DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV 26 1999

The Honorable Dan Burton
House of Representatives
Washington, D.C. **20015**

Dear Mr. Burton:

Thank you for your interest in the anthrax vaccine. This is in response to your letter dated November 3, 1999, co-signed by three of your colleagues, to Dr. Jane E. Henney, Commissioner of the Food and Drug Administration (FDA or the Agency). You raised a number of issues related to the pending license supplement application of BioPort Corporation to produce the anthrax vaccine. Ms. Jarilyn Dupont of my staff has had several conversations with Mr. John Weaver of your staff, on November 12 and November 17, 1999, concerning the status of this response. As was explained to Mr. Weaver, the response provided below is based on information available under the Freedom of Information Act (FOIA) and FDA implementing regulations.

Inspections

As you know, BioPort Corporation, (previously known as Michigan Department of Public Health or Michigan Biologics Products Institute), holds a license to manufacture Anthrax Vaccine Adsorbed. FDA has inspected this facility on many occasions during the past decade, identifying a number of deficiencies requiring correction. Your statement that the anthrax vaccine-specific portion of the manufacturing facility was not physically inspected in 23 years is not accurate. A review of inspection reports from 1972 to 1998 shows that Anthrax Vaccine Adsorbed was covered as part of the inspection on 12 separate occasions either by record review, observation of manufacturing areas or interviews with engineering and manufacturing staff. This information was contained in the written testimony of Dr. Kathryn C. Zoon, Director, Center for Biologics Evaluation and Research (CBER), before the Committee on Government Reform, Subcommittee on National Security, Veterans Affairs and International Relations, on April 29, 1999. In response to Members' questions, Dr. Zoon also stated that FDA did conduct inspections for the anthrax vaccine prior to 1996.

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Product Testing and Specifications

FDA agrees that products must be consistently manufactured to meet specifications prior to product approval. FDA review does include product characterization. Because of the complex manufacturing process for most biological products, each lot of the product undergoes thorough testing for purity, potency, and sterility. Manufacturers may release lots of product only after testing is documented. FDA may require lot samples and protocols showing results of applicable tests to be submitted for review and possible testing by the Agency. The anthrax vaccine manufactured by BioPort is subject to lot release, under which a manufacturer may not distribute a lot of product until CBER releases it. The lot release program is part of FDA's multi-part strategy that helps assure biological product safety by providing a quality control check on product specifications.

Anthrax Vaccine Adsorbed Indications

Dr. Zoon's testimony before the Committee on Government Reform on October 12, 1999, stated that the indication is based on risk. She did not state that the anthrax vaccine is indicated only for individuals at risk for cutaneous exposure to anthrax, nor that the use is for a "limited" population. The labeling for the anthrax vaccine product is enclosed. The labeling for Anthrax Vaccine Adsorbed does not mention route of exposure (e.g., cutaneous), per se. Use of the vaccine for protection against both cutaneous and inhalation anthrax exposure is not inconsistent with the labeling for Anthrax Vaccine Absorbed.

The term "paucity of data," used in the 1997, letter to Dr. Stephen Joseph, then Assistant Secretary of Defense for Health Affairs, from Dr. Michael A. Friedman, then FDA Lead Deputy Commissioner, is used to describe the relatively few reported cases of inhalation anthrax in the efficacy trial. Requiring the anthrax vaccine to be returned to an investigational new drug (IND) status will not generate more human efficacy data, as inhalation anthrax in humans is not amenable to study, due to the low incidence and sporadic occurrence of disease in natural settings. It should be noted that in the United States, in this century, only 18 human cases of inhalation anthrax have been reported (Brachman, P.S. Inhalation anthrax. *Ann N Y Acad Sci* 353:83-93, 1980). This low incidence of naturally occurring inhalation anthrax since introduction of the vaccine makes it impossible to duplicate the findings in the Brachman and the Centers for Disease Control and Prevention (CDC) surveillance data of the 1950's to early 1970's. In the past several years, the Department of Defense (DOD)

In the past several years, the Department of Defense (DOD) has concluded that the threat of biological attack is great enough that troops should be considered part of the high-risk population for which this vaccine is an appropriate prophylactic measure. (This information was provided to Chairman Dan Burton, in a response to an August 11, 1999, letter seeking information on vaccines.) You may wish to contact DOD to discuss its risk assessment.

There is presently no basis for concluding that the anthrax vaccine, a licensed product, when used in accordance with current labeling, should be used pursuant to an IND application or, as requested in your letter, that FDA "place the anthrax vaccine back under IND status."

Data to Support **Indications and Administration Schedule**

There is a misperception that no clinical or scientific studies have been conducted to support the current Anthrax Vaccine Adsorbed-dosing schedule. The currently licensed anthrax vaccine administration schedule was used in the Brachman efficacy trial and CDC IND.

The Brachman et al. trial was used to support the licensure of the anthrax vaccine. This trial was a single-blinded, well-controlled trial conducted in four United States textile mills processing imported goat hair with an 'exposed, susceptible, supervised population." The average incidence of anthrax prior to the study was 1.2 cases per 100 employees per year. The dose administration schedule was the same as the currently licensed vaccine dose administration schedule: 0, 2 and 4 weeks; 6, 12, and 18 months, followed thereafter by annual boosters. Of the 1,249 mill workers, 909 individuals participated in the controlled part of the study. Individuals who received neither vaccine nor placebo served as an unvaccinated observational control. A total of 26 anthrax **cases** occurred during the trial: 21 cutaneous cases and five inhalation cases (four fatal). Of these 26 cases, three (all cutaneous) occurred in anthrax vaccine recipients. One **case** occurred after two doses, one case occurred 13 months after the third dose (fourth dose not given), and one case occurred five months after the third dose. Five cases of inhalation anthrax occurred at one site (the Manchester, New Hampshire goat hair processing plant) during the trial. Two of the inhalation cases were in the placebo group and three inhalation cases were in the unvaccinated group. **No cases of *inhalation anthrax occurred in anthrax vaccine recipients.***

The efficacy level of 92.5 percent, as presented in the major publication of the efficacy trial (Brachman, et. al., 1962 Field evaluation of a human anthrax vaccine. *Am J* Public Health. 52:632-645) includes anthrax cases in the vaccine and placebo groups and is not limited to cutaneous anthrax cases. The efficacy of the anthrax vaccine in this study was calculated to be 92.5 percent. This calculation (92.5 percent) is sometimes erroneously presented as the vaccine efficacy against cutaneous anthrax.

Following the 1957 trial and the five cases of inhalation anthrax in placebo and unvaccinated individuals, the Manchester, New Hampshire goat hair processing plant vaccinated all employees against anthrax (starting in December 1957). The case rate in this plant fell from 8.2 cases per year prior to 1957 to 0.4 cases per year from December 1957 to June 1966, the latter consisting of four cutaneous cases. In July 1966, an employee (unvaccinated) of an adjacent facility (metal fabricator shop) died from inhalation anthrax. The source of the agent was thought to be the adjacent goat hair processing plant. In a follow-up investigation by CDC (January 30 - February 6, 1967), environmental sampling of both facilities identified *B. anthracis* inhalation anthrax (LaForce FM et al.: Epidemiologic study of a fatal case of inhalation anthrax. *Arch* Environ Health 18:798-*805,* 1969).

Under CDC IND, approximately 16,000 doses of the vaccine were administered to approximately 7,000 study participants who were at risk for anthrax. These doses were administered according to the same six-dose schedule that is the approved dosing schedule today.

Furthermore, in CDC surveillance data (1962-1974), 27 cases of anthrax occurred in 'at-risk" industrial settings: *24* cases in unvaccinated individuals, one case after one dose of vaccine and two cases after two doses of vaccine. No cases of anthrax were reported in individuals who received all six doses of anthrax vaccine.

It is interesting to note that CDC publication, *Biosafety in Microbiological and Biomedical Laboratories 4th Edition* (1999), states that laboratory associated cases of anthrax have not been reported in the United States since the late 1950s when the human anthrax vaccine was introduced. Before that date, numerous cases of laboratory associated anthrax, occurring primarily at facilities conducting anthrax research, were reported.

Additional Findings Supporting Anthrax Vaccine Adsorbed

The Public Health Service Act, under which biologicals such as vaccines were licensed in 1970, requires evidence of safety, purity and potency. After the Division of Biologic Standards was transferred from the National Institutes of Health to FDA, expert panels were assigned to review information on biological products, including vaccines that had been licensed prior to the transfer. The review was initiated in order to assess the safety, effectiveness and labeling of products licensed prior to July 1, 1972. Based upon their review of available data, the Advisory Review Panel recommended that marketing of Anthrax Vaccine Adsorbed manufactured by Michigan Department of Public Health be allowed to continue based upon substantial evidence of safety and effectiveness of the product. The safety data from CDC IND, as well as the efficacy data from the Brachman et al. trial, and CDC surveillance data (1962-1974) from "at-risk" industrial settings were the basis for these findings. These findings were published in the Federal Register of December 13, 1985.

Furthermore, data from a well-controlled monkey study has become available since the time of the 1985 Panel report. The efficacy of the Anthrax Vaccine Adsorbed licensed for use in humans also was tested in rhesus monkeys challenged by an aerosol of virulent Bacillus *anthracis* spores. The data from this study suggests vaccine efficacy against inhalation anthrax. It should be noted that monkeys are quite similar to humans with regard to the clinical course and pathological findings following inhalation anthrax.

While these studies cannot prove that the vaccine would be 100 percent effective in a terrorist or wartime situation, they are the only known data on pre-exposure protection currently available against inhalation anthrax.

DOD Vaccine Administration Schedule

In the September 29, 1999, letter to Dr. Sue Bailey, Assistant Secretary of Defense Health Affairs, Dr. Kathryn C. Zoon, Director, CBER, stated in the final paragraph, "We reiterate our previous statement made to DOD on December 16, 1997, that FDA approval of the anthrax vaccine is based on the six-dose regime found in the approved labeling. Because we are unaware of any data demonstrating that any deviation from the approved intervals of doses found in the approved labeling will provide protection from anthrax infection, we strongly recommend that the Anthrax Vaccine Immunization Program follow FDA-approved schedule." Similar information was included in a letter dated

September 28, 1999, to Dr. Sue Bailey from Dr. Jane E. Henney. Copies of both of these letters are enclosed.

DOD has conducted a pilot study, under a BioPort IND, to evaluate several dosing schedules and routes of administration for the anthrax vaccine. This pilot study used full informed consent. The pilot study evaluated anti-protective antigen antibody levels in vaccines. One purpose of the pilot study was to evaluate the feasibility of eliminating the week two dose **as** well as to evaluate differences between the subcutaneous and intramuscular routes of administration. This pilot study was intended to select a dosing schedule(s) for further evaluation in a larger, comparative, statistically definitive study to potentially support a change in the label. In December 1998, DOD met with FDA representatives to discuss such a study. To date, DOD has not yet submitted a definitive study protocol to evaluate and potentially support a change in the dosing schedule for the anthrax vaccine.

Product Expiration Dating

The expiration date of a biological product may be changed pursuant to Title 21, Code of Federal Regulations (CFR) 5610.50, Date of Manufacture, which states in part that the date of manufacture shall be the date of initiation by the manufacturer of the last valid potency test. As stated in 21 CFR §610.53 (b), the dating period for a product shall begin on the date of manufacture, as prescribed in section 610.50. A valid potency assay is required prior to an extension of dating. The expiration date is based on the last valid potency assay.

BioPort's License Application

The content of license applications under FDA review, including the number and characterization of lots, are not releasable under FOIA. Please be assured, however, that FDA will not approve an application until a manufacturer demonstrates that a product can be consistently manufactured under current good manufacturing practices (cGMPs) to meet product specifications. Lots manufactured to support a license application or supplement cannot be sold without approval of the application or supplement and remain subject to FDA lot release requirements as described above.

Proposed rule

In response to your comments on the proposed rule for animal studies, FDA agrees that there needs to be a scientifically verifiable extrapolation from animal data. FDA's Proposed Rule, "New Drug and Biological Drug Products; Evidence Needed to Demonstrate Efficacy of New Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted," was published in the October 5, 1999, Federal Register. The docket is open for comment until December 20, 1999. Your letter will be forwarded to the docket so that your comments regarding the proposed rule can be entered into the docket for consideration. After the comment period has closed, FDA will review the comments and determine the appropriate next step in the process. At this time, there is no date for publication of a final rule.

We trust this information responds to your concerns. If you have further questions, please let us know. A similar response has been provided to your co-signers.

Sincerely,

Melinda K. Plaisier
Associate Commissioner
for Legislation

3 Enclosures
"Package Labeling for Anthrax Vaccine Adsorbed"
"September 28, 1999 letter to Dr. Sue Bailey, Assistant Secretary of Defense Health Affairs, from Dr. Jane E. Henney, Commissioner, FDA"
"September 29, 1999, letter to Dr. Sue Bailey, Assistant Secretary of Defense Health Affairs, Dr. Kathryn Zoon, Director, CBER"

cc: Dockets Management Branch

Congress of the United States'

Washington, DC 20515

November 3, 1999

The Honorable Jane E. Henney, M.D.
Commissioner
Food and Drug Administration
14-7 l Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Henney:

We are writing to express our serious concerns regarding the pending license supplement application of BioPort to produce the anthrax vaccine. We strongly urge that each of the items contained in the letter be fully addressed and a response provided to us prior to the approval of BioPort's license supplement application.

As you are aware, in 1997 the Department of Defense mandated the implementation of a force-wide Anthrax Vaccine Immunization Program (AVIP). Since the announcement of this plan to inoculate all 2.4 million members of our Armed Services, FDA documented deficiencies in the manufacturing process have caused widespread and persistent concerns regarding the safety of the vaccine.

Of particular concern is that despite the licensure of the anthrax vaccine in 1970, 23 years passed before your agency physically inspected the anthrax-specific portion of the manufacturing facility. In testimony before the House Government Reform Committee, Dr. Zoon, the Director of FDA's Center for Biologics Evaluation and Research, indicated that two inspections of the production facilities in 1997 and 1998 revealed significant deviations from the Federal Food, Drug, and Cosmetic Act, FDA's regulations, and the standards in the Michigan Biological Product Institute (MBPI) license. Inspection reports of the production facilities following its purchase by BioPort revealed some progress but many remaining deviations. In large part, the significant ongoing deviations prompted the company to close the facility for remodeling rather than face the likelihood of FDA revoking their license.

Given the documented deviations from approved practices in the manufacturing process, it is imperative that the FDA follow it's own prescribed regimen of thorough testing for purity, potency, identity, and sterility. As a prerequisite for approval of the license supplement, the testing must reveal lot-to-lot consistency for the vaccine. Included within the testing requirements, the FDA must ensure lot-to-lot consistency for the antigen level. FDA mandated lot-to-lot consistency will ensure we can accurately measure the efficacy of the vaccine. The lack of clinical data detailing the relationship between antigen levels and the amount of protection provided argues strongly for greater vaccine consistency data so correlates of

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immunity can be studied. In that regard, please provide information on the status of FDA's request of BioPort to characterize the vaccine. Any failure to characterize the vaccine must preclude the approval of the license supplement application.

We also urge that the FDA place the anthrax vaccine back under Investigational New Drug (IND) status. As Dr. Zoon testified before the Government Reform Committee, the MBPI vaccine was licensed for use by a limited population of individuals at risk for coetaneous exposure to anthrax through infected animals or animal products. The December 13, 1985 Federal Register and the FDA approved package inserts indicate: "Since the risk of exposure to anthrax infection in the general population is slight, routine immunization is not recommended." However, the Department of Defense, in its implementation of the AVIP, is performing a large-scale inoculation for protection against inhalation anthrax. The scope of the vaccination program and the form of exposure anticipated by DoD were not addressed in the initial license. A March 13, 1997, letter from Dr. Michael Friedman, FDA Lead Deputy Commissioner, to Stephen Joseph, then Assistant Secretary of Defense for Health Affairs, acknowledged the "paucity of data regarding the effectiveness of the anthrax vaccine for prevention of inhalation anthrax." This lack of significant data strongly suggests the need for further study under IND status.

Additionally, the data submitted for licensure of initial vaccine did not include scientifically valid support for the current dosing structure. GAO stated that no studies have been conducted to determine the optimum number of doses of the anthrax vaccine. Although annual boosters are recommended, the need for a six-shot regimen and annual booster shots has not been evaluated. There is also no clinical data to accurately conclude that the prescribed regimen provides a consistent level of protective antigen to be efficacious against inhalation anthrax. A September 29, 1999 letter from Dr. Zoon to Dr. Sue Bailey, the Assistant Secretary of Defense for Health Affairs indicated that there is lack of data on the impact of deviations from the approved vaccine regimen. Prior to the approval of the license supplement application, the FDA must scientifically verify the clinical data supporting the six-dose regimen. We would like to be apprised of FDA's plans to accomplish this goal and be provided the clinical data supporting the correlation between the dosage and anti-body levels.

We are also requesting the status of FDA's proposed rule regarding the use of animal data to support claims of human efficacy. Human efficacy information for the current license and the license supplement application is based overwhelmingly upon the application of data from animal anthrax vaccinations and exposure. However, there have been great discrepancies between various animal models regarding the efficacy of the anthrax vaccine. We acknowledge and support the moral argument against human testing to determine the efficacy of the vaccine. At the same time, we must ensure there is a scientifically verifiable extrapolation from animal data that can be applied to humans. It is our understanding the proposed rule would attempt to establish protocols to provide that information. If that rule has not been approved, we would like

Should you have any questions regarding this letter, please do not hesitate to contact us or any member of our staffs. Please provide this information by November 18. Thank you for your consideration of these serious matters. We look forward to your prompt reply.

Sincerely,

Walter B. Jones
Member of Congress

Dan Burton
Member of Congress

Benjamin A. Gilman
Member of Congress

Christopher Shays
Member of Congress

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

September 28, 1999

Sue Bailey, M.D.
Assistant Secretary of Defense
Health Affairs
1200 Defense Pentagon
Room 3E346
Department of Defense
Washington, D.C. 20301-1200

Dear Dr. Bailey:

It was a pleasure meeting with you on August 24 to discuss issues of mutual concern. Subsequent to our meeting, Dr. Kathryn Zoon, Director of FDA's Center for Biologics Evaluation and Research, advised me of additional information that she reviewed related to anthrax vaccination for our military troops.

Dr. Zoon has reviewed information from congressional sources that some troops may not be receiving the vaccine in accordance with the schedule found in the approved labeling. As you are aware this schedule is the only regimen shown to be effective in protecting humans against anthrax and is the only schedule approved by FDA. I have asked Dr. Zoon to communicate our concerns on this important matter to you directly. Thank you in advance for your prompt attention to this.

Sincerely,

Jane E. Henney, M.D.
Commissioner of Food and Drugs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20852-1448

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Sue Bailey, M. D.
Assistant Secretary of Defense
Health Affairs
1200 Defense Pentagon
Room 3E346
Department of Defense
Washington, DC 20301-1200

Dear Dr. Bailey:

On December 16, 1997, Food and Drug Administration (FDA) officials met with the Department of Defense (DOD) officials to discuss DOD's Anthrax Vaccine Immunization Program (Am). During that meeting, Dr. Ed Martin acting Assistant Secretary of Defense, Health Affairs, briefed Dr. Michael Friedman, Lead FDA Deputy Commissioner on DOD's plan to implement anthrax vaccinations of the U.S. military forces. As part of that briefing, Dr. Martin emphasized that the anthrax vaccine immunization program would not vary from the FDA approved labeling.

Recently, it has come to the agency's attention through congressional sources, that some troops may not be receiving the vaccine in accordance with the schedule found in the approved labeling. As you know, the approved anthrax labeling states that full immunization involves six (6) doses administered over 18 months to complete the primary series Labeling calls for doses of the vaccine to be administered, following the first dose, at 2 and 4 weeks, 6 months, 12 months and 18 months, with yearly boosters thereafter. This schedule is the only regimen shown to be effective in protecting humans against anthrax and is the only schedule approved by FDA Data received by FDA from congressional sources indicate that a number of reserve and active military personnel are receiving their anthrax vaccine doses significantly later than the FDA approved schedule.

WC reiterate our previous statement made to DOD on December 16, 1997 that FDA approval of the anthrax vaccine is based on the six-dose regimen found in the approved labeling. Because we are unaware of any data demonstrating that any deviation from the approved intervals of doses found in the approved labeling will provide protection from anthrax infection, WC strongly recommend that the Anthrax Vaccine Immunization Program follow the FDA approved schedule. We would like to hear from you as soon as possible regarding *this* important *matter.*

Sincerely yours,

Kathryn C. Zoon, Ph.D.
Director
Center for Biologics Evaluation
and Research

ANTHRAX VACCINE ADSORBED

DESCRIPTION

Anthrax Vaccine Adsorbed is a sterile product made from filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *Bacillus anthracis* which elaborates the protective antigen during the growth period. The cultures are grown in a synthetic liquid medium and the final product is prepared from the sterile filtered culture fluid. The potency of this product is confirmed according to the U.S. Food and Drug regulations (21 CFR 620.23): Additional Standards for Anthrax Vaccine Adsorbed. The final product contains no more than 2.4 mg aluminum hydroxide (equivalent to 0.83 mg aluminum) per 0.5 cc dose. Formaldehyde, in a final concentration not to exceed 0.02%, and benzethonium chloride, 0.0025%, are added as preservatives.

CLINICALPHARMACOLOGY

Anthrax Vaccine Adsorbed is used in man to promote increased resistance to *Bacillus anthracis* by active immunization (1,2).

INDICATIONS AND USAGE

Immunization with Anthrax Vaccine Adsorbed is recommended for individuals who may come in contact with animal products such as hides, hair, or bones which come from anthrax endemic areas and may be contaminated with *Bacillus anthracis* spores; and for individuals engaged in diagnostic or investigational activities which may bring them into contact with *B. anthracis* spores (1-5). It is also recommended for high risk persons such as veterinarians and others handling potentially infected animals. Since the risk of exposure to anthrax infection in the general population is slight, routine immunization is not recommended.

If a person has not previously been immunized against anthrax, injection of this product following exposure to anthrax bacilli will not protect against infection.

CONTRAINDICATIONS

A history of a severe reaction to a previous dose of anthrax vaccine is a contraindication to immunization with this vaccine.

WARNINGS

1. Any acute respiratory disease or other active infection is generally considered to be adequate reason for deferring an injection.
2. Persons receiving cortico-steroid therapy or other agents which would tend to depress the immune response may not be adequately immunized with the dosage schedule recommended. If the therapy is short termed, immunization should be delayed. If the therapy is long termed, an extra dose of vaccine should be given a month or more after therapy is discontinued.

PRECAUTIONS

1. *General:* Epinephrine solution, 1:1000, should always be available for immediate use in case an anaphylactic reaction should occur, even though such reactions are rare.
2. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* Studies have not been performed to ascertain whether Anthrax Vaccine Adsorbed has carcinogenic action, or any effect on fertility.
3. *Pregnancy:* PREGNANCY CATEGORY C. ANTHRAX VACCINE ADSORBED
   Animal reproduction studies have not been conducted with Anthrax Vaccine Adsorbed. It is also not known whether Anthrax Vaccine Adsorbed can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Anthrax Vaccine Adsorbed should be given to a pregnant woman only if clearly needed.
4. *Pediatric Use:* This antigen should be administered only to healthy men and women from 18 to 65 years of age because investigations to date have been conducted exclusively in that population.

ADVERSE REACTIONS

Local Reactions: Mild local reactions occur in approximately thirty per cent of recipients and consist of a small ring of erythema, 1-2 cm in diameter, plus slight local tenderness(1). This reaction usually occurs within 24 hours and begins to subside by 48 hours. Occasionally, the erythema increases to 3 to 5 cm in diameter. Local reactions tend to increase in severity by the 5th injection and then may decrease in severity with subsequent doses.

Moderate local reactions which occur in 4 per cent of recipients of a second injection are defined by an inflammatory reaction greater than 5 cm diameter.

These may be pruritic. Subcutaneous nodules may occur at the injection site and persist for several weeks in a few persons. A moderate local reaction can occur if the vaccine is given to anyone with a past history of anthrax infection.

More severe local reactions are less frequent and consist of extensive edema of the forearm in addition to the local inflammatory reaction.

All local reactions have been reversible.

Systemic Reactions: Systemic reactions which occur in fewer than 0.2 per cent of recipients have been characterized by malaise and lassitude. Chills and fever have been reported in only a few cases. In such instances, immunization should be discontinued.

DOSAGE AND ADMINISTRATION

Dosage

Primary immunization consists of three subcutaneous injections, 0.5 mL each, given 2 weeks apart followed by three additional subcutaneous injections, 0.5 mL each, given at 6, 12 and 18 months(1).

If immunity is to be maintained, subsequent booster injections of 0.5 mL of anthrax vaccine at one year intervals are recommended.

Administration

1. Use a separate sterile needle and syringe for each patient to avoid transmission of viral hepatitis and other infectious agents.
2. Shake the bottle thoroughly to ensure that the suspension is homogeneous during withdrawal. The rubber stopper should be treated with an appropriate disinfectant and allowed to dry before inserting the needle.
3. This preparation must be given subcutaneously after cleansing the overlying skin with an antiseptic.
4. Follow the usual precautions to avoid intravenous injection.
5. After withdrawing the needle, the injection site may be massaged briefly and gently to promote dispersal of the vaccine.
6. The same site should not be used for more than one injection of this vaccine.
7. Do not syringe-mix with any other product.
8. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Anthrax Vaccine Adsorbed is supplied in 5 mL vials containing 10 doses each.

STORAGE

THIS PRODUCT SHOULD BE STORED AT 2 TO 8 °C (35.6 to 46.4 °F). Do not freeze. Do not use after the expiration date given on the package.

REFERENCES

1. Brachman, P.S., *et. al.* Field Evaluation of a Human Anthrax Vaccine. Amer. J. Pub. Health, *52*:632-645 (1962).
2. Editorial: Vaccine Against Anthrax. Brit. Med. J., *2*:717-718 (1965).
3. Advisory Committee for Immunization Practices. Adult Immunization, Morbidity and Mortality Report, *33*(15):33-34, 1984.
4. Committee on Immunization, *Guide for Adult Immunization, 1985*, Amer. Col. Physicians, Philadelphia, PA (1985).
5. Report of Committee on Infectious Diseases, 19th Edition, Amer. Acad. Pediatrics, Evanston, IL (1982).

These recommendations are prepared by the Michigan Department of Public Health only for the guidance of the physician. They do not replace the experience and judgment of the physician, who should be familiar with the recent pertinent medical literature before administering any biologic product.

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