DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Russell E. Dingle
71 Shaughnessey Drive
East Hartford, CT 06118

AUG 28 2002

Re: Docket No. 01P-0471/CP1

Dear Mr. Dingle:

This responds to your Citizen Petition dated October 12, 2001 and to relevant comments submitted to the above-referenced docket. We previously sent you an interim response dated April 11, 2002. In your Petition you asked that the Commissioner of Food and Drugs take the following actions regarding anthrax vaccine manufactured by the BioPort Corporation (BioPort):

1. "Issue a Final Rule on the drug category placement of anthrax vaccine as Category II (unsafe, ineffective, or misbranded) amending the as yet to be finalized Proposed Rule as published in the Federal Register on December 13, 1985."

2. "Declare as adulterated all stockpiles of anthrax vaccine adsorbed in the possession of BioPort Corporation and all doses in private, public, U.S., or foreign government possession."

3. "Enforce FDA Compliance Policy Guide, Section 400.200, A Consistent Application of CGMP Determinations (CPG 7132.12), with respect to anthrax vaccine adsorbed (license # 1260)."

4. "Revoke the anthrax vaccine adsorbed license (license # 1260) held by BioPort Corporation."

Petition at p. 1.

For the reasons stated below, we grant your request in part and deny it in part. We agree that the Food and Drug Administration (FDA or the agency) should complete the Biologics Review for anthrax vaccine by issuing a final rule. Due to the pendency of this rulemaking, at this time we do not know what the result of the rulemaking will be. In the proposed rule, however, FDA agreed with the Panel on Review of Bacterial Vaccines and Toxoids (the Panel) recommendation and conclusion concerning anthrax vaccine, and FDA proposed to classify anthrax vaccine in Category I (safe, effective, and not misbranded). 50 Fed. Reg. 51002 (December 13, 1985). We deny your request to declare all anthrax vaccine in "private, public, U.S., or foreign government possession" to be adulterated. Furthermore, as we explain below, FDA Compliance Policy Guide 400.200 does not require or authorize FDA to take the actions you request. Finally, we do not agree to revoke the license for anthrax vaccine.

01P-0471

PAV1

I. *Anthrax Vaccine in the Biologics Review*

A. *Background*

In November 1970, the Division of Biologics Standards of the National Institutes of Health (NIH) licensed anthrax vaccine manufactured by the Michigan Department of Public Health (MDPH).[1] At that time NIH regulated biological products. NIH's decision to license the anthrax vaccine was based on an adequate and well-controlled study conducted by Philip S. Brachman *et al.,* in the 1950s (the Brachman study) and safety and epidemiological/surveillance data collected by the Centers for Disease Control (CDC) in the 1960s.

In 1972, the Department of Health, Education, and Welfare (HEW) redelegated authority and responsibility to regulate biological products from NIH to FDA.[2] Shortly thereafter, FDA initiated a comprehensive review of the safety, effectiveness, and labeling of all licensed biologics (the Biologics Review). 21 CFR 601.25. In the Biologics Review, independent advisory panels of scientific experts from outside the federal government review different categories of biological products. Based on their review, the panels recommend to FDA that the agency classify individual biological products in one of three categories: Category I – safe, effective, and not misbranded; Category II – unsafe, ineffective, or misbranded; or Category III – insufficient information to classify, further testing required. 21 CFR 601.25(e). After reviewing the Panel's recommendations and conclusions, FDA publishes a proposed order that proposes to classify the biological products under review. 21 CFR 601.25(f). After an opportunity for public comment, FDA then issues a final order with final product classifications.[3] 21 CFR 601.25(g).

The Panel reviewed the safety, effectiveness, and labeling of anthrax vaccine manufactured by MDPH. Based on its review of the available data (the Brachman study and the CDC studies), the Panel concluded that the anthrax vaccine is safe, effective, and not misbranded and, accordingly, recommended that FDA place anthrax vaccine in Category I. FDA issued a proposed rule proposing to adopt the Panel's recommendations.[4] 50 Fed. Reg. 51002 (December 13, 1985). FDA has not yet issued any final rule for anthrax vaccine.

The current approved labeling for anthrax vaccine states that it is indicated for the active immunization 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. The labeling further states that the anthrax vaccine is also indicated for individuals at high risk of exposure to *Bacillus anthracis* spores such as

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1. In late 1995, MDPH became the Michigan Biologic Products Institute (MBPI). In September 1998, BioPort purchased MBPI.
2. 37 Fed. Reg. 4004 (February 25, 1972). HEW later became the Department of Health and Human Services (HHS).
3. FDA would then initiate license revocation proceedings for those products in Category II. 21 CFR 601.25(f)(2).
4. 21 CFR 601.25 states that FDA shall, after reviewing the conclusions and recommendations of the advisory review panel, issue a proposed order. The Federal Register document that contained FDA's proposals concerning the Panel report for anthrax vaccine was called a proposed rule because it proposed to amend certain existing biologics regulations. 50 Fed. Reg. 51002 (December 13, 1985).

veterinarians, laboratory workers and others whose occupation may involve handling potentially infected animals or other contaminated materials.[5] According to the approved labeling, the vaccination schedule consists of six 0.5 ml doses administered subcutaneously. After the first dose is administered, the subsequent doses are administered two weeks, four weeks, six months, 12 months, and 18 months thereafter, followed by annual boosters.

B. *The Evidence of Effectiveness*

1. *The Biologics Review and Anthrax Vaccine*

You requested that FDA "[i]ssue a Final Rule on the drug category placement of anthrax vaccine as Category II (unsafe, ineffective, or misbranded) amending the as yet to be finalized proposed rule as published in the Federal Register 13 December 1985." Petition at pp. 1, 2. FDA has reviewed your petition carefully. We agree that FDA should complete the Biologics Review for anthrax vaccine by issuing a final rule pursuant to 21 CFR 601.25. Although we cannot say precisely when this final rule will issue, FDA's Center for Biologics Evaluation and Research (CBER) is working to complete this rulemaking as soon as possible.

As you know, the Panel determined anthrax vaccine to be safe, effective, and not misbranded. One reason why the Biologics Review rulemaking for anthrax vaccine has not been completed is that FDA has focused on removing Category II products from the market and completing the final classification of the Category III products, which, unlike anthrax vaccine, could not initially be classified because of insufficient data. See, e.g., 65 Fed. Reg. 31003 (May 15, 2000); 52 Fed. Reg. 11123 (April 4, 1987).

At this stage of the 601.25 rulemaking process, it would be premature for FDA to evaluate the adequacy of the Panel recommendation as you have requested, and the agency declines to do so. Given the pendency of this rulemaking, FDA believes that the proper vehicle to respond to the issues you have raised is the final rule that will classify anthrax vaccine. We reiterate, however, that the Panel recommended that anthrax vaccine be classified in Category I, and that FDA adopted the Panel recommendation in its proposed rule.[6] 50 Fed. Reg. 51104 (December 13, 1985).

This response to your petition represents FDA's position at this time on the issues that you have raised. This response does not constitute FDA's final decision in the Biologics Review for anthrax vaccine. The Agency will issue its final decision concerning the classification of anthrax vaccine in its final rule.

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5. The package insert (PI) for BioPort's anthrax vaccine was amended in January 2002. The prior version of the PI stated that immunization was recommended for individuals who may come in contact with animal products that may be contaminated with *Bacillus anthracis* spores and for individuals engaged in diagnostic or investigational activities which may bring them into contact with *Bacillus anthracis* spores. Immunization was also recommended for persons at high risk, such as veterinarians and others handling potentially infected animals.

6. As described below in sections I B 2 b ii and I B 2 b iii, FDA does not agree with the Panel report for anthrax vaccine in every respect.

2. *The Effectiveness of the Anthrax Vaccine*

One basis for your request that FDA place anthrax vaccine in Category II is your assertion that the Panel's recommendation to place anthrax in Category I "clearly conflicts with the guidelines established by the Commissioner and with the evaluation criteria used by the Panel." Petition at p. 3. You argue that the Panel's recommendation is deficient because there was no controlled clinical investigation of the anthrax vaccine as required by FDA's regulations.

We disagree with your assertion. As we describe below, there is ample evidence to demonstrate that the Brachman study was an adequate and well-controlled clinical investigation that met the applicable requirements.

(a) 21 CFR 601.25

21 CFR 601.25(d) provides, in pertinent part, that

> [t]he advisory review panel, in reviewing the submitted data and preparing the panel's conclusions and recommendations, and the Commissioner of Food and Drugs, in reviewing and implementing the conclusions and recommendations of the panel, shall apply the following standards to determine that a biological product is effective ...
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> (2) ... Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.126 of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness. Alternate methods, such as serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations, may be adequate to substantiate effectiveness where a previously accepted correlation between data generated in this way and clinical effectiveness already exists. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing ...

(b) The Brachman Study

(i) *Study Design*

Philip S. Brachman *et al.*, conducted an adequate and well-controlled clinical trial on anthrax vaccine in the 1950s. This controlled field study involved workers in four textile mills that processed imported animal hides and 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 with a placebo control group to provide a quantitative assessment of effectiveness. 21 CFR 314.126(b)(2). For this trial, employees with no known history of anthrax disease were selected and divided into two groups, treatment and placebo. The groups were balanced with regard to subjects' age, length of employment, department, and job. The participants were not told whether they received anthrax vaccine or a placebo. Overall, 909 out of 1,249 mill workers participated in the controlled part of the study. The dose administration schedule in the trial was the same as the currently licensed vaccine dose administration schedule: 0, 2, and 4 weeks: 6, 12, and 18 months, followed thereafter by annual boosters.[7]

Individuals who were not part of the controlled study, either because they were ineligible or chose not to participate, were also monitored for anthrax. These individuals were referred to as the observational group. As described below, the observational group was not used to calculate the level of effectiveness. However, data from the observational group was used to corroborate results of the controlled study under 21 CFR 601.25(d)(2).

You argue that the Brachman study did not meet the definition of a well-controlled field trial because "a large percentage of the employees at the various mills were non-volunteers, yet their numbers were considered in the effectiveness calculations." Petition at p. 5, fn. 6. That is incorrect. As we described above, in the Brachman study, mill employees volunteered to participate in the study, and the volunteers were allocated into treatment and placebo control groups. Individuals who decided not to participate or who were ineligible were followed by the study investigators as members of an untreated observational group. The Brachman study's efficacy analysis included only the cases that occurred in the treatment and placebo groups. The Brachman study report described cases from the observational group (your so-called "non-volunteers"), but did not include such cases in the efficacy analysis.

You also claim that the Brachman study was deficient because it "had no means to identify the strain of, or determine, regulate, or calculate the exposure to either the vaccinated or the control group of *Bacillus anthracis.*" Petition at p. 5, fn. 6. We disagree. The features you suggest, such as the ability to determine, regulate, or calculate exposure to *Bacillus anthracis*, would be found in an immunization-challenge study but not in a field study. In a field study, the product's effectiveness is evaluated in the context of natural routes of exposure in various natural or field settings. Thus, the Brachman study did not need to focus on identifying a particular *Bacillus anthracis* strain or strains. Instead, the study focused properly on the extent of exposure (e.g., spore content of the various animal products entering the facility or aerosolized spore content in various working sections or areas of the woolen mill), to assess the anthrax vaccine's risk-benefit

7. The immunization schedule used in the trial consisted of a "primary" series of three injections given at two week intervals, followed by three "booster" doses given at six month intervals. The schedule is the same as the currently licensed schedule. See infra section I C.

ratio for potential recipients. In general, it is not possible or expected to quantify environmental exposures in vaccine field efficacy trials.

(ii) *Study Results*

During the Brachman trial, 26 cases of anthrax infection were reported – 21 cutaneous and five inhalation.

Of the 21 cutaneous cases, 15 individuals had received the placebo, three individuals were in the observational group, and three individuals were in the vaccine group. No cases were reported in individuals receiving the complete vaccination schedule of six doses.[8]

Of the five inhalation cases, two individuals had received the placebo, while three individuals were in the observational group. Four of the five people who developed inhalation anthrax died. Not a single case of inhalation anthrax occurred in subjects who received the anthrax vaccine.

In a comparison of total anthrax cases between the placebo and vaccine groups, the calculated vaccine efficacy level against all reported cases of anthrax combined was 92.5% (lower 95% confidence interval = 65%). This calculation did not include the number of cases in the observational group.

The Panel report states "the vaccine was calculated to give 93 percent (lower confidence limit = 65%) protection against cutaneous anthrax based on comparison with the control group." 50 Fed. Reg. 51058 (December 13, 1985). However, the efficacy analysis actually conducted in the Brachman study includes all cases of anthrax disease regardless of the route of exposure or manifestation of the disease.

There were five cases of inhalation anthrax reported in the course of the Brachman study, which were too few to support an independent statistical analysis. Of these cases, two occurred in the placebo group, three occurred in the observational group, and no cases occurred in the vaccine group. This descriptive information is reflected in the labeling statement for anthrax vaccine, which states that the vaccine is indicated for individuals at high risk of exposure to *Bacillus anthracis* spores. The indication section of the labeling does not specify the route of exposure and thus includes both cutaneous and inhalation exposure.[9]

Finally, the Panel noted that it would be very difficult, if not impossible, to clinically study the efficacy of any anthrax vaccine. 50 Fed. Reg. 51058 (December 13, 1985). Indeed, due to ethical considerations and the low incidence and sporadic occurrence of anthrax disease, further adequate and well-controlled clinical studies of effectiveness are not possible.

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8. See infra section I C concerning labeling and the terminology concerning what constitutes a "full" or "complete" vaccination schedule.

9. Although the Panel states that inhalation anthrax occurred too infrequently to assess the protective effect of vaccine against this form of the disease, as stated above, the overall effectiveness rate of 92.5% applies to both cutaneous and inhalation exposure. See 50 Fed. Reg. 51058 (December 13, 1985). This effectiveness rate did not include the cases of inhalation or cutaneous anthrax from the observational group.

(iii) *The Vaccine Studied*

You state in your petition that the Brachman study was conducted with a "similar, but different" vaccine to BioPort's anthrax vaccine, and that this violates 21 CFR 601.25 and undermines any determination of effectiveness of the anthrax vaccine based on the Brachman study. Petition at p. 4. It is true that the Brachman study results were gathered with a version of the anthrax vaccine other than BioPort's.[10] The records in the Biologics License Application (BLA) for the anthrax vaccine indicate that this initial version was provided to Dr. Brachman by Dr. G. Wright of Fort Detrick, U.S. Army, Department of Defense (DOD). The DOD anthrax vaccine used in the Brachman study (the DOD vaccine) can be seen as a precursor to a Merck, Sharp & Dohme (Merck) experimental vaccine mentioned in the Panel report, 50 Fed. Reg. 51059 (December 13, 1985), and as a precursor to the BioPort vaccine.

As further described below, the DOD vaccine and the Merck vaccine figured in DOD's development of the anthrax vaccine leading up to the anthrax vaccine made by MDPH. And, as we explain below, the Brachman study does, in fact, demonstrate that BioPort's anthrax vaccine is effective because the BioPort vaccine is comparable to the DOD vaccine used in the Brachman study.[11]

Under FDA's comparability policy, a manufacturer may make manufacturing changes in a product without performing additional clinical studies to demonstrate the safety and efficacy of the "successor" product. Put another way, a manufacturer may use data gathered with a previous version of its product to support the efficacy of a comparable version of the same product after a manufacturing change. See FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products (1996) (http://www.fda.gov/cber/gdlns/comptest.txt) (Comparability Guidance Document). FDA's Comparability Guidance Document envisions a continuum of categories of tests. Depending upon the product and the nature of the manufacturing change, a manufacturer may be able to

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10. For the purposes of this section, the BioPort anthrax vaccine can be seen as the same product as the MDPH anthrax vaccine and the MBPI anthrax vaccine. See infra fn. 13.

11. The Panel report states that:

> [t]he vaccine manufactured by the Michigan Department of Public Health has not been employed in a controlled field trial. Brachman employed a similar vaccine prepared by Merck Sharp & Dohme 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 ... This product appears to offer significant protection against cutaneous anthrax in fully immunized subjects. This is adequately established by the controlled field trial of the very similar Merck Sharp & Dohme experimental vaccine....

50 Fed. Reg. 51059 (December 13, 1985). Although it appears that the Brachman study apparently did not use the very vaccine manufactured by Merck, this excerpt from the Panel report is relevant because the Merck vaccine can be seen as the second version of the anthrax vaccine that DOD developed, a second version that ultimately led to the development of the MDPH vaccine.

demonstrate comparability between its products on the basis of analytical testing, bioassays, and preclinical testing without having to resort to full safety or efficacy studies. For the anthrax vaccine, the DOD or precursor version is comparable in terms of formulation and manufacturing process to the BioPort vaccine. There are some differences in formulation and manufacturing process between the DOD vaccine and the BioPort vaccine, but the preclinical and clinical data described below provide assurance that these differences do not result in any meaningful difference in safety or effectiveness.

In the 1950s, DOD first developed a version of the anthrax vaccine using an aerobic culture method.[12] This was the vaccine used in the Brachman study. Subsequent to the Brachman trial, DOD modified the vaccine's manufacturing process to, among other things, optimize production of a stable and immunogenic formulation of vaccine antigen and to increase the scale of manufacture. In the early 1960s, DOD entered into a contract with Merck to standardize the manufacturing process for large scale production of the anthrax vaccine and to produce anthrax vaccine using an anaerobic culture method. This contract resulted in Merck producing a number of lots of the Merck experimental vaccine that the Panel report references. See 50 Fed. Reg. 51059 (December 13, 1985). 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 spores. Under the contract MDPH pursued pre-market approval of the vaccine. This DOD-MDPH contract resulted in the production of the anthrax vaccine that NIH licensed in 1970, that FDA now regulates, and that BioPort presently manufactures.

Therefore, the DOD vaccine used in the Brachman trial can been seen as a prototype or precursor product to the MDPH anthrax vaccine.[13] DOD was involved in the development of the Merck vaccine and the MDPH vaccine; indeed, DOD has been significantly involved in developing the formulation and manufacturing process of all three versions of the anthrax vaccine: The DOD vaccine, the Merck vaccine, and MDPH's vaccine.

DOD's continuous involvement with, and intimate knowledge of, the formulation and manufacturing processes of all of these versions of the anthrax vaccine provide a foundation for a determination that BioPort's anthrax vaccine is comparable to the original DOD vaccine. See Berlex Laboratories, Inc. v. FDA, 942 F. Supp. 19 (D.D.C. 1996) (It is permissible for FDA to license a biological product based upon data generated with the same manufacturer's or related manufacturer's comparable product); FDA Comparability Guidance Document. DOD was involved in developing the three versions of the anthrax vaccine and had knowledge of the manufacturing processes of each version. DOD is thus similar to a manufacturer that made manufacturing changes to its product as contemplated by FDA's Comparability Guidance.

Furthermore, there are animal and clinical data that demonstrate that the current BioPort vaccine is comparable to the DOD vaccine studied in the Brachman trial. The Berlex decision and the

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12. Dr. G. Wright of DOD's Fort Detrick developed this version.

13. We reiterate that, for the purposes of this discussion, the MDPH anthrax vaccine is the same product as the MBPI anthrax vaccine and the BioPort anthrax vaccine.

Comparability Guidance Document make clear that, based on such information, FDA may determine that a product is comparable to a precursor product and thus decide that additional clinical trials for the successor product are not necessary. The comparability of BioPort's anthrax vaccine to the DOD vaccine has been verified through potency data that demonstrate the ability of all three vaccines to protect guinea pigs and rabbits against challenge with virulent *Bacillus anthracis* spores. In addition, there are data comparing the safety and immunogenicity of BioPort's anthrax vaccine with the DOD vaccine. These data, while limited in the number of vaccinees and samples evaluated, reveal that the serological responses to the BioPort vaccine and the DOD vaccine were similar with respect to peak antibody response and serum conversion. Finally, there are ample clinical data and information from the CDC observational safety study, conducted under IND in the 1960s, which demonstrate that the MDPH vaccine is safe. All these data taken together demonstrate that BioPort's anthrax vaccine is safe and effective and is comparable to the vaccine used in the Brachman study.

(c) The CDC Studies

The CDC epidemiological data provide corroborative evidence that supports the Brachman study's findings. 21 CFR 601.25(d)(2). The Panel report, in its section on the evidence of efficacy for the anthrax vaccine, described the CDC epidemiological data as follows:

> The Center [sic] for Disease Control has continued to collect data on the occurrence of anthrax in at-risk industrial settings. These data were summarized for the period 1962 to 1974. Twenty-seven cases were identified. Three cases were not mill employees, but worked in or near mills; none of these cases were vaccinated. Twenty-four cases were mill employees; three were partially immunized (one with 1 dose, two with 2 doses); the remainder (89 percent) being 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 Fed. Reg. 51058 (December 13, 1985).

These epidemiological data, also called surveillance data, consist of anthrax disease case reporting and support the Brachman study results. These data provide confirmation that the risk of disease still existed for those persons who were not vaccinated. These data also demonstrate that those persons who had not received the full vaccination series (six doses) were susceptible to anthrax infection, while no cases were reported in those who had received the full vaccination series.

During the period in which these surveillance data were collected, either the MDPH vaccine or the Merck vaccine described above were being administered. The CDC data from 1967 on involved surveillance of persons receiving the MDPH vaccine and thus constitutes results actually generated with BioPort's anthrax vaccine. The CDC epidemiological data corroborate the Brachman study. See 21 CFR 601.25(d)(2).

You argue that the Panel erroneously cited CDC safety data, collected under CDC IND 180, in the *Critique* section of the Panel report to support the effectiveness of the anthrax vaccine. Petition at p. 4, fn. 4. In this section of its report, the Panel states that "significant protection" is "adequately established" by the CDC surveillance data. 50 Fed. Reg. 51059 (December 13, 1985). First, if the Panel intended to indicate that the CDC data, standing alone, established the effectiveness of the anthrax vaccine, we would agree with you. But since the Panel regarded the CDC data as corroborative or supportive of the Brachman study findings, we therefore disagree with your assertion that the Panel's reliance on these data is misplaced. Secondly, the CDC surveillance data refers to the epidemiological data described above, rather than to the safety data collected under IND 180. They support the effectiveness of the anthrax vaccine and were correctly relied upon by the Panel.[14]

C. *Labeling*

You claim that the anthrax vaccine is "improperly labeled". Petition at p. 6. You cite the Panel report, which states the following: "The labeling seems generally adequate. There is 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 a primary immunization as 6 doses (0, 2, and 4 weeks plus 6, 12, and 18 months)." 50 Fed. Reg. 51059 (December 13, 1985).

We disagree with your assertion that the anthrax vaccine is misbranded. First, FDA revoked 21 CFR 620.24 in 1996 as part of a final rule that revoked 21 CFR 620 and other biologics regulations because they were obsolete or no longer necessary. 61 Fed. Reg. 40153 (August 1, 1996). Secondly, the labeling of the anthrax vaccine, from at least 1978 on, has described the vaccination schedule as three "primary" doses followed by three additional doses and annual boosters thereafter. This labeling was not inconsistent with 21 CFR 620.24(a), before FDA revoked that regulation. 21 CFR 620.24(a) simply did not mention the additional three doses. However, it is clear that the Brachman study and the CDC observational study under IND 180 contemplated a total of six doses. Therefore, there is and was no real difference between referring to the primary immunization as three or six doses, because in either case the total number of doses is six, followed by an annual booster.

II. *The Anthrax Vaccine is Safe and Effective*

You requested that FDA "[d]eclare as adulterated all stockpiles of anthrax vaccine adsorbed in the possession of BioPort Corporation and all doses in private, public, U.S. or foreign government possession." Petition at pp. 1, 11. You argue that FDA should declare the anthrax vaccine to be adulterated for the following reasons:

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14. You are correct that the CDC conducted an open-label safety study and submitted the results under IND 180. However, these safety data are separate and distinct from the CDC epidemiological or surveillance data that supports the effectiveness of the anthrax vaccine.

- "All anthrax vaccine adsorbed (AVA) produced since 1991 is adulterated by virtue of its' [sic] having been produced using unapproved procedures in unapproved equipment." Petition at p. 12.

- "The manufacturer of AVA has been found to be in violation of current Good Manufacturing Practice during every FDA inspection since 1988." Petition at p. 14.

- "AVA has been redated without an FDA approved procedure and has been labeled improperly." Petition at p. 18.

- "The equipment used to manufacture AVA has not been used exclusively for the production of AVA." Petition at p. 19.

We deny your request to "declare" the anthrax vaccine adulterated for several reasons. FDA has no policy or procedure by which it "declares" a product adulterated. There is no provision in the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, no regulation, and no guidance document under which FDA simply "declares" that a product is adulterated.[15] In any case, and as we describe below, several of your above-listed assertions are factually inaccurate. As we also make clear, other claims that you make, such as those involving current good manufacturing practice (cGMP) inspectional observations, do not necessarily render the anthrax vaccine unsafe or ineffective.

It is important to note that currently there is no FDA-lot released anthrax vaccine, which was manufactured during the timeframes you cite in your petition (1988-1998), available for military or civilian use. In January 1998, MBPI halted production of anthrax vaccine, prior to the sale of MBPI to BioPort, in order to begin comprehensive renovations of the anthrax vaccine production facilities. These renovations required FDA approval in the form of a license supplement before BioPort could resume shipping licensed anthrax vaccine made in the renovated facilities. BioPort, therefore, did not ship any licensed finished product anthrax vaccine, made after January 1998, until FDA approved two BLA supplements related to the renovations. FDA approved one BLA supplement in December 2001 for the anthrax vaccine production facility and another in January 2002 for a contract filling facility. FDA approved these supplements after the agency inspected BioPort and determined that the firm appeared to be in compliance with cGMP for the manufacture of anthrax vaccine.

Moreover, after an FDA inspection in 1998, MBPI quarantined 11 lots of anthrax vaccine. Also, BioPort currently has an additional number of lots of anthrax vaccine, manufactured prior to 1998, in storage. FDA does not intend to lot release these additional lots. The agency, therefore, does not intend to release the quarantined or additional lots of anthrax vaccine that MBPI manufactured during the period of time that you cite in your petition.

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15. To the extent that you are asking that FDA initiate enforcement action against BioPort or the anthrax vaccine, FDA declines to do so for the reasons set forth in this response. See Heckler v. Chaney, 470 U.S. 821 (1985); Community Nutrition Institute v. Young; 818 F.2d 943 (D.C. Cir. 1987).

A. *FDA Approved or Did Not Need to Approve Fermentation Train Changes in the Manufacturing Process; the Filter Change Did Not Adversely Affect the Safety, Purity, or Potency of the Anthrax Vaccine*

You argue that MDPH made significant changes in the manufacturing process of anthrax vaccine without first obtaining FDA approval. You specifically refer to MDPH's change in fermentation trains and to a change in filters. You contend that these changes adversely affected the anthrax vaccine. For the following reasons, we disagree.

Fermenters are used in the production process of anthrax vaccine to grow the bacterial cell culture. In 1990, MDPH submitted a supplement to FDA for approval to change from a glass-lined fermentation train to stainless steel fermentation trains. FDA approved the supplement in 1993. FDA did not lot release any lots manufactured in the stainless steel fermenters until the agency had approved the supplement.

After BioPort purchased the MBPI facility, it discovered that MDPH had not submitted a supplement to FDA for additional fermentation trains 3 and 4, which MDPH had added to the production process. In July 1999, BioPort submitted a supplement to FDA to cover the addition of trains 3 and 4, and FDA approved the supplement in May 2001. Fermentation trains 3 and 4 were identical to fermentation trains 1 and 2, for which FDA had previously approved a supplement in 1993.

Certain lots of anthrax vaccine were manufactured using fermentation trains 3 and 4 and were lot released by FDA prior to the agency's approval of the supplement in May 2001. However under FDA's regulations, MDPH did not have to obtain prior FDA approval for the change to fermenters 3 and 4 because fermenters 3 and 4 are identical to fermenters 1 and 2. FDA therefore considered this change to be one that required a supplement but not prior approval by the agency. 21 CFR 601.12(c).[16]

In many vaccine production processes, manufacturers use filters to remove cell debris from the cell culture after fermentation. When MDPH changed the filter in use at the time of licensure from a ceramic to a nylon filter in 1990, it did not notify FDA of the change. We learned about the change after a former BioPort employee in Michigan filed a lawsuit claiming, among other things, that BioPort had made changes to the anthrax vaccine production process. The U.S. General Accounting Office investigated the claim and asked FDA about the effect of the change in filters. In February 2001, FDA sent a letter to BioPort requesting specific information about the changes in filters, and BioPort responded in April 2001. We reviewed BioPort's response

16. 21 CFR 601.12(c) requires a manufacturer to submit a supplement for certain manufacturing changes at least 30 days prior to distribution of the product made using the change. Prior to the agency's amendment of 21 CFR 601.12 in 1997, FDA interpreted 601.12 as permitting a manufacturer to implement certain changes without prior approval. See Changes to be Reported for Product and Establishment License Applications; Guidance, FDA Guidance Document. 60 Fed. Reg. 17535 (April 6, 1995). The Food and Drug Administration Modernization Act of 1997 (FDAMA) codified this scheme in the Federal Food, Drug, and Cosmetic Act. 21 USC 356a. The current 21 CFR 601.12 reflects FDAMA's statutory change.

and found that it adequately addressed FDA's questions and concerns. In addition, we reviewed the lot release protocols, which include product release test results, for all lots of anthrax vaccine released between 1978 and 2001. Based on this information, we concluded that the filter change did not adversely affect the product's safety, purity, or potency.

B. *Inspectional Observations Concerning cGMP Did Not Necessarily Cause Anthrax Vaccine To Be Unsafe or Ineffective*

In your petition you list various cGMP inspectional observations that FDA recorded between 1988 and 1998. You cite a Warning Letter that FDA issued to MDPH in 1995 and a subsequent Notice of Intent to Revoke (NOIR) letter to MBPI in 1997. Petition at pp. 14-17.

These cGMP observations are largely irrelevant to the anthrax vaccine that is currently available. At this time there is no FDA-lot released anthrax vaccine, that was manufactured during the timeframes you cite in your petition (1988-1998), available for military or civilian use. In January 1998, MBPI halted production of anthrax vaccine, prior to the sale of MBPI to BioPort, in order to renovate the anthrax vaccine production facilities. It was necessary for FDA to approve these renovations before BioPort could resume shipping licensed anthrax vaccine made in the renovated facilities. BioPort, therefore, did not ship any licensed finished product anthrax vaccine, made after January 1998, until FDA subsequently approved two BLA supplements related to the renovations. FDA approved one BLA supplement in December 2001 for the anthrax vaccine production facility and another in January 2002 for a contract filling facility. FDA approved these supplements after the agency inspected BioPort and the contract filling facility and determined that they appeared to be in compliance with cGMP for the manufacture of anthrax vaccine.

Through an NOIR, FDA notifies a biologics manufacturer that the grounds exist for FDA to revoke the manufacturer's license. 21 CFR 601.5(b)(1). Although the NOIR that FDA sent to MBPI stated that if MBPI's corrective actions proved to be inadequate, MBPI would risk losing its license, the NOIR did not require closure of the MBPI facility.

MBPI responded to the NOIR in April 1997, by presenting a "Strategic Plan for Compliance." The plan called for periodic submissions of data to FDA to demonstrate MBPI's progress towards achieving compliance with FDA requirements. FDA agreed to review the data and monitor and verify MBPI's progress through follow-up inspections.

As mentioned previously, in January 1998, MBPI halted production of anthrax vaccine, prior to the sale to BioPort, in order to begin comprehensive renovations of the anthrax vaccine production facilities. In February 1998, FDA inspected the MBPI facility to evaluate the implementation and effectiveness of MBPI's corrective actions and make an assessment of the overall compliance status. Our inspection revealed deviations from FDA's regulations and led to the agency's request that MBPI quarantine 11 lots of anthrax vaccine held in storage, pending our review of additional information from MBPI.

We communicated with MBPI and later with BioPort to resolve these issues. FDA inspections in October 1998, and later in October 2000, disclosed that BioPort had made continued progress toward meeting the objectives of the strategic plan and bringing the facility into compliance. We did not initiate license revocation proceedings against BioPort because the firm had implemented corrections and demonstrated its commitment to comply with all applicable FDA requirements.[17] BioPort did this by, among other things, renovating its manufacturing facility, discontinuing the manufacture and distribution of all non-anthrax related products, closing its aseptic filling facility, and moving the anthrax vaccine filling operations to a contract manufacturer.

BioPort's corrective measures resulted in FDA approving a BLA supplement for the firm's anthrax vaccine manufacturing facility in December 2001. FDA also approved another supplement for the contract filling operation in January 2002. As we mentioned above, in addition to the 11 quarantined lots, BioPort has, in storage, a number of lots of additional anthrax vaccine manufactured prior to 1998. FDA has not and does not intend to lot release these lots.

C. *All Lots of Anthrax Vaccine Have Had a Valid Expiration Date*

Your petition claimed that the manufacturer re-dated anthrax vaccine without FDA's approval and failed to give new lot numbers to the re-dated product. Petition p. 18. You assert that this caused certain lots of anthrax vaccine to be misbranded. *Id.* at 18.

Under 21 CFR 610.53(b), a product's expiration date is determined, in part, by the date of manufacture. Under 21 CFR 610.50(a), the date of manufacture is determined by "the date of initiation by the manufacturer of the last valid potency test."

From approximately 1994 through 1998, MDPH and MBPI had certain lots of FDA-lot released anthrax vaccine in inventory for which the expiration dates had expired. MDPH and MBPI, respectively, then conducted potency tests to extend the dating period. On the basis of these tests, FDA extended the dating period of these lots and lot released them again.

However, when FDA so extended the dating period on the previously released lots of anthrax vaccine, the agency's computer-based tracking system for the released lots would not accept the same lot number a second time. Therefore, when FDA sent the lot release notification to the manufacturer, we assigned an additional number to the existing lot number. For example, a lot identified as FAVxxx, when redated, would have been assigned an additional (-1) or (-2) resulting in lot number FAVxxx-1 (or -2). However, we did not specifically notify BioPort or its predecessors that they needed to place the "-1" or " -2" additional number on the labeling of lots for which dating had been extended.

The manufacturer (MDPH, MBPI, and BioPort) and FDA permissibly extended the expiration date of these lots of anthrax vaccine. There was no confusion on the part of FDA or the

17. Except in situations involving suspension of a license pursuant to 21 CFR 601.6, or in cases involving willfulness, FDA provides a licensee with the opportunity to demonstrate or achieve compliance before instituting proceedings to revoke a license. 21 CFR 601.5(b)(2). FDA provided MBPI and BioPort with such an opportunity.

manufacturer concerning which lots actually had their dating periods extended, and there would have been no difficulty tracing the complete manufacturing history of a particular lot, package, or vial. For these reasons, we do not consider this issue concerning the lot number on the vaccine's labeling sufficient to cause the anthrax vaccine to be misbranded.

D. *The Alleged Use of Equipment to Manufacture Other Products*

You assert that "[t]he manufacturer has, at times, used the equipment approved by FDA for the manufacture of anthrax vaccine to manufacture other biological products." Petition at p. 19. You also contend that if this were true, "a true safety hazard exists." *Id.* at 19. Based on inspectional information available to us, it is not evident that BioPort or its precursors used the same equipment to manufacture anthrax vaccine and other products.

Although information concerning the particular manufacturing processes of BioPort may constitute trade secret or confidential commercial information, we are able to provide the following information.[18] First, the suggestion that MDPH or MBPI produced a product other than anthrax vaccine in the same facility as the anthrax vaccine does not necessarily mean that the manufacturer used the same equipment to manufacture both products. Indeed, no documents from FDA inspections of BioPort record such activity. Secondly, if MDPH or MBPI did, in fact, alternate production runs of anthrax vaccine and another product on the same equipment, there is no evidence of any safety hazard. Your exhibit 8 indicates that MDPH/MBPI decontaminated and requalified the facility in September 1995 before resuming manufacture of anthrax vaccine in January 1996. In addition, MDPH's supplement for switching from glass to stainless steel fermenters contained a validated procedure for sterilizing the equipment between production runs. FDA approved this supplement in 1993. FDA is thus not aware of any related evidence that would raise concerns regarding the safety of the anthrax vaccine.

III. *There Are No Pending Drug Marketing Applications or Government Contracts For FDA To Disapprove Pursuant To FDA Compliance Policy Guide 400.200*

You cited FDA Compliance Policy Guide (CPG) 400.200, "Consistent Application of CGMP Determinations." CPG 400.200 states that

> the issuance of a warning letter or initiation of other regulatory action based upon cGMP deficiencies must be accompanied by disapproval of any pending drug marketing application, or government contract for a product produced under the same deficiencies.

Based on this CPG, a 1995 Warning Letter from FDA to MBPI, and the 1997 NOIR from FDA to MBPI, you request that we order all current and/or pending government contracts and drug marketing applications for anthrax vaccine adsorbed be disapproved and the appropriate government agencies informed in accordance with Sec. 400.200. Petition at p. 23. You

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18. FDA is prohibited from publicly disclosing trade secret or confidential commercial information. See 21 USC 331(j); 18 USC 1905.

reference DOD contracts for anthrax vaccine and refer to a DOD Investigational New Drug Application (IND) as a pending drug application.

First, a CPG is not a regulation and thus does not legally bind FDA. See Professional and Patients For Customized Care v. Shalala, 56 F.3d 592 (5th Cir. 1995). Second, FDA does not have the authority to disapprove a contract between DOD and BioPort for the anthrax vaccine. As you request, over the last several years FDA has informed DOD and the Department of Health and Human Services (HHS) about the inspectional history of BioPort, MBPI, and MDPH. DOD and HHS are well aware of FDA investigators' observations during inspections of BioPort. FDA has had many meetings with DOD and HHS and has worked closely with DOD and HHS concerning the anthrax vaccine. Third, an IND is not a "drug marketing application" because it does not permit commercial distribution of the product. See 21 CFR 312.7(a).

IV. *The Grounds Do Not Exist for FDA to Revoke BioPort's License for Anthrax Vaccine*

You argue that FDA should revoke the license for anthrax vaccine because (a) the anthrax vaccine license was improperly issued, and (b) even with a newly renovated production facility, BioPort is incapable of complying with cGMP and of producing anthrax vaccine of consistent safety, purity, potency, and quality. Petition at pp. 24 and 28. As discussed below, we do not agree and do not find that any grounds currently exist to revoke BioPort's license under 21 CFR 601.5.

A. *The Anthrax Vaccine Was Properly Licensed*

NIH licensed the anthrax vaccine in 1970. The clinical evidence supporting licensure consisted of the Brachman study and the CDC data, described above in section I. You cite statements from the chairperson of the committee that reviewed the license application. Petition at p.25. You claim that these statements may have raised questions concerning the evidence of efficacy.[19]

Notwithstanding any such questions, the chairperson and the committee recommended that NIH issue a license for the anthrax vaccine, and NIH did so. Furthermore, as discussed above in section I B, the Panel in the Biologics Review evaluated this evidence and concluded that it demonstrated the effectiveness of the anthrax vaccine. FDA, based on the Panel report, proposed that anthrax vaccine be classified in Category I.

B. *FDA Approved BioPort's Manufacturing Facility in December 2001 and Approved BioPort's Contract Filling Facility in January 2002*

On December 27, 2001, FDA approved BioPort's manufacturing facility in Lansing, Michigan after an extensive inspection. As you know, MBPI, BioPort's predecessor, had halted production of the anthrax vaccine in 1998 in order to comprehensively renovate the manufacturing facility. FDA's most recent pre-approval inspection, conducted in December 2001, determined that

19. You also cited the committee chairperson's comments earlier on p. 5 of your Petition.

BioPort appeared to be in compliance with applicable cGMP requirements for the manufacture of anthrax vaccine.

On January 31, 2002, FDA, by approving a supplement to BioPort's BLA, approved Hollister-Stier Laboratories in Spokane, Washington as a contract filling facility for the anthrax vaccine. The agency approved this supplement after an FDA inspection of the contract filling facility.

You also argue that FDA should immediately suspend BioPort's license. Petition at pp. 30-31. We disagree. There are no grounds to suspend BioPort's license. The standard for suspension of a biological product's license under 21 CFR 601.6(a) is that the Commissioner has reasonable grounds to believe that any of the grounds for revocation exist and that by reason thereof there is a danger to health. Currently, there are no grounds for the revocation of BioPort's license to manufacture anthrax vaccine, and furthermore, there is no evidence of a danger to health.

V. *Conclusion*

This response represents FDA's current position concerning the issues you raise in your petition. This response does not constitute FDA's final decision in the Biologics Review for anthrax vaccine. FDA will complete the Biologics Review administrative process for the anthrax vaccine as soon as practicable. The Advisory Panel in the Biologics Review evaluated the evidence upon which the anthrax vaccine was licensed. The Panel concluded that the anthrax vaccine is safe and effective. FDA adopted the Panel conclusion and recommendation in the Biologics Review proposed rule.

BioPort has implemented comprehensive renovations and a cGMP compliance program in order to comply with FDA's cGMP regulations. From a recent pre-approval inspection, FDA determined that BioPort appeared to be in compliance with cGMP for the manufacture of anthrax vaccine. FDA then approved a license supplement for BioPort's anthrax vaccine manufacturing facility and a license supplement for a contract filling facility. After FDA approved these supplements, BioPort resumed manufacturing and shipping licensed anthrax vaccine.

Sincerely yours,

Margaret M. Dotzel
Associate Commissioner
For Policy

cc: Docket No 01P-0471

DOCKET NO. 01P-0471/CP-1
SUPPORTING DOCUMENTS FOR PETITION RESPONSE

Tab A:

FDA/ORA CPG 7132.12, Sec. 400.200 Consistent Application of CGMP Determinations (sic) (Issued 4/1/81; Revised 3/95).

Tab B:

60 FR 17535 – 17538, April 6, 1995, Changes to be Reported for Product and Establishment License Applications; Guidance.

Tab C:

FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products, April 1996.