conducted a surveillance inspection of MBPI in November 1996. During that inspection, FDA investigators documented numerous significant deviations from the FD&C Act, FDA's regulations and the standards in MBPI's license. Based upon the documented deviations, FDA issued a Notice of Intent to Revoke (NOIR) letter to MBPI in March 1997. The NOIR letter did not mandate the closure of the facility or lead to seizure of finished product. The letter, however, did state that if MBPI's corrective actions proved to be inadequate, the facility would run the risk of license revocation.

MBPI responded to the NOIR with a "Strategic Plan for Compliance" presented to FDA in April 1997. This plan called for the periodic submission of data to FDA that would serve as evidence of MBPI's progress towards achieving compliance with FDA's regulations. Under the plan, FDA would review this data and then monitor MBPI's progress through follow-up inspections. In February 1998, FDA conducted a follow-up inspection of the MBPI facility to evaluate MBPI's compliance with its strategic plan. It should be noted that this inspection and the November 1996 inspection included blood product and vaccine product

facilities in addition to the anthrax vaccine production facility.

The February 1998 inspection disclosed significant deviations from FDA's regulations. These deviations included, but were not limited to, those related to the manufacture of the anthrax vaccine. In addition, the inspection resulted in a request by FDA that MBPI quarantine 11 lots of anthrax vaccine held in storage, pending review of additional information to be submitted by MBPI (at the time the request was made) regarding the lack of investigations into possible problems with potency, sterility and particulate matter. FDA continues to work closely with BioPort to resolve issues concerning the use of these lots. If satisfactory resolution is not obtained, BioPort has stated that the lots will be rejected. FDA also noted that MBPI had made progress in achieving its compliance goals, but additional work remains in order to correct the deviations related to the manufacture of the anthrax vaccine. Pursuant to its purchase of the MBPI facility in September 1998, BioPort agreed to abide by the strategic plan and other commitments for corrective actions made by the management of MBPI. It should be noted that MBPI temporarily halted production of anthrax vaccine sublots in January 1998, prior to the sale to BioPort, to begin a

comprehensive renovation of the anthrax production facilities. Although there has been a resumption of manufacturing in order to produce lots in support of the license application supplement to include the renovated facility, no lots of anthrax vaccine manufactured in the renovated facility have been released.

In its most recent GMP inspection of BioPort in October 1998, FDA found continuing improvement. FDA believes that the previously manufactured and CBER released products not presently quarantined by BioPort are safe and effective for the labeled indications. FDA found that the firm had made progress toward meeting objectives under its strategic plan in bringing the facility into full compliance. Based on BioPort's progress to date, FDA is hopeful that the company will continue to demonstrate improvement. We will continue to work closely with BioPort to ensure that the goals outlined in their strategic plan are met.

PRE-APPROVAL INSPECTIONS

When a sponsor submits an application or manufacturing supplement to FDA, the Agency sets an internal review goal to complete the review that may be determined by statute or by goals established in conjunction with the Prescription Drug User

Fee Act (PDUFA). The period between the receipt of the submission and the final decision by the Agency is called the review cycle. The team of FDA reviewers, which may include a medical officer, microbiologist, statistician, biologist, chemist, and other specialties, examines the clinical, chemistry, and manufacturing controls data along with other data submitted by the sponsor. The review team may decide to request the initiation of a pre-approval or pre-license inspection depending on whether the application meets certain criteria. For biological products, these inspections are performed by CBER staff serve to help ensure compliance with current GMPs; verify or clarify information in the marketing application; possibly observe the actual manufacturing of products; and/or, evaluate the manufacturer's ability to produce a product that meets FDA standards of quality. The inspector, or the team of inspectors, conducting the pre-approval or pre-license inspection, typically focuses on the processes that are specific to the application or manufacturing supplement under review, although there is not always such a clear distinction, given that the same facility, personnel, equipment and procedures may be used to manufacture many products. In some instances there are facilities dedicated to the manufacture of only one product.

When conducting an inspection, the FDA inspector or team typically covers a number of areas including: manufacturing; training; product testing; support systems; and, records. After obtaining a general overview of the facility and operations, the FDA inspector then focuses on problem areas. The scope of the inspection depends on the nature of the inspection and the problems encountered. At the conclusion of the inspection, the FDA inspector issues a Form FDA-483, or Inspectional Observations, which is a list of significant items observed or that pose a potential problem as noted during inspection. The firm may, if it chooses, immediately start implementing corrections in response to the observations noted by the inspector.

Upon implementing the corrective actions, the firm may notify FDA, typically though a letter to their application that it believes that adequate corrections have been achieved. FDA reviewers will determine whether the firm’s corrective actions are adequate. Prior to the end of the review cycle, if the corrective actions pertaining to the manufacturing issues are found to be adequate, and any other information (such as clinical data or statistical data) associated with the submission is found to be adequate, then the application or supplement may be approved.

If the corrective actions appear to be inadequate or have not been implemented prior to the end of the review cycle, or if FDA determines that a follow-up inspection is necessary to verify the corrective actions, FDA will send a complete response letter to the sponsor which means that the application is not approved. If FDA sends such a letter, it is important to understand that FDA's review of an application is a continuing process and the sponsor has the opportunity to once again attempt to correct the manufacturing deviations and any other deficiencies found in the application. The sponsor, again, may submit information to FDA to start another review cycle. The FDA team may review the amended application or supplement and initiate a follow-up inspection if necessary. It is possible that the application may be approved during a subsequent review cycle.

Due to the rules of confidentiality, the FDA can not generally disclose details of, or even acknowledge the existence of, a pending application unless that information has already become public. In the case of BioPort, press reports and information made public by BioPort has disclosed various aspects of the anthrax vaccine. Because the information has been made public, we can disclose that BioPort does have a pending supplement for renovations to their anthrax vaccine manufacturing facility.

Renovations are assessed by review of a prior approval supplement and by performing a pre-approval inspection.

In order to examine the manner, in which BioPort implemented the renovations to the manufacturing facility, FDA conducted an inspection from November 15 through November 23, 1999. At the conclusion of the inspection, BioPort received a Form FDA 483 with observations and possible deviations in some of the following areas: validation, failure to investigate, deviation reporting, aseptic processing, filling operations, standard operating procedures, stability testing, and environmental monitoring. All observations must be addressed adequately before FDA will approve this supplement.

POST-MARKETING ACTIVITIES

LOT RELEASE

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. Before a lot of anthrax vaccine can be used, the manufacturer must submit a sample of the vaccine lot and a lot release protocol to the Agency. The lot release documents contain the results of the manufacturer's

tests for potency, safety, sterility and any additional assays mandated by their license and a summary of relevant manufacturing details. FDA reviews the manufacturing and testing information provided in the lot release protocol and may elect to perform confirmatory testing on submitted samples. The manufacturer may not distribute a lot of the product until CBER releases it. The lot release program is one component of FDA's multi-part strategy that helps assure product quality.

VACCINE ADVERSE EVENT REPORTING SYSTEM

Following issuance of an approved license, there is continued post-marketing surveillance of the product by monitoring adverse events, e.g., VAERS. It should be emphasized that it is not always possible to attribute a cause and effect relationship between a reported event and a vaccination. Since the beginning of VAERS operations in 1990, through June 30, 2000, 1404 reports of adverse events associated with use of the anthrax vaccine have been reported to VAERS. FDA understands that from 1990 to present, approximately 2,000,000 doses of the vaccine were distributed.

Of those reports, 73 are considered serious events, which are events considered either fatal, life threatening, or resulting

in hospitalization or permanent disability. These reports are for diverse conditions, such as hospitalization for severe injection-site reaction, Guillain-Barré syndrome, widespread allergic reaction, aseptic meningitis and multi-focal inflammatory demyelinating disease. There are no clear patterns emerging at this time. The remaining reports describe a variety of symptoms, including injection site hypersensitivity, injection site edema (swelling with fluid in tissue), injection site pain, headache, joint pain and pruritus (itching).

None of these events, except for the injection site reactions, can be attributed to the vaccine with a high level of confidence, nor can contribution of the vaccine to the event reported be entirely ruled out. With the exception of injection site reactions, all of the adverse events noted above occur in the absence of immunization.

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. With all vaccines, as the number of people that receive the vaccine increases, so will the number of adverse events reported to FDA. Thus, our knowledge of the vaccine will grow accordingly. FDA continues

to view the anthrax vaccine as safe and effective for individuals at high risk of exposure to anthrax, when used in accordance with the approved labeling.

THE ANTHRAX VACCINE IMMUNIZATION PROGRAM OF DoD

FDA did not have an official role in the development or operation of the DoD's Anthrax Vaccine Immunization Program, 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 U.S. military personnel according to the FDA-approved labeling for six doses administered on a specified schedule over 18 months. Subsequently, FDA learned that DoD had formally adopted this plan.

In July 1998, DoD requested that the Department of Health and Human Services (DHHS) 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 DHHS in the fall of 1998 as the Anthrax Vaccine Expert Committee (AVEC). AVEC has met approximately every three to six weeks since fall of 1998. 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.

Upon learning last year that some DoD personnel reported they had been told that they were fully protected against anthrax after receiving three doses of the anthrax vaccine, both Jane E. Henney, M.D., Commissioner of Food and Drugs, and I, sent letters to DoD. In the letters we asked DoD to expeditiously investigate this matter as we are unaware of any data demonstrating that any deviation from the approved schedule found in the approved labeling will provide protection from anthrax infection.

CONCLUSION

We appreciate the Committee's interest in the Anthrax Vaccine, Adsorbed and BioPort. Please let me assure you that FDA appreciates the unique situation that DoD's anthrax vaccine immunization program presents to all of the individuals and organizations involved. We continue to believe that the vaccine is safe and effective protection for those individuals at high

risk for exposure. We will continue to work with BioPort, as we would with any manufacturer, in an appropriate manner to resolve all situations involving pending submissions and inspectional issues. By manufacturing products in a facility that is operating in a full state of GMP compliance, we can help assure that any product that is released by the company is safe and effective.