Control System, Medicare contractors and the Coordination of Benefit Contractor, Common Working File, CMS Regional Offices, an agency of a State government, Medicare beneficiaries and non-Medicare beneficiaries that have an approved or denied WC Medicare Set-aside arrangement to cover future medical costs resulting from an injury incurred while employed and the Social Security Administration.

SYSTEMS EXEMPTED FROM CERTAIN PROVISION OF THE ACT:

None.

[FR Doc. E5–7486 Filed 12–16–05; 8:45 am]

BILLING CODE 4120–03–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

Proposed Information Collection Activity; Comment Request

Proposed Projects

Title: Sanction Policies Task Order.

OMB No.: New Collection.

Description: This study is designed to determine how local welfare offices implement sanction policies in the Temporary Assistance for Needy Families program. This study will survey local welfare staff to gather in-depth qualitative information on how workers interpret the policies and apply them in specific instances. The results of this study should give the Administration for Children and Families (ACF) a better understanding of possible outcomes of various sanction policies, which in turn will help ACF design a research program to study the effect of sanctions.

Respondents: A maximum of 324 welfare staff in local welfare offices.

ANNUAL BURDEN ESTIMATES

Instrument	Number of respondents	Number of responses per respondent	Average burden hours per response	Total burden hours
In-person Survey and Telephone Interviews	324	1	.85	275

Estimated Total Annual Burden Hours: 275.

In compliance with the requirements of section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, the Administration for Children and Families is soliciting public comment on the specific aspects of the information collection described above. Copies of the proposed collection of information can be obtained and comments may be forwarded by writing to the Administration for Children and Families, Office of Administration, Office of Information Services, 370 L'Enfant Promenade, SW., Washington, DC 20447, Attn: ACF Reports Clearance Officer. E-mail address: *infocollection@acf.hhs.gov.* All requests should be identified by the title of the information collection.

The Department specifically requests comments on: (a) Whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information shall have practical utility; (b) the accuracy of the agency's estimate of the burden of the proposed collection of information; (c) the quality, utility, and clarity of the information to be collected; and (d) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques or other forms of information technology. Consideration will be given to comments and suggestions submitted within 60 days of this publication.

Dated: December 12, 2005.

Robert Sargis,

Reports Clearance Officer.

[FR Doc. 05–24174 Filed 12–16–05; 8:45 am]

BILLING CODE 4184–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 1980N–0208]

Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Anthrax Vaccine Adsorbed; Final Order

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) proposed, among other things, to classify Anthrax Vaccine Adsorbed (AVA) on the basis of findings and recommendations of the Panel on Review of Bacterial Vaccines and Toxoids (the Panel) on December 13, 1985. The Panel reviewed the safety, efficacy, and labeling of bacterial vaccines and toxoids with standards of potency, bacterial antitoxins, and immune globulins. After the initial final rule and final order was vacated by the United States District Court for the District of Columbia on October 27, 2004, FDA published a new proposed rule and proposed order on December 29, 2004. The purpose of this final order is to categorize AVA according to the evidence of its safety and effectiveness, thereby determining if it may remain licensed and on the market; issue a final response to recommendations made in the Panel's report, and; respond to comments on the previously published proposed order. The final rule and final order concerning bacterial vaccines and toxoids other than AVA is published elsewhere in this issue of the **Federal Register**.

DATES: The final order on categorization of AVA is effective December 19, 2005.

FOR FURTHER INFORMATION CONTACT: Kathleen Swisher, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Introduction

Biological products licensed before July 1972 are subject to a review procedure described in § 601.25 (21 CFR 601.25). AVA was licensed before July 1972. The purpose of this document is to: (1) Categorize AVA under § 601.25 according to the evidence of its safety and effectiveness, thereby determining if it may remain licensed and on the market, (2) issue a final response to recommendations made in the Panel's report, and (3) respond to comments on the proposed order (69 FR 78281, December 29, 2004).

II. Background

A. General Description of the ''Efficacy Review'' for Biological Products Licensed Before July 1972

In 1972, in an effort to assure that regulatory standards for drugs and biological products were harmonized, the National Institutes of Health (NIH) announced a review of all licensed biological products (37 FR 5404, March 15, 1972). However, on July 1, 1972, NIH's Division of Biologics Standards, which had been charged with administering and enforcing the licensing provisions of the Public Health Service Act, was transferred to FDA (37 FR 12865, June 29, 1972). FDA then assumed responsibility for reviewing the previously licensed biological products. In the **Federal Register** of February 13, 1973 (38 FR 4319), FDA issued procedures for the review of the safety, effectiveness, and labeling of biological products licensed before July 1, 1972. This process was eventually codified in § 601.25 (38 FR 32048 at 32052, November 20, 1973). Under the panel assignments published in the **Federal Register** of June 19, 1974 (39 FR 21176), FDA assigned each review of a biological product to one of the following groups: (1) Bacterial vaccines and bacterial antigens with ''no U.S. standard of potency,'' (2) bacterial vaccines and toxoids with standards of potency, (3) viral vaccines and rickettsial vaccines, (4) allergenic extracts, (5) skin test antigens, and (6) blood and blood derivatives.

Under § 601.25, FDA assigned the initial review of each of the six biological product categories to a separate independent advisory panel consisting of qualified experts. Each panel was charged with preparing for the Commissioner of Food and Drugs an advisory report which was to: (1) Evaluate the safety and effectiveness of the biological products for which a license had been issued, (2) review their labeling, and (3) identify the biological products that are safe, effective, and not misbranded. Each advisory panel report was also to include recommendations classifying the products reviewed into one of three categories.

- Category I, designating those biological products determined by the panel to be safe, effective, and not misbranded.
- Category II, designating those biological products determined by the panel to be unsafe, ineffective, or misbranded.
- Category III, designating those biological products determined by the panel not to fall within either Category I or Category II on the basis of the panel's conclusion that the available data were insufficient to classify such biological products, and for which further testing was therefore required. Category III products were assigned to one of two subcategories. Category IIIA products were those that would be permitted to remain on the market pending the completion of further studies. Category IIIB products were those for which the panel recommended license revocation on the basis of the panel's assessment of potential risks and benefits.

In its report, the panel could also include recommendations concerning any condition relating to active components, labeling, tests appropriate before release of products, product standards, or other conditions necessary or appropriate for a biological product's safety and effectiveness.

In accordance with § 601.25, after reviewing the conclusions and recommendations of the review panels, FDA would publish in the **Federal Register** a proposed order containing: (1) A statement designating the biological products reviewed into Categories I, II, IIIA, or IIIB, (2) a description of the testing necessary for Category IIIA biological products, and (3) the complete panel report. Under the proposed order, FDA would propose to revoke the licenses of those products designated into Category II and Category IIIB. After reviewing public comments, FDA would publish a final order on the matters covered in the proposed order.

B. The December 1985 Proposal

The Panel was convened in a July 12, 1973, organizational meeting, which was followed by multiple working meetings until February 2, 1979. The Panel completed its final report in August 1979. In that report, the Panel found that AVA, manufactured by Michigan Department of Public Health (MDPH, now BioPort), License No. 99,[1] was safe and effective for its intended use and recommended that the vaccine be placed into Category I. The Panel based its evaluation of the safety and efficacy of AVA on two studies: The Brachman study, a well-controlled field study conducted in the 1950s (Ref. 1), and an open label safety study conducted by the National Center for Disease Control (CDC, now the Centers for Disease Control and Prevention) (50 FR 51002 at 51058, December 13, 1985). The Panel also considered surveillance data on the occurrence of anthrax disease in the United States in at-risk industrial settings as supportive of the effectiveness of the vaccine (50 FR 51002 at 51059, December 13, 1985).

In the **Federal Register** of December 13, 1985 (50 FR 51002), FDA issued a proposed rule that contained the full Panel report on bacterial vaccines and toxoids with standards of potency,

[1] On December 17, 1965, the company name was changed from the Division of Laboratories, Michigan Department of Health to the Bureau of Laboratories, Michigan Department of Public Health. On April 10, 1979, the name was changed to the Michigan Department of Public Health. On May 14, 1996, the name was changed to the Michigan Biologics Products Institute. On November 11, 1998, FDA accepted a name change to BioPort Corporation (BioPort) with an accompanying license number change to 1260.

including the anthrax vaccine,[2] and FDA's response to the recommendations of the Panel (the December 1985 proposal). In the December 1985 proposal, FDA proposed regulatory categories (Category I, Category II, or Category IIIB as defined previously in this document) for each bacterial vaccine and toxoid reviewed by the Panel, and responded to other recommendations made by the Panel. FDA agreed with the Panel's recommendation and proposed to place AVA into Category I.

The public was provided 90 days to submit comments in response to the December 1985 proposal. FDA received four letters of comments in response to the December 1985 proposal, but none of those comments pertained to AVA. We discuss them in a final rule and final order concerning bacterial vaccines and toxoids other than AVA published elsewhere in this issue of the **Federal Register**.

FDA addressed the review and reclassification of bacterial vaccines and toxoids classified into Category IIIA through a separate administrative procedure (see the **Federal Register** of May 15, 2000 (65 FR 31003), and May 29, 2001 (66 FR 29148)).

C. Additional Proceedings Following the December 1985 Proposal

On October 12, 2001, a group of individuals filed a citizen petition requesting that FDA find AVA, as currently manufactured by BioPort, ineffective for its intended use, classify the product as Category II, and revoke the license for the vaccine. The petitioners complained that the December 1985 proposal that placed AVA into Category I had not been finalized. FDA responded separately in a written response to the petitioners on August 28, 2002 (Docket No. 2001P–0471).

In March 2003, six plaintiffs, known as John and Jane Doe 1 through 6, filed suit in the U.S. District Court for the District of Columbia (the Court) asking the Court to enjoin the Anthrax Vaccine Immunization Program (AVIP) of the Department of Defense (DoD), and to declare AVA an investigational drug when used for protection against inhalation anthrax. On December 22, 2003, the Court issued a preliminary injunction enjoining inoculations under the AVIP in the absence of informed consent or a Presidential waiver of informed consent (see § 50.23 (21 CFR 50.23)). *Doe* v. *Rumsfeld*, 297 F.Supp. 2d 119 (D.D.C. 2003).

In the **Federal Register** of January 5, 2004 (69 FR 255), FDA published a final rule and final order amending the biologics regulations and categorizing certain biological products in response to the report and recommendations of the Panel. The final order placed AVA into Category I. Following FDA's issuance of the final rule and final order, on January 7, 2004, the Court lifted the preliminary injunction except as it applied to the six Doe plaintiffs. *Doe* v. *Rumsfeld*, 297 F.Supp. 2d 200 (D.D.C. 2004).

On October 27, 2004, the Court issued a memorandum opinion vacating and remanding the January 2004 final rule and final order to FDA for reconsideration, requiring an additional opportunity for comment. *Doe* v. *Rumsfeld*, 341 F.Supp. 2d 1 (D.D.C. 2004). On December 29, 2004 (69 FR 78280), FDA published a withdrawal of the January 5, 2004, final rule and final order. Concurrently with the withdrawal of the final rule and final order, FDA published again a proposed rule and proposed order (69 FR 78281) (the December 2004 proposal) to provide notice and to give interested persons an opportunity to comment on FDA's proposals relating to bacterial vaccines and toxoids classified into Category I, Category II, and Category IIIB, including AVA. In the December 2004 proposal, FDA reopened the comment period for 90 days on the entire Bacterial Vaccines and Toxoids efficacy review document.

Most of the comments received in response to the December 2004 proposal pertained to the anthrax vaccine (AVA). We provide a response to comments about AVA under section IV of this document. A discussion of comments to the December 2004 proposal concerning bacterial vaccines and toxoids other than AVA is provided in a final rule and final order published elsewhere in this issue of the **Federal Register**.

III. Categorization of Anthrax Vaccine Adsorbed—Final Order

After review of the comments and finding no additional scientific evidence to alter the proposed categorization, FDA accepts the Panel's recommendation and adopts Category I as the final category for AVA and determines AVA to be safe and effective and not misbranded.

In this section of this document, we describe the data supporting our conclusion that AVA is safe and effective for its labeled indication to protect individuals at high risk for anthrax disease. Anthrax disease can be fatal despite appropriate antibiotic therapy. We also discuss points of disagreement with certain statements in the Panel's report.

In order to provide clarity to the reader, we use the following terms to refer to studies relevant to this final order. The versions of vaccine used in these studies reflect the optimization of anthrax vaccine during product and clinical development.

1. *Brachman study*—The Brachman study was an adequate and well-controlled clinical study conducted from 1954 to 1959 to evaluate the effectiveness of the anthrax vaccine. The vaccine used in the Brachman study (the DoD vaccine) was supplied by Dr. G. G. Wright and associates of the U.S. Army Chemical Corps., Fort Detrick, Frederick, MD.

2. *CDC open label safety study*—The CDC open label safety study was conducted from 1966 to 1971. Merck Sharp & Dohme (MSD) manufactured anthrax vaccine (DoD/MSD vaccine) under contract to DoD in 1960 and 1961. The Michigan Department of Public Health (MDPH) also manufactured anthrax vaccine (DoD/MDPH/AVA) under contract to DoD starting in the mid–1960s. CDC used one lot of DoD/MSD vaccine and one lot of DoD/MDPH/AVA vaccine in the first year of the CDC open label safety study, but only DoD/MDPH/AVA vaccine was used for the remainder of that study. The vaccine manufactured by MDPH was licensed by the NIH, Bureau of Biologics, in November 1970 as AVA. MDPH subsequently underwent a name change to Michigan Biologic Products Institute (MBPI) and later, BioPort Corporation (BioPort).

3. *DoD pilot study*—The DoD pilot study was conducted from 1996 to 1999. The purpose of the study was to make an initial assessment of the effects that alternative immunization schedules and/or an alternative route of administration may have on the safety and immunogenicity of AVA. The DoD pilot study used the licensed DoD/MDPH/AVA vaccine.

A. Efficacy of Anthrax Vaccine Adsorbed

The Brachman study was conducted in four textile mills where, prior to initiation of the study, the yearly average number of human anthrax cases was 1.2 cases per 100 mill employees. These textile mills were located in the northeastern United States and processed imported goat hair. The study included 1,249 workers from these

[2] In addition to publication in the **Federal Register** of December 13, 1985 (50 FR 51002), the full Panel report is available on FDA's Web site at *http://www.fda.gov/ohrms/dockets/default.htm* (Docket No. 1980N–0208). A copy of the Panel report is also available at the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

mills. Of these 1,249 workers, 379 received anthrax vaccine, 414 received placebo, 116 received incomplete inoculations of either anthrax vaccine or placebo, and 340 received no treatment but were monitored for the occurrence of anthrax disease as an observational group. The Brachman study used DoD vaccine administered subcutaneously at 0, 2, and 4 weeks and 6, 12, and 18 months. During the study, 26 cases of anthrax were reported across the four mills: 5 inhalation and 21 cutaneous anthrax cases. Of the five inhalation anthrax cases (four of which were fatal), two received placebo, three were in the observational group, and none received anthrax vaccine. Of the 21 cutaneous anthrax cases, 15 received placebo, 3 were in the observational group, and 3 received anthrax vaccine. Of the three cases in the vaccine group, one case occurred just prior to administration of the third dose, one case occurred 13 months after the individual received the third of the six doses (but no subsequent doses), and one case occurred prior to receiving the fourth dose of vaccine.

In its report, the Panel stated that the Brachman study results demonstrate ''a 93 percent (lower 95 percent confidence limit = 65 percent) protection against *cutaneous* anthrax'' (emphasis supplied) and that ''inhalation anthrax occurred too infrequently to assess the protective effect of vaccine against this form of the disease'' (50 FR 51002 at 51058, December 13, 1985). We do not agree with the Panel's statement that the protection was limited to cutaneous anthrax cases. The Brachman study's comparison between anthrax cases in the placebo and vaccine groups included both inhalation and cutaneous anthrax cases. Accordingly, the calculated effectiveness of the vaccine to prevent both types of anthrax disease combined was 92.5 percent (lower 95 percent confidence interval = 65 percent) as described in the Brachman, et al. report (Ref. 1). We agree that the cases of inhalation anthrax reported in the course of the Brachman study, if analyzed separately, are too few to support a meaningful statistical conclusion. However, the Brachman study's analysis of the effectiveness of the vaccine appropriately included all cases of anthrax disease that occurred in individuals who received at least three doses of vaccine or placebo and were on schedule for the remaining doses of the six-dose schedule regardless of the route of exposure or manifestation of disease, and was not limited to cutaneous cases. Thus, the study supports AVA's indication for active immunization against *Bacillus anthracis*, independent of the route of exposure.

As stated previously in this document, the Panel also considered epidemiological data—which we refer to as the CDC surveillance data—on the occurrence of anthrax disease in at-risk industrial settings collected by the CDC and summarized for the years 1962 to 1974, as supportive of the effectiveness of AVA. In that time period, individuals received either DoD/MDPH/AVA vaccine or an earlier version of anthrax vaccine. The Panel explained,

> Twenty-seven cases of anthrax disease were identified. Three cases were not mill employees but worked in or near mills; none of these cases had been vaccinated. Twenty-four cases were mill employees; three were partially immunized (one with 1 dose, two with 2 doses); the remainder (89 percent) were unvaccinated. Therefore, no cases have occurred in fully vaccinated subjects while the risk of infection has continued. These observations lend further support to the effectiveness of this product.
> (50 FR 51002 at 51058, December 13, 1985).

In 1998, the DoD initiated the Anthrax Vaccine Immunization Program, calling for mandatory vaccination of service members. Thereafter, questions about the vaccine caused the U.S. Congress to direct DoD to support an independent examination of AVA by the Institute of Medicine (IOM).[3] The IOM committee was charged with reviewing data regarding the efficacy and safety of the currently licensed anthrax vaccine—Anthrax Vaccine Adsorbed (AVA)—and assessing the efforts to resolve manufacturing issues and resume production and distribution of vaccine. The committee in its published report concluded that AVA, as licensed, is an effective vaccine to protect humans against anthrax, including inhalation anthrax (Ref. 2). FDA agrees with the report's finding that certain studies in humans and animal models support the conclusion that AVA is effective against *B. anthracis* strains that are dependent upon the anthrax toxin as a mechanism of virulence, regardless of the route of exposure.[4] However, our review of AVA, is independent of the IOM's review. We discuss later in this document comments that we received related to the IOM review.

[3]In October 2000, the Institute of Medicine (IOM) convened the Committee to Assess the Safety and Efficacy of the Anthrax Vaccine. In March 2002, the Committee issued its report: The Anthrax Vaccine: Is It Safe? Does It Work? (Ref. 2). The report concluded that the vaccine is acceptably safe and effective in protecting humans against anthrax.

[4]For example: The Brachman study (Ref. 1); the CDC surveillance data described in the December 1985 proposal; Fellows (2001) (Ref. 3); Ivins (1996) (Ref. 4); and Ivins (1998) (Ref. 5).

B. Safety of Anthrax Vaccine Adsorbed

CDC conducted the CDC open label safety study under an investigational new drug application (IND) between 1966 and 1971 in which approximately 7,000 persons, including textile employees, laboratory workers, and other at-risk individuals, were vaccinated with DoD/MDPH/AVA vaccine[5] and monitored for adverse reactions to vaccination. The vaccine was administered in 0.5–mL doses according to a 0-, 2-, and 4-week initial dose schedule followed by additional doses at 6, 12, and 18 months, with annual boosters thereafter. Several lots (approximately 15,000 doses) of DoD/MDPH/AVA vaccine were used in this study period. In its report, the Panel found that the CDC data ''suggests that this product is fairly well tolerated with the majority of reactions consisting of local erythema and edema. Severe local reactions and systemic reactions are relatively rare'' (50 FR 51002 at 51059).

Subsequent to the publication of the Panel's recommendations, from 1996 to 1999, DoD conducted the DoD pilot study, a small, randomized clinical study of AVA, administered by alternative route and schedules, compared to the vaccine administered according to the approved labeling. Safety data from the group that received the vaccine according to the labeling as well as post-licensure adverse event surveillance data available from the Vaccine Adverse Event Reporting System (VAERS), which FDA regularly reviews, further support the safety of AVA. These data provided the basis for labeling revisions approved by FDA in January 2002 (Ref. 6) to better describe the types and severities of adverse events associated with administration of AVA.

C. The Panel's General Statement: Anthrax Vaccine, Adsorbed, Description of Product

The Panel report states:

> Anthrax vaccine is an aluminum hydroxide adsorbed, protective, proteinaceous, antigenic fraction prepared from a nonproteolytic, nonencapsulated mutant of the Vollum strain of *Bacillus anthracis*. (50 FR 51002 at 51058).

The Panel's description of the anthrax vaccine has an inaccuracy. While the *B. anthracis* strain used in the manufacture of AVA is the nonproteolytic, nonencapsulated strain identified in the Panel report, it is not a mutant of the Vollum strain but was derived from a *B. anthracis* culture originally isolated from a case of bovine anthrax in Florida.

[5]In addition, one lot of the DoD/MSD vaccine was used during the CDC open label safety study.

D. The Panel's Specific Product Review: Anthrax Vaccine Adsorbed: Efficacy

The Panel report states:

3. *Analysis—a. Efficacy*—(2) *Human.* The vaccine manufactured by the Michigan Department of Public Health has not been employed in a controlled field trial. A similar vaccine prepared by Merck Sharp & Dohme for Fort Detrick was employed by Brachman * * * in a placebo-controlled field trial in mills processing imported goat hair * * *. The Michigan Department of Public Health vaccine is patterned after that of Merck Sharp & Dohme with various minor production changes.

(50 FR 51002 at 51059, December 13, 1985).

FDA found that contrary to the Panel's statement, the vaccine used in the Brachman study was not manufactured by MSD, but instead this vaccine was manufactured by DoD and provided to Dr. Brachman by Dr. G. G. Wright of Fort Detrick, U.S. Army, DoD (Ref. 1). The DoD vaccine used in the Brachman study was manufactured using an aerobic culture method (Ref. 7). Subsequent to the Brachman study, DoD modified the vaccine's manufacturing process to, among other things, optimize production of a stable and immunogenic formulation of vaccine antigen and increase the scale of manufacture. In the early 1960s (after the Brachman study), DoD entered into a contract with MSD to standardize the manufacturing process for large-scale production of the anthrax vaccine and to produce anthrax vaccine using an anaerobic method.

Thereafter, in the 1960s, DoD entered into a similar contract with MDPH to further standardize the manufacturing process and to scale up production for further clinical testing and immunization of persons at risk of exposure to anthrax. This DoD-MDPH contract resulted in the production of the anthrax vaccine that CDC used in the CDC open label safety study and that was licensed in 1970.

We have reviewed the historical development of AVA and conclude that DoD directed the development of the vaccine, including its formulation and manufacturing process, from the vaccine used in the Brachman study (DoD vaccine) to the vaccine that was ultimately licensed and manufactured by BioPort (DoD/MDPH/AVA vaccine). All three versions of anthrax vaccine, DoD vaccine, DoD/MSD vaccine, and DoD/MDPH/AVA vaccine, were tested in animals and demonstrated to protect test animals (e.g., guinea pigs, rabbits) against challenge with virulent *B. anthracis* spores. In addition, there are clinical data comparing the safety and immunogenicity of DoD/MDPH/AVA vaccine with DoD vaccine. These data, while limited in the number of vaccinees and samples evaluated, reveal that the serological responses to DoD/MDPH/AVA vaccine and DoD vaccine were similar with respect to peak antibody response and seropositivity.

Under FDA's long-standing approach to comparability, a manufacturer may make manufacturing changes in a product without performing additional clinical studies to demonstrate the safety and effectiveness of the similar product if data regarding the manufacturing changes support the conclusion that the versions are comparable. Put another way, after a manufacturing change, a manufacturer may use data gathered with a previous version of its product to support the effectiveness of a comparable version of the same product. These principles are further reflected in FDA's ''Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products'' (1996) (Ref. 8). As discussed previously in this document, DoD vaccine and DoD/MDPH/AVA vaccine are comparable in their ability to protect test animals against challenge with virulent strains of *B. anthracis* and to elicit similar immune responses in humans.

E. The Panel's Specific Product Review: Anthrax Vaccine Adsorbed: Labeling

The Panel report states:

3. *Analysis—d. Labeling*: The labeling seems generally adequate. There is a conflict, however, with additional standards for anthrax vaccine. Section 620.24 (a) (21 CFR 620.24(a)) defines a total primary immunizing dose as 3 single doses of 0.5 mL. The labeling defines primary immunization as 6 doses (0, 2, and 4 weeks plus 6, 12, and 18 months).

(50 FR 51002 at 51059, December 13, 1985).

The Panel was concerned with whether the vaccination schedule conformed to a standard set out in former § 620.24(a), a rule that FDA revoked in 1996 with certain other biologics regulations because they were obsolete or no longer necessary (Ref. 9). The dosing schedule for AVA has always consisted of three doses of 0.5 mL administered in short succession at 0, 2, and 4 weeks, and three additional doses at 6, 12, and 18 months, with additional doses at 1-year intervals to maintain immunity. However, the use of certain terminology has varied as discussed in this section of this document. Pre-licensure labeling (submitted to the license application with a letter dated January 25, 1968) described the vaccination schedule as three initial doses, followed by three additional doses, and yearly subsequent doses. This schedule is consistent with the additional standards of AVA that were originally published on October 27, 1970 (35 FR 16631), immediately before the licensure of AVA. The 1979 labeling referred to ''primary immunization'' as consisting of six injections, with recommended yearly subsequent injections. The 1987 labeling of AVA, approved after the publication of the Panel's report, described the vaccination schedule as a ''primary immunization'' consisting of three doses followed by three additional doses (for a total of six doses), followed by annual injections. While the labeling has variously used the term ''primary'' to describe the AVA vaccination schedule, the licensed schedule itself has always consisted of three initial doses administered at 2-week intervals, followed by three additional doses at 6, 12, and 18 months, with additional annual doses to maintain immunity.

IV. Comments on the December 2004 Anthrax Vaccine Adsorbed (AVA) Proposed Order and FDA's Responses

We received about 350 comments on the December 2004 proposal. Most comments related to AVA. To provide clarity to readers, we separated the AVA final order from the final rule and final order for other bacterial vaccines and toxoids. We are describing and responding to comments about AVA in this section of this document. Comments relating to other portions of the December 2004 proposal are discussed in a final rule and final order concerning bacterial vaccines and toxoids other than AVA published elsewhere in this issue of the **Federal Register**.

We carefully reviewed all comments submitted to the Docket, including those attaching copies of articles and other references. However, a number of comments submitted to the Docket simply referred to articles or other publications, or to Web site materials, without providing copies of the materials. FDA regulations governing submissions to the Docket expressly provide that ''information referred to or relied upon in a submission is to be included in full and may not be incorporated by reference unless previously submitted in the same proceeding.'' (§ 10.20(c) (21 CFR 10.20(c)). Without a copy to review, we were unable to review all references cited but not included in the comments. We obtained and reviewed readily available recognized medical or scientific textbooks (see § 10.20(c)(1)(iv)). The provision of Web site addresses, without substantive material, posed an additional problem. Since Web sites change continually, we were unable to review material at the Web site addresses provided with any

degree of certainty that the comment intended to incorporate the material we found. Also, many Web sites we checked contained irrelevant information. It was often difficult to determine a connection between the Web site and the comment's submission. FDA regulations require that only relevant information is to be submitted (§ 10.20(c)(3)) and failure to comply with these requirements results in exclusion from consideration of any portion of the comment that fails to comply (§ 10.20(c)(6)).

Many comments agreed with the Panel's recommendation that AVA is safe and effective and supported licensure of the vaccine; other comments advocated a need for a panel of experts to review in depth the data on AVA. Many of the comments did not support placing AVA into Category I as recommended by the Panel. Many comments described adverse events and suggested a relationship between the administration of AVA and the adverse events. Other comments recommended further testing of AVA through the conduct of clinical studies or other means. Numerous miscellaneous comments were received, some of which are not relevant to the proposed order. Many of the comments expressed an opinion about the conduct of vaccination administration programs, the need for compensation from public funds to individuals suffering injury from vaccinations, or other activities that are outside of FDA's jurisdiction, authority, and control.

To make it easier to identify comments and our responses, the word ''Comment,'' in parentheses, will appear before the description of comments, and the word ''Response,'' in parentheses, will appear before our response. We numbered the comments to help distinguish between different types of comments. The number assigned to a comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which the comment was received.

A. Comments Supporting Placing AVA into Category I

(Comment 1) We received a number of comments expressing support for the safety and effectiveness of AVA, and for FDA's proposal to accept the Panel's recommendation to place AVA into Category I. Some of these comments were specific in their support of the Brachman study as evidence of effectiveness against anthrax regardless of route of exposure; others discussed or described results of animal studies that they regarded as providing additional supporting evidence that AVA is effective in preventing inhalation anthrax. Some were from vaccine recipients and medical personnel who expressed support for the DoD vaccination program in its effort to protect military personnel from anthrax used as a biological weapon. Others were supportive of the work conducted by DoD to document and evaluate adverse events experienced by military personnel enrolled in the vaccination program.

One comment was from a former director of the Division of Biological Standards (DBS) of the NIH and subsequently within the FDA, who stated his recollection that AVA had been subject to a careful review by DBS staff prior to approval in 1970. He stated that there have been three detailed, unbiased, and scientifically sound reviews, including the initial review by DBS, the expert Panel review in the 1970s (published in the December 1985 Proposal), and the IOM review more recently; and all three reviews concluded that the vaccine is safe and effective. Two comments were submitted by scientists who had been clinical investigators in the Brachman study. One stated that during the study he was blinded to group assignment when evaluating the reactions; i.e., he did not know whether the subject had received the placebo or the vaccine. He also stated that the pathophysiology of human anthrax, regardless of where the organism gains entrance to the body, is a result of the toxin released by the organism. Thus, it is appropriate to combine inhalation and cutaneous disease in the analysis. The other scientist stated that the vaccine has demonstrated effectiveness in animal and human studies, as described in published scientific literature articles.

We received comments from Army research scientists in support of placing AVA into Category I. One of these included tables of data from anthrax spore inhalation challenge studies in non-human primates and rabbits evaluating the effectiveness of AVA in prevention of death from disease. The comment noted that a high degree of protection was observed in these animals following only one or two doses of AVA, and that the IOM committee concluded that these animal models are representative of the human form of inhalation anthrax. Another research scientist also noted that, in addition to the Brachman study, inhalation anthrax challenge studies in non-human primates provide evidence of AVA's effectiveness in preventing disease caused by anthrax spores. Further, he noted that current knowledge of the pathogenesis of anthrax would indicate that, regardless of the route by which spores enter the body, toxins produced after those spores germinate into growing bacilli are essential for the anthrax organism to cause disease. Current scientific understanding of how the toxins work indicates that antibodies induced by AVA block the activities of anthrax toxins such that they would be effective in preventing any form of the disease regardless of the route of exposure to *B. anthracis* spores. Another researcher discussed further and in more detail how the pathology of cutaneous and inhalation anthrax at the cellular level is fundamentally the same, i.e., dependent upon the actions of anthrax toxin, such that cytotoxic activities are blocked by antibodies produced in response to AVA in the same manner despite the route of exposure.

Military personnel involved in the vaccine's administration under the DoD vaccination program also filed comments in support of classifying AVA into Category I, reasoning that the vaccine is important for soldiers entering potentially dangerous areas; however, one comment stated that long-term use of the vaccine should be studied further. Another comment was submitted by a physician who thought that there was evidence that AVA protects against inhalation anthrax and that the side effects of vaccination were comparable to other adult vaccines. Comments supportive of placing AVA into Category I were also submitted by a representative of the Armed Forces Epidemiological Board (AFEB), a civilian advisory body to the Assistant Secretary of Defense for Health Affairs and the military Surgeons General. This comment described the AFEB deliberations on the use of anthrax vaccine by the military and the recommendations made by the AFEB to the DoD supporting use of AVA as an appropriate force protection measure. A representative of the Partnership for Anthrax Vaccine Education, a coalition of public and private organizations, also submitted comments reflecting that organization's support for placing AVA into Category I.

(Response) We agree with those comments that provided support for placing AVA into Category I.

B. Comments on the Evidence of Safety and Effectiveness of AVA

(Comment 2) Some comments were concerned about the safety of AVA.

(Response) With regard to safety, FDA finds that AVA is safe for its indicated use as noted in the 2002 package insert:

BioThrax [the Tradename for AVA] is indicated for the active immunization against *Bacillus anthracis* of individuals between 18 and 65 years of age who come in contact with animal products such as hides, hair or bones that come from anthrax endemic areas, and that may be contaminated with *Bacillus anthracis* spores. BioThrax is also indicated for individuals at high risk of exposure to *Bacillus anthracis* spores such as veterinarians, laboratory workers and others whose occupation may involve handling potentially infected animals or other contaminated materials. (Ref. 6)

The adverse reactions observed after administration of AVA in clinical study settings are described in the product labeling approved in 2002. At that time, FDA conducted an extensive review of the clinical study data from the DoD pilot study, reports from DoD safety surveys conducted as part of their Anthrax Vaccine Immunization Program, and reports submitted to the Vaccine Adverse Event Reporting System (VAERS). Since approval of the revised labeling in 2002, FDA has conducted periodic evaluations of the reports in the VAERS database, and, as discussed elsewhere in this document, continues to find AVA to be safe for its intended use: To protect individuals at high risk for anthrax disease. Anthrax disease can be fatal despite appropriate antibiotic therapy.

1. Brachman Study

(Comment 3) Some comments expressed criticisms of the design and conduct of the Brachman study (Ref. 1).

(Response) The Brachman study was an adequate and well-controlled clinical study that involved workers in four textile mills that processed imported goat hair in the northeastern United States. 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 infections among workers in these mills was 1.2 cases per every 100 employees.

The Brachman study design permitted a valid comparison of the vaccine group with the placebo control group to provide a quantitative assessment of effectiveness. For this study, employees with no known history of anthrax disease were assigned to one of two groups, treatment and placebo. The groups were balanced with regard to the individual's age, length of employment, department and job; both men and women were enrolled into the study. Voluntary cooperation was solicited and those who refused did not receive inoculations but were monitored for anthrax disease as part of the observational group. The subjects who chose to receive inoculations were not told whether they received anthrax vaccine or placebo. The published report of the Brachman study (Ref. 1) described all anthrax cases that occurred in the study, including ones in the vaccine, placebo, and observational groups. The Brachman study's efficacy analysis included only the cases that occurred in the treatment and placebo groups in completely vaccinated subjects (i.e., those receiving at least three inoculations and on schedule to receive the remaining three doses of the six-dose series), an approach that remains typical of vaccine analyses to date. We determine that the original statistical analysis presented in the report from the Brachman study was correct in its estimation of vaccine effectiveness. Some of the specific criticisms of the Brachman study included in the submitted comments claimed that the sample size was too small and that it was inappropriate to combine data from all four mills in the efficacy analysis.

Clinical studies are designed with a sample size sufficient to assure with high probability that, if there is a true effect of the intervention under study, that effect will be ''detected;'' that is, a comparison of outcomes in the treatment and control groups will show a ''statistically significant'' difference. To obtain the required sample size, investigators often have to implement the study at multiple sites (i.e., a multicenter study). The number of patients enrolled at any given site may be small, relative to the total number, and may not afford a high probability of achieving statistical significance at each individual site independently. Thus, when analyzing a multicenter clinical study, it is not reasonable to expect a statistically significant result at each site. Instead, consistent effects among individual study sites are the standard for multicenter studies (Ref. 10).

The Brachman study, a multicenter study, was based on an adequate sample size and appropriately combined the data from all mills in its analysis of vaccine efficacy. The site-specific data for the Brachman study are quite consistent in that at all sites, the vaccine group had fewer cases of anthrax than the placebo group. The strength of the overall finding of vaccine efficacy is such that, even with small numbers at each site, differences in outcome between the treatment and control groups are clearly statistically significant in one site and marginally significant in another. Thus, the site-specific data are fully supportive of the overall result, which showed a large reduction in risk of anthrax among those receiving vaccine.

(Comment 4) One comment noted that a 1960 publication by Brachman et al. stated ''The efficacy of the anthrax cell-free antigen as a vaccine was not fairly tested in this epidemic. Although none of the 9 cutaneous plus inhalation cases occurred in vaccinated individuals, only approximately one fourth of the employees had received the vaccine. There was an apparent difference in attack rates between workers who received placebo inoculations and those who received vaccine, but analysis of their job categories suggested that the vaccinated group was not at as high a risk as the placebo or uninoculated control groups.'' The comment makes several critical statements, based upon this 1960 publication, about FDA's reliance upon the Brachman study as evidence of vaccine effectiveness, claiming that the placebo group was at a greater risk of anthrax disease than the vaccine group.

(Response) Prior to publication of the complete study report in 1962, Brachman et al. published two papers (Refs. 11 and 12) describing the clinical features and epidemiology of an outbreak of inhalation and cutaneous anthrax cases that occurred in the Manchester, New Hampshire mill, one of the four mills included in the field study. The publication describing the epidemiology of that outbreak does include the statement quoted previously; however, the statement is specifically in reference to one study site and not to the field study as a whole, across the four woolen mills. The subsequent 1962 publication (Ref. 1) of the complete study across all four sites includes a table depicting participation of employees from all four mills included in the study. The table shows whether employees worked in high or low risk work areas and whether they received vaccine, placebo, or refused to participate in the study (Ref. 1 at Table 2). Of note, the totals for recipients of vaccine, placebo, incomplete inoculation and refusals in high risk work areas were 209, 226, 65 and 89, respectively. The same totals in low risk work areas were 170, 188, 51 and 251, respectively.

The distribution of vaccine recipients, placebo recipients, and incompletely inoculated subjects was similar for both the high and low risk work areas, which means that the vaccine and placebo groups were balanced with regard to the exposure risk factor. A larger number of persons who did not participate in the study (observation group) were in the low risk work areas than in the high risk areas, but the efficacy analysis did not

include cases that occurred in the observational group. The effectiveness calculation described in the 1962 publication included the anthrax cases that occurred in participants who received at least three doses of either vaccine or placebo and remained on schedule for the remainder of the six doses for all four mills, not just the Manchester, New Hampshire mill described in the 1960 publications. Thus, FDA's consideration of the Brachman study as evidence of effectiveness is based upon the complete analysis across all four study sites.

(Comment 5) One comment stated that it was inappropriate for the Brachman study to include both cutaneous and inhalation cases in the efficacy analysis.

(Response) The efficacy analysis presented in the Brachman study includes both cutaneous and inhalation anthrax cases that occurred in individuals who received at least three doses of vaccine or placebo and were on schedule for the remaining doses of the six-dose schedule. It did not include cases that occurred in the observation group. Based on this analysis, the calculated effectiveness level against all reported cases of anthrax combined in those subjects was 92.5 percent (lower 95 percent confidence interval = 65 percent). The efficacy analysis included the combined outcome of cutaneous and inhalation anthrax cases and thus included anthrax cases regardless of the route of exposure or manifestation of the disease.

The inclusion of both cutaneous and inhalation cases of anthrax in the analysis of the Brachman study was appropriate because it was not possible to predict the route of exposure (cutaneous versus inhalation) that would occur within the environmental setting of the woolen mills. With regard to the known pathophysiology of anthrax, the signs and symptoms of disease arise due to the production of toxins by anthrax bacteria growing within the infected individual. The toxins produced by anthrax bacteria do not vary based on the route of exposure. The antibodies produced in response to vaccination contribute to the protection of the vaccinated individual by neutralizing the activities of those toxins. Thus, AVA elicits an antibody response to disrupt the cytotoxic effects of toxins produced by anthrax bacteria, regardless of the route of infection.

(Comment 6) One comment stated that any decision by FDA to license AVA must provide a scientifically valid explanation of how FDA has assessed this vaccine's effectiveness against anthrax infection by inhalation in humans in the absence of an adequate and well-controlled clinical study specifically studying its effectiveness against anthrax infection by inhalation. The comment contends that in the absence of such data, or unless FDA uses the ''animal efficacy rule,'' FDA should not license AVA as a Category I biological product.

(Response) AVA has been licensed since 1970. The Panel, as reflected in its report published in the December 1985 proposal, and the FDA, as reflected in this final order, have determined that AVA is safe and effective for its labeled indication, decisions based in part on the Brachman study, which was an adequate and well-controlled study. Even if the referenced ''animal efficacy rule''[6] had been in effect at the time of AVA licensure, it would not have been applicable because there are sufficient data from adequate, well-controlled clinical studies to assess the safety and effectiveness of AVA as a vaccine against anthrax infection regardless of route of exposure. The ''animal efficacy rule'' does not apply to products that can be approved based on efficacy standards described in other regulations (§ 601.90 (21 CFR 601.90)).

(Comment 7) One comment pointed out that the route of exposure to an infectious agent can be a critical factor influencing vaccine effectiveness.

(Response) We agree that the route of exposure to an infectious agent may potentially have an impact on the effectiveness of a vaccine. The impact likely depends on the nature of the infectious agent in terms of its mechanism of virulence and the pathophysiology of infection and disease, and the mechanism of protection afforded by the vaccine. The Brachman study showed the anthrax vaccine to be effective in preventing anthrax disease regardless of route of exposure (Ref. 1). This finding is consistent with our current knowledge of the critical role played by anthrax toxins in the pathophysiology of cutaneous and inhalation anthrax and how antibodies generated in response to vaccination with AVA disrupt cytotoxic activities of those toxins. Furthermore, aerosolized anthrax spore challenge studies in both rabbits and nonhuman primates do demonstrate the ability of AVA to protect the test animals against inhalation anthrax (Refs. 3, 4, and 5).

(Comment 8) One comment proposed that a vaccine would have to be inhaled in order to protect against inhalation anthrax, noting that the lungs are susceptible to anthrax.

(Response) Vaccines generally do not need to be administered by the same route of exposure as the infectious agent uses to infect humans. In fact, there are numerous examples to the contrary. For example, vaccines against pertussis, pneumococcus, Hemophilus influenzae type b, meningococcus, measles, varicella, and influenza are administered by injection, although the infectious agents gain entry into humans by the respiratory route. The inactivated poliovirus vaccine is administered by injection, although the poliovirus infects humans by way of the intestinal tract. Although these vaccines are administered by a route that differs from the route of exposure, clinical trials have demonstrated their effectiveness against the targeted infectious disease. The same is true of anthrax vaccine. The vaccine is administered by injection, but has been shown to be effective against anthrax in a study that included both cutaneous and inhalation cases (Ref. 1). Furthermore, animal studies in which injected AVA protected animals from inhalation anthrax challenge are consistent with the finding of effectiveness in the clinical study. (Refs. 3, 4, and 5)

(Comment 9) One comment stated that FDA has deviated from the 1985 Panel recommendations (i.e., ''No meaningful assessment of its value against inhalation anthrax is possible due to its low incidence.'' 50 FR 51002 at 51059) and that FDA should not dispute its advisory committee's analysis of the safety and effectiveness data.

(Response) A critical component of the efficacy review process is FDA's consideration of the Panel's recommendations (§ 601.25(f)). Such consideration, by necessity, provides for the possibility that FDA might disagree with the Panel's recommendations. Indeed, in the preamble to § 601.25, FDA stated that ''the report of each panel is advisory to the Commissioner, who has the final authority either to accept or to reject the conclusions and recommendations of the panel.'' (38 FR 4319 at 4321, February 13, 1973). As noted in section III.A of this document, and as stated in the December 2004 proposal, we do not agree with the Panel's assessment that the vaccine is 93 percent efficacious against cutaneous anthrax only. In fact, the calculation of effectiveness presented in the published report of the Brachman study pertains to both cutaneous and inhalation anthrax. The Brachman study included in the effectiveness calculation both the

[6] New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible; Final Rule (21 CFR 601.90 through 601.95) (67 FR 37988, May 31, 2002).

cutaneous and inhalation cases that occurred in vaccine and placebo recipients who received at least three doses and remained on schedule to receive the rest of the six-dose series.

2. CDC Surveillance Data

(Comment 10) One comment stated that the CDC surveillance data do not provide a reliable basis for an assessment of effectiveness because: (1) They represent the use of at least two earlier versions of anthrax vaccine, which are not the same vaccine currently produced by BioPort; (2) they are not statistically significant; and (3) these data may not be accurate and complete. Other comments asked why the CDC surveillance data for the years 1962 to 1974 are not regarded as supportive of safety of anthrax vaccine.

(Response) During the time these surveillance data were collected by CDC, both DoD/MSD vaccine and DoD/MDPH/AVA vaccine were available for use. The DoD/MDPH/AVA vaccine was licensed in 1970 and is the same vaccine currently manufactured and distributed by BioPort. An additional response to comments regarding different versions of the anthrax vaccine is addressed later in this document.

Although we do not consider the CDC surveillance data to be statistically significant, we regard the data as indicative that, during this time period, workers continued to be at risk of exposure, because anthrax cases were identified in unvaccinated and partially vaccinated individuals employed at woolen mills. The data are supportive of the effectiveness evidenced by the Brachman study, in that no anthrax cases were reported in fully vaccinated individuals during that time period. We do not regard the CDC surveillance data as contributing to an assessment of safety because the data do not describe adverse events occurring after vaccination.

The comment provides no support for the conclusion that the CDC surveillance data were unreliable. The comment described an anecdotal report of an additional anthrax case that occurred in an unspecified year and apparently was not included in the CDC surveillance data. We recognize that there is a potential for underreporting in disease surveillance systems. However, this one report does not provide a basis for concluding that the CDC surveillance data were unreliable for the purposes of supporting the effectiveness of the vaccine.

3. CDC Open Label Safety Study

(Comment 11) Some of the comments questioned the reliability of the CDC open label safety study, alleging that the open label safety study conducted by CDC ''made no attempt to identify, quantify or follow systemic adverse vaccine reactions'' and thus would be of no value in establishing vaccine safety, or that the study did not use consistent standards to identify and grade adverse events occurring at different study sites.

(Response) As described previously in this document, FDA believes that there are adequate data to demonstrate the safety and effectiveness of AVA. Moreover, the CDC open label safety study appropriately collected and analyzed adverse event reports. The IND protocol for the CDC open label safety study included specific criteria to be used to categorize mild, moderate and severe local reactions reported in the course of the study. In addition, the annual study reports submitted to the IND included information regarding systemic reactions reported during the respective reporting periods, and those data are described in the current product labeling for AVA: ''In the same open label safety study, four cases of systemic reactions were reported during a five-year reporting period (<0.06% of doses administered). These reactions, which were reported to have been transient, included fever, chills, nausea and general body aches.'' (Ref. 6)

(Comment 12) One comment claimed that one annual safety report for the CDC open label safety study might have underreported adverse reaction rates for that period, alleging that arithmetic miscalculations caused underreporting in one May 1967 reactogenicity table.

(Response) The commenter refers to the May 1967 table included in an appendix to one of the annual reports to the CDC trial; the appendix describes a protocol and the results of a small safety and immunogenicity study comparing DoD vaccine and DoD/MDPH/AVA vaccine. The safety data from this small study were reported separately from the CDC open label safety study due to differences in protocol design, such as the administration of one-half volume booster doses to some subjects instead of the full 0.5 mL human dose. Inclusion of safety data from the small ancillary safety study with a different protocol design does not support the inference that the annual safety report for the CDC open label safety study might have underreported adverse reaction rates for that period.

(Comment 13) One comment stated that in the course of the CDC open label safety study, Ft. Detrick and mill employees were required to be vaccinated as a condition of employment and therefore, they may have underreported adverse reactions to the vaccine from fear of losing their jobs. The comment also states that the employees did not provide free informed consent to participate in the study because they were compelled to be vaccinated, and no informed consent documents were signed by Ft. Detrick employees. Thus, the study did not comply with FDA requirements for informed consent.

(Response) The comment provides no support for the assumption that subjects in the CDC open label safety study may have underreported adverse reactions to the vaccine. With regard to the statements that mill workers in the CDC open label safety study were compelled to be vaccinated, and therefore did not provide informed consent, and that the Ft. Detrick subjects in the study did not sign informed consent documents, we note that the CDC open label safety study was conducted under IND 180 from 1966 through 1971. The NIH was responsible for reviewing IND 180 and the subsequent marketing application for AVA under the regulations then in effect. Significantly, the NIH did not reject the study, or place it on hold. Moreover, the comment does not identify a legal basis for requiring FDA to reject the study for this reason.

FDA is committed to assuring the protection of human subjects in clinical trials, as evidenced by the comprehensive regulations now in place (see FDA's current informed consent regulations, 21 CFR part 50, in effect since 1981, and IND regulations, 21 CFR part 312, in effect since 1987). Other data and studies, such as the DoD pilot study, conducted subsequent to the CDC open label safety study and under current informed consent regulations, provide additional safety evidence that corroborate the CDC open label safety study findings. We decline to reject the findings of the CDC open label safety study and we continue to view them as supportive of safety.

4. DoD Pilot Study and Safety Data

(Comment 14) One comment inquired whether the results of the DoD pilot study relating to the vaccine's safety required changes to AVA labeling in 2002, and whether additional data were considered in support of the new labeling. Other comments asked whether the DoD pilot study was also regarded as supportive of effectiveness.

(Response) BioPort voluntarily submitted to FDA proposed revised labeling for AVA for review and comment as part of an ongoing process of updating product and manufacturing information. In the course of FDA's review, revisions were made to the proposed labeling. Following our

review, in 2002 we approved revised product labeling that incorporated more recently acquired safety information from the DoD pilot study and FDA's ongoing review of reports to VAERS. The DoD pilot study was not intended to assess effectiveness; rather its purpose was to make an initial assessment of the effects that alternative immunization schedules and/or an alternative route of administration may have on the safety and immunogenicity of AVA.

(Comment 15) One comment claimed that the 1996 to 1999 DoD pilot study as reported is entirely inadequate to determine the safety of AVA, noting that the study was ''uncontrolled'' and that a quarantined lot was used in the study.

(Response) As discussed previously in this document, the CDC open label safety study, involving approximately 7,000 subjects who received DoD/MDPH/AVA vaccine,[7] demonstrated the safety of AVA. The DoD pilot study, which included 28 subjects randomized to receive the licensed vaccine according to the labeling, was conducted subsequent to licensure and provided additional data in support of the safety of AVA. The DoD pilot study was a controlled clinical study; the group receiving AVA according to the licensed schedule and route of administration served as the control group for the other groups receiving the vaccine under alternative vaccination schedules and/or route of administration. The purpose of the DoD pilot study was to make an initial assessment of the effects that alternative immunization schedules and/or an alternative route of administration may have on the safety and immunogenicity of AVA. The alternative schedules were alterations of the 0-2-4 week initial series of the licensed six-dose schedule (i.e., 0-4 weeks, 0-2 weeks). These alternative schedules were administered intramuscularly and subcutaneously. However, because one of the arms of the study included individuals vaccinated according to the labeling, we appropriately took such information into account as we continued to assess the safety of AVA. In this arm of the study, volunteers received subcutaneous doses of AVA according to the licensed schedule. Each volunteer was scheduled for follow-up evaluations at 1 to 3 days, 1 week, and 1 month after vaccination, and reactions were reported up to 30 days after each dose. For subjects who received the vaccine according to the licensed route and schedule, the latest follow-up occurred 30 days after the 18-month dose (Ref. 13).

In the December 2004 proposal, FDA discussed the safety data collected under this study for subjects receiving the vaccine according to the labeling. Similarly, descriptive information regarding adverse reactions reported in individuals receiving the vaccine according to the licensed schedule under this study was included in the 2002 labeling. Thus, the December 2004 proposal and the 2002 labeling reported this recently acquired safety information, which had been collected in a planned and prospective manner.

In addition, we believe no subjects in the study received quarantined doses of lot FAV 016, the lot mentioned in the comment. We understand that some subjects received lot FAV 032 while the voluntary quarantine of that lot was being implemented. However, this information does not provide an adequate basis for us to refuse to consider the data derived from the study. It is important to note that one of the chief uses of the study was as one of the bases for the expanded description of adverse events included in the 2002 labeling. Thus, the study results provided additional information for individuals administering and receiving AVA. We believe that this limited use of lot FAV 032 did not cause the results of the entire study to be unreliable, particularly in light of the purposes for which we use the data derived from this arm of the study. We will continue to monitor all available sources of information relating to the safety of AVA.

(Comment 16) One comment was critical of the fact that the results of the DoD pilot study were included in the 2002 labeling when the data were not peer reviewed or available to the public.

(Response) FDA performs its own review of data that are submitted in support of labeling changes. There is no requirement for peer review of data submitted to FDA in support of a labeling change. The DoD pilot study was intended to serve as a pilot study of alternative vaccination schedules and an alternative route of administration (intramuscular) to provide information for the design of a larger, more statistically robust study of promising alternative vaccination schedules and route of administration. The investigators published their report of this study in a peer-reviewed journal (Ref. 13).

5. Long-Term Safety Monitoring and Additional Studies

(Comment 17) A number of comments discussed the absence of a long-term safety study using AVA and the absence of studies of the potential effects of vaccination on vaccine recipients' children.

(Response) The pre-licensure safety evaluation of a new vaccine may include clinical studies that extend several months to several years after administration of the first dose. For example, the CDC open label safety study spanned from 1966 through 1971. Pre-licensure safety studies focus on those adverse reactions closely associated with the time of vaccine administration such as local injection site reactions and systemic reactions such as fever, malaise and allergic reactions. However, all serious adverse events that are reported during the conduct of the study are evaluated regardless of when they occur relative to vaccination. Longer-term controlled clinical trials (i.e., those extending more than several years after vaccination) are not generally conducted prior to approval of any medical product, including vaccine products.

The attribution to a vaccine or other drug product of adverse events or health conditions that develop long after administration is difficult to make with confidence because other factors such as environmental exposures, general health, genetic predisposition, etc., may also contribute to the development of health problems, symptoms or diseases. Elsewhere in this document, we provide a more detailed discussion of FDA's approach to post-licensure safety monitoring of AVA.

With regard to the potential effects of vaccination on offspring, the current approved labeling for AVA addresses administration of AVA to pregnant women. The labeling describes a preliminary assessment of the possibility that an increase in the rate of birth defects may be associated with AVA vaccination during pregnancy. Based upon the limited information available, the vaccine was assigned a Pregnancy Category D designation. The labeling states that ''Although these data are unconfirmed, pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination have been determined to outweigh the potential risk to the fetus.'' (Ref. 6)

DoD has undertaken to verify these preliminary results. We will review those results, when available, and we will continue to review adverse events.

(Comment 18) Many comments expressed concern about FDA's process of monitoring the safety of AVA.

(Response) For any drug or biological product, rare adverse events not observed during pre-licensure clinical studies may occur post-licensure. The

[7] In addition, one lot of the DoD/MSD vaccine was used during the CDC open label safety study.

need to understand the relationship between vaccination and adverse events that occur after licensure, and the limitations of clinical trials, have led to the use of other methods to detect and evaluate the link between vaccination and rare events. Post-marketing monitoring of vaccine safety involves the identification of possible adverse effects of vaccination, followed in some cases by evaluation of these ''signals'' for a possible causal link to the vaccine.

The most common method of signal generation is through the evaluation of spontaneous reports of cases of adverse events reported to manufacturers or government-sponsored systems such as the Vaccine Adverse Event Reporting System (VAERS). The identification of ''signals'' and their prioritization for evaluation involves qualitative and quantitative aspects, along with medical and epidemiological judgment. Evaluation of signals can involve literature review and clinical, laboratory, and epidemiological studies.

Surveillance for adverse events after vaccination is undertaken using VAERS, which is jointly managed by FDA and CDC. Uses of VAERS include detecting unrecognized adverse events, monitoring known reactions, identifying possible risk factors, and vaccine lot surveillance. Established in 1990, VAERS receives approximately 15,000 adverse event reports annually. Reports are submitted by vaccine manufacturers, vaccine providers, other health care givers, vaccine recipients and their relatives, attorneys, and other interested parties. While vaccine manufacturers are responsible for investigating and evaluating reports made to them, FDA and CDC also follow up reports from other parties of deaths and adverse events resulting in life-threatening illness, hospitalization, prolongation of hospitalization, persistent or significant disability, or congenital anomaly/birth defect, by telephone to obtain additional information about the event and the patient's prior medical history.

Passive surveillance systems such as VAERS are subject to limitations. Vaccine-associated adverse events will inevitably be underreported to an unknown extent. Moreover, adverse events reported in association with vaccination may or may not be caused by vaccination. For example, some adverse events might be expected to occur by coincidence after vaccination. Temporal associations often are reported with little data to evaluate whether any causal connection with the vaccine exists. Given these limitations, while safety signals may be detected, incidence rates cannot be determined from VAERS data. A particularly important limitation on the usefulness of VAERS reports as a means of investigating the possible causal relationship between an event and a vaccination generally is the lack of a direct, concurrent and unbiased comparison group from which to determine the incidence of the same type of adverse events among people who have not been vaccinated.

Another important limitation is the lack of standardization of diagnoses in VAERS reports. Reporting of unconfirmed diagnoses is common with VAERS reports. On follow-up, initially reported diagnoses are sometimes found to be inaccurate. Reports are coded by non-physicians, without the benefit of standardized case definitions, using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) to describe the adverse event in a computerized database. Report coding depends on the reporter's use of certain words or phrases. This results in the use of the same COSTART term for reports with different degrees of diagnostic precision. For example, a report may simply say, ''I developed arthritis after I received the vaccine,'' without any other supporting medical information. Such a report would likely be coded as ''arthritis,'' as would a report that included a complete medical record in which a physician documents joint swelling and tenderness. As a result, coding terms must be interpreted very cautiously.

Because of the limitations of passive surveillance data, it is usually not possible to assess whether a vaccine caused the reported adverse event, except for conditions such as injection site reactions, some hypersensitivity conditions (e.g., anaphylaxis occurring shortly after vaccination), and illnesses consistent with the naturally occurring disease where vaccine components can be recovered from tissue specimens (e.g., recovery of live attenuated vaccine virus from vaccine-associated paralytic polio).

Analysis of VAERS data focuses on describing clinical and demographic characteristics of reports and looking for patterns to detect ''signals'' of adverse events plausibly linked to a vaccine. In FDA's guidance document on ''Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment'' (Ref. 14), we define a safety signal as a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. This guidance document also details approaches for signal evaluation. Evidence of a signal in case reports and in case series of spontaneous reports includes unexpected patterns in clinical conditions by such factors as age, gender, time to onset, and dose. Three reports of an event can be used as the minimum number for case series analysis of rare conditions. Positive rechallenge is defined as the same event occurring after more than one dose of the same vaccine in the same subject and may also be considered evidence of a signal. Signals detected through analysis of VAERS data do not necessarily represent a causal relationship with the vaccine and almost always require confirmation through additional study.

In addition to the approach combining descriptive epidemiology with medical judgment, described above, several quantitative approaches, sometimes referred to as ''data mining'' methods, have been proposed. A common feature of data mining methods is that they identify patterns in the data that consist of a condition or group of conditions that are reported as a higher proportion of all adverse events after a particular vaccine or combination of vaccines than after other vaccines.

Calculations of reporting rates (number of adverse events reported/number of doses of vaccine distributed) and reporting rate ratios (ratio of reporting rate in the vaccine of interest to the reporting rate in the comparison vaccine(s)) of adverse events have been used to generate signals. Comparison of reporting rates with background incidence rates for an adverse event is also sometimes advocated. Biases in reporting, inadequate denominator data, uncertainty of the risk interval (the interval after vaccination during which a person might be at risk for the adverse event under study) and lack of background incidence rates from an appropriate comparison population for some conditions limit the utility of the reporting rate approach.

Regardless of the method used, interpretation of vaccine-adverse event combinations that are identified as possible signals with any quantitative method must use medical knowledge about the disorders and take into account biases in reporting, misclassification of reports that occur with adverse event coding systems, and other limitations of passive surveillance systems previously discussed. Signals generated through such quantitative analysis need to be subject to the same clinical, descriptive epidemiological, and other analysis as for case reports and case series of spontaneous reports. Elevated reporting rate ratios or proportional reporting ratios or similar scores from data mining should not by themselves be interpreted as

establishing a causal relationship between an adverse event and a vaccine, but almost always require independent confirmation through additional study.

In spite of these limitations, use of VAERS data has provided initial reports that upon further evaluation have raised suspicions, later confirmed, about rare reactions to vaccines (e.g., intussusception after rotavirus vaccine). VAERS data also have suggested the need for further study of other adverse events (e.g., myopericarditis after smallpox vaccine).

Many possible signals[8] can be generated with these methods and prioritization for further evaluation is required. Because information submitted to VAERS is often incomplete, it is sometimes necessary to do enhanced follow-up of reports to systematically collect information as the first stage in the signal evaluation process. Objective factors such as seriousness and ''newness'' of the adverse event, size of the population potentially affected, ability to prevent the adverse event, and ability to study the question, influence priority for further evaluation.

VAERS reports are not the only source of information used to evaluate the safety of a vaccine. Evaluation of signals usually requires a literature review followed by epidemiological studies, sometimes combined with clinical and laboratory analysis. To evaluate specific hypotheses it is sometimes necessary to conduct cohort, population-based case series, case-control or other epidemiological studies using large administrative databases with medical record review.

If a clinical trial with sufficient statistical power to evaluate the adverse event of interest has not been conducted, assessing the potential causal link between a vaccine and an adverse event often requires integration of different types and quality of information (e.g., laboratory studies, case reports, epidemiological studies, and clinical studies). Causal inference criteria, patterned after those proposed by A. Bradford Hill in 1965 and adapted by others, and formal risk assessment have been applied to vaccine safety assessments. In a study of pertussis and rubella vaccines in the early 1990s, the IOM used the strength of association, the nature of the dose-response relation, the existence of a temporally correct association, consistency of association, specificity of the association, and the biological plausibility of the association for assessing whether evidence indicates a causal relationship between an adverse event and vaccine exposure (Ref. 15). These criteria were also used in other more recent vaccine safety reviews performed by the IOM in 2001 through 2004 (Ref. 16).

(Comment 19) Many comments questioned the role of VAERS.

(Response) Data from VAERS cannot generally be used to determine if a vaccine causes an adverse event, but VAERS data can be useful for hypothesis generation. As noted in the AVA labeling, a report of an adverse event is not proof that the vaccine caused the event.

From 1990 through March 31, 2005, approximately 1.3 million military personnel received 5.3 million doses of AVA. We evaluated the 4,370 VAERS reports of adverse events following administration of AVA submitted to VAERS from 1990 through August 15, 2005, (4,279 through March 31, 2005) using a combination of the techniques described previously in this section of this document (e.g., pattern assessment using frequency calculations, identification and descriptive analysis of case series, assessment of reporting rates for certain clinical conditions in the context of available information about background incidence rates and risk intervals, and data mining). Based on our review, we cannot conclude that there is a causal relationship between serious adverse events (other than some injection site reactions and some reports of allergic reactions) or deaths and AVA (Ref. 17). However, as with any medical product, FDA cannot rule out that some rare adverse events could be caused by AVA. As described in our response to Comment 21, VAERS data were used, along with other data, to develop a list of certain adverse events that were considered for further study by the Vaccine Analytic Unit. The Vaccine Analytic Unit has selected five topics for initial study to determine whether AVA has a causal role in certain serious adverse events. FDA continues to perform surveillance and periodic evaluations of adverse event reports, and will review post-marketing data from any studies that become available to FDA.

(Comment 20) Some comments on the December 2004 proposal seemed to interpret the spontaneously reported adverse events that are listed in the AVA labeling as being caused by the vaccine.

(Response) To make physicians and others aware of what is being reported, adverse events are sometimes included in the vaccine labeling even though it has not been shown that the vaccine actually caused the adverse event. Thus, for AVA, that section of the labeling is preceded by the statement, ''The following four paragraphs describe spontaneous reports of adverse events, without regard to causality'' to indicate that the relationship to the vaccine cannot be determined from the information provided in the reports for those events.

(Comment 21) One comment asked if FDA has required BioPort or DoD to conduct focused studies of any safety signals.

(Response) We encourage and support the expeditious conduct of well-designed studies evaluating the relationship between AVA and adverse events. The Vaccine Analytic Unit (VAU) was formed as a collaboration between DoD and CDC to conduct vaccine post-marketing surveillance investigations of AVA and other vaccines using data collected by the Defense Medical Surveillance System, which holds information on vaccinations, hospitalizations, outpatient visits, occupational variables, and demographics for all U.S. military personnel. FDA worked with the VAU to develop a list of adverse events for further study based on VAERS and other data sources. In 2004, VAU participants and a workgroup of the National Vaccine Advisory Committee (NVAC) agreed that the VAU's research agenda would include five topics for initial study: Systemic lupus erythematosus, optic neuritis, arthritis, erythema multiforme, and multiple, near-concurrent vaccinations.[9]

(Comment 22) Some comments suggested that new clinical studies be conducted using anthrax spores milled to a fine powder or using all 60 strains of anthrax. Others asked why it would

[8] Safety signals that may warrant further investigation may include, but are not limited to, the following: (1) new unlabeled adverse events, especially if serious; (2) an apparent increase in the severity of a labeled event; (3) occurrence of serious events thought to be extremely rare in the general population; (4) new product-product, product-device, product-food, or product-dietary supplement interactions; (5) identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities); (6) confusion about a product's name, labeling, packaging, or use; (7) concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment); (8) concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a risk minimization action plan goal); and (9) other concerns identified by the sponsor or FDA. (''Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment,'' March 2005.)

[9] Description of the VAU and the topic selection process are available at *http://www.cdc.gov/nip/webutil/about/annual-rpts/ar2005/2005annual-rpt.htm#online* (click on ''Leadership in Vaccine Safety'') and *http://cdc.confex.com/cdc/nic2004/techprogram/session_787.htm.*

be unethical to conduct additional human efficacy studies.

(Response) It is generally accepted that due to the significant health risks associated with exposure to anthrax spores, it would not be ethical to actively expose human study subjects to *B. anthracis* spores in order to assess the effectiveness of an anthrax vaccine in a controlled clinical trial. Furthermore, naturally occurring anthrax is now so rare that a field study of vaccine effectiveness is no longer feasible in the United States. For any future effectiveness studies, it is likely that the efficacy studies will need to be conducted in well-characterized animal models with an appropriate bridge to human immunogenicity data as described under the ''animal efficacy rule''[10] where human efficacy studies are not feasible or ethical (§§ 601.90 and 601.91(a)).

C. Comments Describing Adverse Events

1. Review of Adverse Event Reports Submitted to the Docket[11]

(Comment 23) Many comments to the docket described adverse events stated to have occurred following administration of AVA. For approximately 111 individuals, information was provided to the docket about specific adverse events experienced by the person filing the comment, a family member, or another person. Several comments indicated that a report about the adverse event had been submitted previously to VAERS. However, most of these comments did not mention whether a report to VAERS had been submitted.

(Response) The comments submitted to the docket for the December 2004 proposal described adverse events after administration of AVA in approximately 111 individuals. Multiple submissions were received for some individuals. To facilitate analysis of this information and to compare the comment reports with other VAERS reports, we entered into VAERS the adverse events reported in comments to the extent possible based on the information provided. Comments to the docket that reported only non-specific adverse events such as became ''ill'' or had a ''bad reaction'' were not entered into VAERS because of the lack of adequate specificity. Also, submissions that described groups of persons, adverse event statistics, or otherwise lacked key individual-level details used in VAERS, were not entered into VAERS, but were reviewed and considered.

More than one source (e.g., health care provider, patient, and manufacturer) might submit to VAERS information concerning a single individual's adverse events following a particular vaccination date, resulting in multiple reports. Routine report processing in VAERS includes steps aimed at identifying and linking such related reports. Using these processes, we found that 48 (43 percent) of the individuals described in adverse event reports submitted in comments to the docket were the subjects of reports previously entered into VAERS.

We categorized 106 of the 111 reports as serious, including 6 deaths. Most described one or more chronic symptoms or illnesses, though the duration was not always evident. VAERS reports had previously been received for two of the persons who died.

2. Summary of Adverse Event Reports Submitted to the Docket

The adverse event reports submitted to the docket did not provide substantially different information about possible new safety signals than the previous reports to VAERS. The previous reports to VAERS, together with the reports to the docket, do not establish a causal relationship between death or serious adverse events (other than some injection site reactions and some reports of allergic reactions) and AVA (Ref. 17). We entered into the VAERS database the conditions described in comments to the docket. These conditions will be considered along with all other adverse event reports received through continuing surveillance and incorporated into the periodic evaluations of these reports.

D. Comments on the Vaccine Used in the Studies

(Comment 24) Several comments raised issues about the versions of vaccine used in the Brachman study, the CDC open label safety study, and the vaccine made by MDPH at the time of licensure.

(Response) While the December 2004 proposal discussed the historical development of AVA, in light of the comments received, we believe that additional clarification of the historical development is warranted. In the 1950s, Brachman, et al., conducted a well-controlled field study in four woolen mills in the United States using DoD vaccine provided by Dr. G. G. Wright of Fort Detrick, U.S. Army (Ref. 1). This vaccine was produced from the growth of a nonencapsulated, nonproteolytic mutant (R1–NP) of the Vollum strain of *B. anthracis* using an aerobic culture method and evaluated for potency (i.e., ability to protect test animals against challenge with virulent *B. anthracis* spores) (Ref. 7).

In the early 1960s, subsequent to completion of the Brachman study, DoD modified the vaccine manufacturing process to, among other things, optimize production of a stable and immunogenic formulation of vaccine antigen and to increase the scale of production. These changes included a change in the mutant *B. anthracis* strain (V770–NP1–R) used to produce the vaccine and use of an anaerobic culture method (Refs. 18 and 19). These changes coincided with initiation of a contractual agreement between DoD and Merck Sharp & Dohme (MSD) to standardize the manufacturing process for large-scale production of anthrax vaccine and to produce anthrax vaccine using an anaerobic method. Vaccine lots manufactured by MSD under this contract were evaluated for potency (i.e., ability to protect test animals against challenge with virulent *B. anthracis* spores). One lot of vaccine manufactured by MSD (Merck–9) was also used during the first year of the CDC open label safety study.

In the mid–1960s, DoD entered into a similar contract with MDPH to further standardize the manufacturing process and to scale up production for further clinical testing and immunization of persons at risk of exposure to anthrax spores. This DoD/MDPH/AVA vaccine was made using the same strain of *B. anthracis* as that used under the DoD contract with MSD (DoD/MSD vaccine) and similar culture conditions. Vaccine lots manufactured by MDPH under this contract with DoD were evaluated for potency (i.e., ability to protect test animals against challenge with virulent *B. anthracis* spores). DoD/MDPH/AVA vaccine lots were used in the CDC open label safety study. Under the contract with DoD, MDPH pursued pre-market approval of the vaccine. The DoD-MDPH contract resulted in the production of AVA, which the NIH Bureau of Biologics licensed in 1970, FDA now regulates, and BioPort presently manufactures.

The safety and immunogenicity of the three generations of the anthrax vaccine were evaluated in three groups of vaccinees, one receiving DoD vaccine, another receiving DoD/MSD vaccine, and the third group receiving DoD/MDPH/AVA vaccine. Vaccine recipients were monitored for local and systemic adverse events. Antibody responses, expressed as Geometric Mean Titers and

[10] New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible; Final Rule (21 CFR 601.90 through 601.95) (67 FR 37988, May 31, 2002).

[11] Docket Number 1980N–0208.

percent seropositives, were measured in blood samples collected at regular intervals following administration of the third vaccine dose utilizing an agar-gel precipitin-inhibition (AGPI) test. These data, while limited in the number of vaccinees and samples evaluated, reveal that the serological responses to DoD/MDPH/AVA vaccine and DoD vaccine were similar with respect to peak antibody response and percent seropositives and support our conclusion that data generated by administration of DoD and DoD/MSD generations of the vaccines support licensure of DoD/MDPH/AVA vaccine.

(Comment 25) Some comments mentioned that, in the 1985 report, the Panel noted that DoD/MDPH/AVA vaccine had not been employed in a controlled field study.

(Response) Although the Panel Report included the statement described in Comment 25, the Panel immediately followed with a statement that a ''similar'' vaccine was employed in a placebo-controlled field trial. The Panel then concluded that DoD/MDPH/AVA vaccine was ''patterned after'' the vaccine used in that trial (which the Panel mistakenly referred to as DoD/MSD vaccine, rather than DoD vaccine) ''with various minor production changes.'' (50 FR 51002 at 51059, December 13, 1985). Thus, the Panel concluded that the Brachman study, which used DoD vaccine, supported a finding of safety and effectiveness of DoD/MDPH/AVA vaccine. It is common practice for a product to undergo manufacturing changes as it moves from initial development to product approval. If an earlier generation is comparable, then studies using that earlier-produced product are relevant to the later product. As we discuss elsewhere in this section of this document, the controlled field study using DoD vaccine was relevant to DoD/MDPH/AVA vaccine, since the two vaccines were comparable in terms of their ability to protect test animals against challenge with *B. anthracis* and to elicit an immune response in humans.

(Comment 26) One comment stated that FDA is using potency data ''that it knows are unreliable to assert comparability of two different anthrax vaccines [DoD and DoD/MDPH/AVA vaccines]'' and if reliable ''would only establish comparable animal efficacy for the two vaccines, and fail to establish human efficacy, human safety and the comparability of the vaccines for humans.''

(Response) We note here that the comment did not provide evidence to support the statement that the potency data are ''unreliable.'' The potency data described in the response to Comment 24 demonstrated that the products are comparable. In addition, the clinical data described in response to Comment 30 demonstrated clinical comparability between the vaccines with regard to Geometric Mean Titer and seropositivity rates.

(Comment 27) One comment inquired about whether the differences in the versions of AVA resulted in differences in their safety.

(Response) There are ample clinical data and information from the CDC open label safety study, conducted under IND in the 1960s, which demonstrate that the DoD/MDPH/AVA vaccine is safe.

FDA's assessment of vaccine safety considered the data collected under the CDC open label safety study (1966 through 1971). During the first year of this study, CDC used one lot of DoD/MSD vaccine and one lot of DoD/MDPH/AVA vaccine, but only DoD/MDPH/AVA vaccine was used during the remainder of the safety study. Thus, the majority of the safety data accumulated in that study was from the use of vaccine manufactured by MDPH. Information pertaining to the incidence and severity of adverse reactions associated with administration of DoD/MDPH/AVA vaccine was collected for approximately 7,000 individuals participating in the CDC open label safety study. In addition, the safety of the vaccine is evaluated on an ongoing basis through review of new studies, such as the DoD pilot study, and periodic assessments of VAERS data.

(Comment 28) One comment stated that the differences in reported systemic reaction rates for the Brachman study and the later DoD pilot study indicate that DoD vaccine and DoD/MDPH/AVA vaccine are distinctly different such that the effectiveness associated with DoD vaccine cannot be regarded as evidence of effectiveness of DoD/MDPH/AVA vaccine.

(Response) We agree that the rates of reported systemic reactions associated with administration of anthrax vaccine in the Brachman study are lower than the rates reported in the DoD pilot study. However, we believe that the Brachman study provided evidence of effectiveness of the licensed vaccine. Differences between the Brachman study and the DoD pilot study in reported systemic reactions are attributable to a number of factors. The latter study was specifically designed to closely monitor and solicit subjects' information pertaining to adverse reactions associated with administration of the vaccine in accordance with the licensed schedule and route of administration so that comparisons of adverse reaction rates could be made between the licensed schedule and route and the alternative schedules and route also under investigation in that study. Differences in methodologies and design as well as a heightened awareness and sensitivity toward adverse reactions on the part of both study investigators and study subjects has resulted in a more comprehensive description of adverse reactions experienced in association with vaccination in the more recent DoD pilot study.

As discussed more fully previously in this document, DoD/MDPH/AVA vaccine was used in the CDC open label safety study; the production strain and culture methods were the same as those currently used by BioPort. To provide a more current picture of the types and severities of reactions associated with DoD/MDPH/AVA vaccine, the product labeling now includes descriptions of adverse events reported in association with administration of AVA in the DoD pilot study. Although the reporting rates for certain reactions are greater in the DoD pilot study, we continue to regard AVA to be safe for its intended use: To protect individuals at high risk for anthrax disease. Anthrax disease can be fatal despite appropriate antibiotic therapy.

(Comment 29) One comment stated that the anthrax vaccine produced in Michigan has undergone a series of manufacturing changes since it was licensed, resulting in a materially altered product that is much more concentrated than the original MDPH vaccine.

(Response) We note that the comment did not provide evidence to support the claim that DoD/MDPH/AVA vaccine is ''more concentrated'' now than when originally licensed. The DoD/MDPH/AVA vaccine currently manufactured by BioPort was licensed in 1970. Since then, the strain of *B. anthracis* used to produce the vaccine has not changed and the vaccine formulation has not changed. Changes in the manufacturing process (including equipment changes) have been reviewed and approved by FDA. Each lot of final vaccine product must pass certain criteria, including potency testing, as described subsequently in this document in the response to Comment 33.

(Comment 30) Some comments inquired about whether the change in vaccine during the 1962 to 1974 surveillance period altered the vaccine's effectiveness. One comment was critical of FDA's assessment that both the DoD generation and the DoD/MDPH/AVA

generation of the vaccine stimulated similar peak antibody responses and seropositivity rates since there was not an ELISA assay available at the time the antibody responses were measured. The comment argued that antibody levels cannot be used as a surrogate marker for effectiveness.

(Response) The antibody responses were measured by agar-gel precipitin-inhibition test, which was an acceptable assay. The immunogenicity data resulting from this testing showed that the DoD and the DoD/MDPH/AVA generations of the vaccine were both immunogenic. After the third dose, the peak Geometric Mean Titer for antibodies to anthrax was 1.30 (60 percent seropositivity of samples tested) for DoD/MDPH/AVA vaccine, and 1.4 (60 percent seropositivity of samples tested) for DoD vaccine. Thus, while limited in the number of vaccinees and the number of samples analyzed, the results do indicate comparable immune responses with regards to seropositivity rates and peak antibody titer levels (GMT). Rather than representing a surrogate for effectiveness, these results are a means of bridging the immunogenicity of these generations of the vaccine. In any event, the CDC surveillance data, which were gathered when the DoD/MDPH/AVA and DoD/MSD generations of the vaccine were in use, corroborate the efficacy data provided by the Brachman study.

(Comment 31) Some comments inquired whether the DoD pilot study or a larger ongoing CDC study are intended to provide data to reduce the vaccine dose level. Another comment asked how FDA has validated the current dose and inoculation schedule.

(Response) The DoD pilot study was followed by a larger, more statistically robust and significant CDC study in order to obtain safety and immunogenicity data to support a reduction in the total number of doses to be administered in a complete vaccination schedule. The new CDC study is a double-blind, randomized, placebo controlled trial conducted under IND to compare the licensed AVA schedule and route of administration (subcutaneous) to regimens with a different route of administration (intramuscular) and/or reduced number of doses. Safety and immunogenicity are assessed. The study started in May 2002 and is currently ongoing. The clinical studies referenced in the comment were not intended to seek a change in the amount of vaccine administered with each dose. The current dosage for AVA is 0.5 mL per inoculation and has been used for anthrax vaccine since before the Brachman study was conducted in the 1950s. The current 0.5 mL dosage and 6–dose regimen and schedule are based on the dosage, regimen, and schedule used in the Brachman study.

(Comment 32) One comment noted that there would have been no need to continue to develop newer and different anthrax vaccines had Brachman's vaccine produced acceptable safety and efficacy.

(Response) On the contrary, DoD (in particular, the Army, Dr. G. G. Wright and his colleagues) pursued improvements in the manufacturing process, formulation, and other aspects of anthrax vaccine precisely because it had been shown to be safe and effective in the Brachman study. The changes implemented with the transfer of production to MSD and then to MDPH were with the intent of increasing ease of production and yield to support further study and ultimately licensure of the vaccine. FDA encourages license holders to embrace continuous improvement.

E. Comments about Allegedly Contaminated Vaccine and Inspectional Observations

(Comment 33) Some comments asserted that AVA is contaminated or adulterated, citing FDA inspections of the Michigan Biologic Products Institute (MBPI, and then BioPort) facility. Some comments expressed concerns about particular lots of AVA received by soldiers in the U.S. military, stating that they were not made under current good manufacturing practice (cGMP) or were contaminated.

(Response) FDA has a lot release program to determine whether lots of the AVA licensed vaccine meet criteria for release, which include sterility, general safety, potency, and specified levels of benzethonium chloride, aluminum, and formaldehyde. All lots released from the manufacturer for administration to military personnel and other individuals met these criteria.

Additionally, FDA performs inspections of all biological product license holders biennially and at additional times when FDA deems that more regulatory oversight is warranted. On the basis of such inspections, FDA issued to AVA's manufacturer a Warning Letter in 1995, and a Notice of Intent to Revoke the license to manufacture all products, including AVA, in 1997. FDA did not initiate license revocation proceedings because BioPort committed to and implemented appropriate corrective and preventive actions to address the issues identified by FDA and demonstrated over time its commitment to comply with all applicable FDA requirements. BioPort did this by, among other things, renovating its AVA manufacturing facility, discontinuing the manufacture and distribution of all non-AVA products, closing its aseptic filling facility, and moving the AVA filling operations to a contract manufacturer. We believe that the manufacture of AVA is currently in compliance with regulatory requirements. We continue to evaluate the production of AVA to assure compliance with applicable federal standards and regulations.

(Comment 34) A number of comments alleged that squalene had been added to AVA and questioned how AVA could be approved when it contains squalene. Others claimed that health problems reported by some recipients of AVA were caused by squalene. Another comment noted the finding of small amounts of squalene in samples of AVA tested by FDA and advocated the testing of all lots of AVA for the presence of squalene. One comment claims that squalene ''overcharges'' the immune system when injected into the body even in tiny amounts.

(Response) Squalene is a naturally occurring biodegradable oil found in plants, animals, and humans. Squalene is an intermediate in the cholesterol biosynthetic pathway and is a natural constituent of dietary products including both vegetable and fish oils. Squalene is synthesized in the liver and circulates in the bloodstream and is present in human serum at 250 parts per billion (250 nanograms per milliliter) (Ref. 20). Antibodies to squalene occur naturally in humans, have an increased prevalence in females, are not correlated with vaccination with AVA, and appear to increase in prevalence with age (Ref. 21). Squalene is not used in the AVA manufacturing process and is not a component of the vaccine.

In 1999, FDA performed testing to determine whether squalene was added to AVA as an adjuvant. FDA believes that the testing was adequate for the intended purpose of determining whether squalene had been added to AVA as an adjuvant, and demonstrated that this was not the case. The values reported from FDA's testing of certain lots were minute (10 to 83 parts per billion, which is below the low levels normally detected in human serum (Ref. 20)) and at the low end of the analytical sensitivity of the test method. Given the extremely low level detected, more extensive testing and validation would be needed to ascertain whether any squalene was actually present.

At DoD's request, Stanford Research International (SRI) conducted testing designed to detect low levels of impurities (including squalene), in a

quantitative manner. SRI detected squalene at up to 9 parts per billion in 1 lot only of the 33 lots of AVA tested. This value can be contrasted with the amount of squalene added as a component of MF59 adjuvant included in FLUAD, an influenza vaccine which is marketed in many European countries and whose safety has been evaluated by European regulatory authorities. (The current version of this adjuvant is technically named MF59C.1.) According to the ''Summary of Product Characteristics,'' the amount of squalene contained in FLUAD is 9.75 mg per dose of 0.5 mL (about 2 parts per hundred or 20 million parts per billion), which is greater than 2 million times more than that detected by SRI in one lot of AVA.

We do not believe that additional testing of AVA is warranted because squalene is not used in the manufacturing process and is not a component of the vaccine. Moreover, at this time, we reviewed the evidence and conclude that such minuscule amounts of squalene, if even present in AVA, would not alter our view of the safety of AVA. The comment claiming that squalene overcharges the immune system did not provide any data in support of this assertion.

(Comment 35) Some comments noted that AVA contains formaldehyde.

(Response) The comments are correct in that formaldehyde, at a concentration of 100 microgram/mL, is included in AVA as a preservative. We note that formaldehyde has been used in the manufacture and formulation of AVA since MDPH started manufacturing AVA in the 1960s. Formaldehyde was present in the vaccine lots used in the CDC open label safety study and, in similarly small amounts, is a component of numerous other injectable products. The presence of formaldehyde in these small amounts does not alter our view of the safety of AVA.

(Comment 36) One comment was critical of the CDC open label safety study claiming that activities described in a program report for work conducted under contract with DoD indicated that some lots of anthrax vaccine used in the CDC open label safety study were adulterated with formaldehyde because additional formaldehyde was added.

(Response) The report referenced by this comment was written by Merck Sharp & Dohme (MSD). It noted that additional formaldehyde was added to DoD/MSD vaccine Lots 5 and 7, which were not used in the CDC open label safety study. One lot of DoD/MSD vaccine (Lot 9) was used in that study. It was used during the first year of the CDC open label safety study, along with one lot of DoD/MDPH/AVA vaccine; thereafter, only DoD/MDPH/AVA vaccine lots were used. Accordingly, the CDC open label safety study was unaffected by the lots that the comment cites.

F. Comments on Labeling

(Comment 37) Some comments noted the Panel statement regarding an apparent discrepancy between the labeling and a now rescinded section of the Code of Federal Regulations with regards to the number of doses to be administered.

(Response) We addressed this issue in section III.E of this document. The dosing schedule for AVA, from the time of the Brachman study to the present, has always consisted of six doses; a 0.5 mL dose at 0, 2, 4 weeks and then at 6, 12 and 18 months, followed by a subsequent 0.5 mL dose at 1-year intervals to maintain immunity. In any event, perceived variances to a rescinded regulation are not relevant to this final order under § 601.25, where we determine that AVA is appropriately placed into Category I, as a vaccine that is safe, effective, and not misbranded.

(Comment 38) One comment questioned the need for a six-dose immunization schedule referencing studies in animals where two doses of vaccine administered 2 weeks apart protected non-human primates from inhalation challenge with anthrax spores up to 104 weeks later.

(Response) The current immunization schedule described in the AVA labeling was demonstrated to be effective in the Brachman study. That schedule consists of a total of six doses of 0.5 mL administered subcutaneously at 0, 2, 4 weeks, 6, 12 and 18 months with annual boosters thereafter to maintain immunity. Changes to this vaccination schedule may be reviewed and considered for approval by FDA based upon the submission of scientific data to support changes to the product labeling.

G. Additional Comments

(Comment 39) Several comments were critical of FDA for ''relying'' upon the IOM report as the scientific basis for placing AVA into Category I and were critical of the IOM report with respect to its consideration of studies conducted by DoD as supportive of vaccine safety or its consideration of animal studies as evidence of effectiveness against inhalation anthrax. However, other comments stated that FDA was ''somewhat indirect'' regarding the IOM report and suggested that FDA ''accord the IOM report significant weight as expert scientific judgment.''

(Response) In the December 2004 proposal, we agreed with the IOM committee's general conclusion that AVA, as licensed, is an effective vaccine for protection of humans against anthrax infection, including inhalation anthrax and that certain studies in humans and animals support the conclusion that AVA is effective against *B. anthracis* strains that are dependent upon the anthrax toxin as a mechanism of virulence, regardless of the route of exposure. In response to the comments submitted regarding the IOM committee report, we wish to clarify that the general conclusions of the report are consistent with FDA's own independent assessment of the available data regarding the safety and effectiveness of AVA.

In response to public concerns expressed about the use of AVA in the DoD's Anthrax Vaccine Immunization Program, Congress called for DoD to support an independent examination of AVA by the IOM. The IOM committee was charged with reviewing data regarding the effectiveness and safety of the currently licensed anthrax vaccine and assessing the manufacturer's efforts to resolve manufacturing issues and resume production and distribution of vaccine.

While the IOM committee did invite FDA scientists to participate in their open meetings and comment on portions of the draft report, FDA was not a participant in their closed review sessions, nor did FDA participate in the writing or finalization of the IOM report. Similarly, FDA has conducted its review under § 601.25, culminating in this final order, independently of the activities of the IOM committee. FDA did not actively seek input or comment from the IOM committee during its review process.

(Comment 40) Some comments questioned the utility of animal data with one comment stating that animal testing is ''absolutely not at all relevant to the study of safety for humans.'' Another comment noted that AVA provided protection in guinea pigs against spores of some strains of *B. anthracis* but not others.

(Response) We wish to clarify that animal studies have not been relied upon for a determination of the safety of AVA for human use. The safety database is comprised of data from the CDC open label safety study in the late 1960s to early 1970s during which approximately 15,000 doses manufactured at MDPH were administered to approximately 7,000 subjects. In addition, safety data from the DoD pilot study (Ref. 13) and adverse reactions reported to VAERS as associated with administration of AVA were considered as part of FDA's continual process for assessing the

safety of AVA. In 2002, information from the DoD pilot study and VAERS were included in the sections of the labeling describing safety and adverse reactions. We continue to perform periodic evaluations of adverse events reported to VAERS.

With regard to data suggesting that the vaccine protected guinea pigs against spores from some strains of *B. anthracis* but not others, we note that different animal species may exhibit different levels of susceptibility to an infectious organism. The course of infection and disease may depend greatly upon the strain of the infectious organism for some species but not so much for other species (Refs. 3, 4, and 5). Thus, based on the strain used or other factors, studies in some animal species are likely to produce different results than studies in other species.

(Comment 41) One comment suggested that AVA had been administered to military personnel during Desert Storm/Desert Shield under an IND.

(Response) NIH's Division of Biologics Standards originally licensed AVA under the Public Health Service Act in 1970. Administration of AVA, an approved product, to military personnel by DoD during Desert Storm/Desert Shield was not under an IND.

(Comment 42) Many comments claimed that AVA was not properly licensed.

(Response) We disagree. AVA has been legally licensed since November 1970.

The purpose of the biologics efficacy review procedures is to determine whether biological products licensed before July 1, 1972, are safe and effective and not misbranded. In 1972, the Department of Health, Education, and Welfare redelegated from the NIH to FDA authority and responsibility to regulate biological products. FDA initiated a comprehensive review of the safety, effectiveness, and labeling of all licensed biologics, including AVA, shortly after the redelegation of authority. In keeping with § 601.25, independent advisory panels made up of scientific experts from outside the Federal Government, reviewed biological products licensed prior to July 1, 1972, in order to recommend to FDA how the agency should classify the products. One panel reviewed the safety, effectiveness, and labeling of AVA and recommended that FDA place the vaccine into Category I—safe, effective, and not misbranded. This recommendation was based on a review of the available data from the Brachman study and the CDC open label safety study, and the CDC surveillance data, as described elsewhere in this document. FDA followed the requirements of § 601.25(f), requiring publication of a proposed order for classification, and published a proposed rule in the **Federal Register** on December 13, 1985 (50 FR 51002). Since the publication of the December 1985 proposal, FDA has focused on removing Category II products–unsafe, ineffective, or misbranded, from the market and completing the final classification of the Category III products–products with insufficient information to allow classification and further testing is required. The purpose of this final order, and the final rule and final order published elsewhere in this issue of the **Federal Register**, is to complete FDA's categorization of bacterial vaccines and toxoids licensed prior to July 1, 1972. As stated in section III of this document, FDA concludes that AVA is safe, effective, and not misbranded.

(Comment 43) Some comments questioned why FDA did not reconvene an advisory review panel when it reopened the comment period in response to the Court order of October 27, 2004. The comments claim that FDA has attempted to avoid the normal approval process or circumvented its own rules by not convening an advisory review panel to review new data generated by DoD.

(Response) Neither the applicable FDA regulation, § 601.25, nor the Court's order of October 27, 2004, requires that an advisory review panel be convened at this time. FDA regulations at § 601.25 explicitly detail the procedures to be used to determine that biological products licensed prior to July 1, 1972, are safe, effective, and not misbranded. These regulations require FDA to submit a product to an advisory review panel at the initiation of the review. The panel then submits to the Commissioner of Food and Drugs a report containing the panel's conclusions and recommendations with respect to the biological product. The Commissioner, after reviewing the conclusions and recommendations, then publishes a proposed order categorizing the product as safe and effective (Category I), unsafe or ineffective (Category II), or determining that the available data are insufficient to classify such biological product (Category III). Thereafter, any interested person may within 90 days after publication of the proposed order, file written comments. After review of the comments, the Commissioner of Food and Drugs publishes a final order on the classification.

In *Doe* v. *Rumsfeld*, 341 F.Supp.2d 1 (D.D.C. 2004), the Court examined the step in the process involving the opportunity for public comment on the agency's proposed order. The court noted that FDA had published the Panel report in its entirety as a proposed order. However, the Court concluded that the proposed order did not provide public notice that FDA considered the vaccine to be indicated for use against inhalation anthrax, a conclusion that FDA made in its January 2004 final order. Accordingly, the Court remedied what it considered to be an Administrative Procedure Act violation, by vacating the January 2004 final order, and remanding it to FDA to reconsider following an additional opportunity for comment. The Court did not find fault with the Panel report. FDA believes that, with the requirements of § 601.25 satisfied with respect to the advisory review panel report, it is not necessary to consult another advisory panel on these issues. In drafting this final order, FDA has been able to review and consider extensive comments on the December 2004 proposed order.

(Comment 44) Some comments expressed concern that certain Panel members were also involved in developing AVA. They suggest that the members were biased, and their role in the review process self-serving. One comment specifically complained of the bias of Dr. Stanley Plotkin, who was a co-author on the Brachman study (Ref. 1).

(Response) As provided in § 601.25, the Commissioner appointed qualified experts to serve on the advisory review panel and the Panel included persons from lists submitted by organizations representing professional, consumer, and industry interests. A review of the Panel members appointed to review the data and information and to prepare a report on the safety, effectiveness, and labeling of bacterial vaccines, toxoids, related antitoxins, and immune globulins reveals that the list did not include the name of Dr. Stanley Plotkin or any other scientist who worked directly with the development of AVA. (50 FR 51002 at 51003 (December 13, 1985)).

(Comment 45) One comment alleged that FDA and DoD had a conflict of interest and that the agencies were working together to promote vaccinations.

(Response) FDA is charged with implementing the Federal Food, Drug, and Cosmetic Act, as well as certain provisions of the Public Health Service Act. Under these authorities and applicable regulations, including § 601.25, FDA is responsible for reviewing the safety and effectiveness of vaccines. In issuing this order, FDA is

fulfilling this responsibility, and is not working to promote, or discourage, vaccination for members of the armed forces. Rather, as described in this order, FDA has evaluated AVA and concluded that the product is safe, effective, and not misbranded.

(Comment 46) Other comments expressed concern that FDA had not considered alternatives to vaccination such as the use of detection devices and antibiotics to protect individuals from anthrax infection, or expressed the opinion that antibiotics are a better means of protection against anthrax.

(Response) Detection devices, if effective, would not prevent infections, but would simply detect the presence of anthrax spores in the environment. Moreover, a device would provide this information only for the particular location under observation by the device and only if the device was in use and functioning properly at the time.

Moreover, although antibiotic therapies are safe and effective in the treatment of anthrax disease and in the prevention of anthrax disease when administered as part of a post-exposure prophylaxis regimen, the safety and effectiveness of long term use of such therapies in individuals at high risk for anthrax disease, potentially for a period of years, has not been studied. Moreover, the early stages of inhalation anthrax present with flu-like symptoms, and diagnosis may be delayed. The initiation of antibiotic therapy only after a definitive diagnosis of inhalation anthrax has a diminished success rate. Anthrax disease can be fatal despite the use of antibiotics. The fatality rate for inhalation anthrax in the United States is estimated to be approximately 45 percent to 90 percent. From 1900 to October 2001, there were 18 identified cases of inhalation anthrax in the United States, the latest of which was reported in 1976, with an 89 percent (16/18) mortality rate. Most of these exposures occurred in industrial settings, i.e., textile mills. From October 4, 2001, to December 5, 2001, a total of 11 cases of inhalation anthrax linked to intentional dissemination of *B. anthracis* spores were identified in the United States. Five of these cases were fatal (Ref. 6). These fatalities occurred despite aggressive medical care, including antibiotic therapy (Refs. 22 and 23).

Thus, we have considered possible alternatives to AVA, and continue to conclude that AVA is safe, effective, and not misbranded.

H. Comments on Matters Outside the Scope of this Proceeding

(Comment 47) We received numerous comments on the December 2004 proposal that, although they relate to significant issues, are not relevant to the proposed order for placing AVA into Category I. These comments concerned: (1) The need for compensation programs for individuals injured by AVA, (2) statements that the vaccine should be optional for members of the armed forces, (3) statements that antidotes to anthrax should be developed, (4) concerns about DoD responsibilities and recordkeeping, and (5) requests for an investigation of BioPort stock ownership.

(Response) These comments are on matters outside the scope of this final order and FDA's jurisdiction, authority, and control. Accordingly, we do not respond to them.

V. FDA's Responses to Additional Panel Recommendations

In the December 1985 proposal, FDA responded to the Panel's general recommendations regarding the products under review and to the procedures involved in their manufacture and regulation, and to the Panel's general research recommendations. Published elsewhere in this issue of the **Federal Register** in a final rule and final order concerning bacterial vaccines and toxoids other than AVA, FDA responds in final to the Panel's general recommendations.

VI. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm.1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site address, but we note subsequent changes to the Web site might have occurred after this document publishes in the **Federal Register**).

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Dated: December 12, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Clinical Studies of Safety and Effectiveness of Orphan Products; Availability of Grants; Request for Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

I. Funding Opportunity Description

The Food and Drug Administration (FDA) is announcing changes to its Office of Orphan Products Development (OPD) grant program for fiscal year (FY) 2007 and FY 2008. This announcement supersedes the previous announcement of this program, which was published in the **Federal Register** of January 14, 2005 (70 FR 2642). Please note that there is only one receipt date for FY 2007 and one receipt date for FY 2008.

1. Background

OPD was created to identify and promote the development of orphan products. Orphan products are drugs, biologics, medical devices, and foods for medical purposes that are indicated for a rare disease or condition (that is, one with a prevalence, not incidence, of fewer than 200,000 people in the United States). Diagnostic tests and vaccines will qualify only if the U.S. population of intended use is fewer than 200,000 people per year.

2. Program Research Goals

The goal of FDA's OPD grant program is to support the clinical development of products for use in rare diseases or conditions where no current therapy exists or where the product will improve the existing therapy. FDA provides grants for clinical studies on safety and/or effectiveness that will either result in, or substantially contribute to, market approval of these products. Applicants must include, in the application's ''Background and Significance'' section, documentation to support the estimated prevalence of the orphan disease or condition and an explanation of how the proposed study will either help gain product approval or provide essential data needed for product development. All funded studies are subject to the requirements of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 *et seq.*) and regulations issued under it.

II. Award Information

Except for applications for studies of medical foods that do not need premarket approval, FDA will only award grants to support premarket clinical studies to determine safety and effectiveness for approval under section 505 or 515 of the act (21 U.S.C. 355, or 360e) or safety, purity, and potency for licensing under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262).

FDA will support the clinical studies covered by this notice under the authority of section 301 of the PHS Act (42 U.S.C. 241). FDA's research program is described in the Catalog of Federal Domestic Assistance, No. 93.103.

Applicants for Public Health Service (PHS) clinical research grants are encouraged to include minorities and women in study populations so research findings can be of benefit to all people at risk of the disease or condition under study. It is recommended that applicants place special emphasis on including minorities and women in studies of diseases, disorders, and conditions that disproportionately affect them. This policy applies to research subjects of all ages. If women or minorities are excluded or poorly represented in clinical research, the applicant should provide a clear and compelling rationale that shows inclusion is inappropriate.

PHS strongly encourages all grant recipients to provide a smoke-free workplace and to discourage the use of all tobacco products. This is consistent with PHS' mission to protect and advance the physical and mental health of the American people.

FDA is committed to achieving the health promotion and disease prevention objectives of ''Healthy People 2010,'' a national effort designed to reduce morbidity and mortality and to improve quality of life. Applicants may obtain a paper copy of the ''Healthy People 2010'' objectives, vols. I and II, for $70 ($87.50 foreign) S/N 017–000–00550–9, by writing to the Superintendent of Documents, P.O. Box 371954, Pittsburgh, PA 15250–7954. Telephone orders can be placed to 202–512–2250. The document is also available in CD–ROM format, S/N 017–001–00549–5 for $19 ($23.50 foreign) as well as on the Internet at *http://www.healthypeople.gov/*. Internet viewers should proceed to ''Publications'' (FDA has verified the Web site and its address, but we are not responsible for subsequent changes to the Web site or its address after this document publishes in the **Federal Register**).

1. Award Instrument

Support will be in the form of a grant. All awards will be subject to all policies and requirements that govern the research grant programs of PHS, including the provisions of 42 CFR part 52 and 45 CFR parts 74 and 92. The regulations issued under Executive Order 12372 do not apply to this program. The National Institutes of Health (NIH) modular grant program does not apply to this FDA grant program. All grant awards are subject to applicable requirements for clinical investigations imposed by sections 505, 512, and 515 of the act, section 351 of the PHS Act, and regulations issued under any of these sections.

2. Award Amount

Of the estimated FY 2007 funding ($14.2 million), approximately $10 million will fund noncompeting continuation awards, and approximately $4.2 million will fund 10 to 12 new awards subject to availability of funds. It is anticipated that funding for the number of noncompeting continuation awards and new awards in FY 2008 will