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.

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

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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

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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

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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

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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.

Sec. 400.200 Consistent Application of CGMP Determin-ations (CPG 7132.12)

BACKGROUND:

In recent years there has been a growing number of commitments made by FDA to various programs and systems designed to ensure the quality of drug products by carefully monitoring drug manufacturers' compliance with the Current Good Manufacturing Practice (CGMP) regulations. FDA has for many years enforced CGMP as part of its overall drug quality assurance program. The approval process for drug marketing applications (original and abbreviated new drug applications and antibiotic Forms 5 and 6) includes a review of the manufacturer's compliance with the CGMP. More recently, FDA has assumed additional roles in the area of assurance of drug quality involving good manufacturing practice through such programs as the Government-Wide Quality Assurance Programs for drug purchase contracts by the Department of Defense and the Veterans Administration, and the Maximum Allowable Cost program of HHS. Decisions regarding compliance with CGMP regulations are based upon inspection of the facilities, sample analyses, and compliance history of the firm. These data are summarized in profiles which represent several years of history of the firms. In consideration of the growing number of programs dependent upon CGMP assessment, Agency policy must be consolidated in regard to approval or disapproval of drug marketing applications, government purchasing contracts, etc., and the relation of such determinations to regulatory action.

POLICY:

CGMP deficiencies supporting a regulatory action also support decisions regarding non-approval of drug marketing applications, government purchasing contracts, candidates for MAC, etc. Therefore, 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.

Similarly, disapproval of any drug marketing application, government contract, etc., based upon CGMP deficiencies must be accompanied by regulatory and/or administrative action against any other product produced under the same conditions.
Material between asterisks is new or revised

Issued: 4/1/81
Revised: 3/95

which shall be considered the filing date for purposes of the act.

Interested persons may submit relevant information on the application to the Dockets Management Branch (address above) in two copies (except that individuals may submit single copies) and identified with the docket number found in brackets in the heading of this document. These submissions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

The agency encourages any person who submits relevant information on the application to do so by April 17, 1995, and to provide an additional copy of the submission directly to the contact person identified above, to facilitate consid ration of the information during the 30-day review period.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sec. 802 (21 U.S.C. 382)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Center for Veterinary Medicine (21 CFR 5.44).

Dated: March 24, 1995.

Robert C. Livingston,

Director, Office of New Animal Drug Evaluation, Center for Veterinary Medicine.

[FR Doc. 95-8451 Filed 4-5-95; 8:45 am]

BILLING CODE 4160-01-F

[Docket No. 95D-0052]

Changes To Be Reported for Product and Establishment License Applications; Guidance

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing a guidance document entitled "Changes to be Reported for Product and Establishment License Applications; Guidance." The guidance document is intended to provide manufacturers of licensed biological products guidance on changes in manufacturing procedures and establishments which may be implemented with and without prior approval by the Director, Center for Biologics Evaluation and Research (CBER). This document does not apply to manufacturers of Whole Blood, blood components, Source Leukocytes, and Source Plasma, and it does not address labeling changes. By following this guidance document, manufacturers of licensed biologicals may, in some instances, reduce their reporting burden and facilitate implementation of certain changes.

DATES: Written comments may be submitted at any time.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Comments should be identified with the docket number found in brackets in the heading of this document. Two copies of any comments are to be submitted except that individuals may submit one copy. A copy of the guidance document and received comments are available in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Stephen M. Ripley, Center for Biologics Evaluation and Research (HFM-635), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-594-3074.

SUPPLEMENTARY INFORMATION: Under § 601.12 *Changes to be reported* (21 CFR 601.12), manufacturers are required to report important proposed changes in location, equipment, management and responsible personnel, or in manufacturing methods and labeling, of any product for which a license is in effect or for which an application for license is pending, to the Director, CBER. Such reports are to be filed by the manufacturer not less than 30 days in advance of the time that such changes are intended to be made except in case of an emergency. Proposed changes in manufacturing methods and labeling may not become effective until notification of acceptance is received from the Director, CBER.

Reporting changes under § 601.12 represents a significant workload for the industry and the agency. In addition, regulated industry has expressed concern about delays in implementing changes and inconsistencies in reporting requirements for product license applications (PLA's), establishment license applications (ELA's), and new drug applications (NDA's). To reduce the reporting burden on manufacturers of biological products and to facilitate the approval process, FDA is issuing this guidance document, which describes CBER's current interpretation of § 601.12(a) and (b).

The guidance document is not intended to affect the reporting requirements currently specified in § 601.12, but to provide clarifying descriptions of the types of changes that are currently considered to be "important" within the meaning of that section. In addition, the document clarifies the types of changes which may be implemented 30 days after submission of a supplement and those which must await approval of a supplement prior to implementation. Thus, the guidance document outlines three categories for reporting changes, based on the importance and nature of the changes. The document lists examples of changes that would fall into each category.

This document does not apply to changes in manufacturing processes and facilities associated with the manufacture of Whole Blood, blood components, Source Leukocytes, or Source Plasma. CBER is currently evaluating reporting requirements in those areas. In addition, the guidance document does not address labeling changes. However, in the Federal Register of August 3, 1994 (59 FR 39570), FDA published a notice of availability for the revised Office of Establishment Licensing and Product Surveillance Advertising and Promotional Labeling Staff (APLS) Procedural Guidance Document. The APLS Procedural Guidance document details the approach that manufacturers and distributors should follow in submitting advertising and promotional material for review by CBER. The APLS Procedural Guidance Document also provides guidance on CBER's current interpretation of § 601.12 as it applies to reporting important proposed changes in labeling; specifically, promotional labeling of biological products for which a license is in effect or for which an application for a license is pending.

As with other guidance documents, FDA does not intend this document to be all inclusive. The document is intended to provide information and does not set forth requirements. Manufacturers may follow the guidance or may choose to use alternative procedures even though they are not provided in this document. If a manufacturer chooses to use alternative procedures, that manufacturer may wish to discuss the matter further with CBER to prevent expenditure of resources on activities that FDA may later determine to be unacceptable.

This guidance document is not binding on either FDA or licensed manufacturers of biological products and does not create or confer any rights, privileges, or benefits for or on any person.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the guidance document. Received comments will be considered to determine if further revision to the guidance document is necessary.

The text of the guidance document follows:

Food and Drug Administration, Center for Biologics Evaluation and Research (CBER); Changes to be Reported for Product and Establishment License Applications; Guidance

I. Introduction and Background

A significant number of supplements to approved biological product and establishment license applications submitted to CBER during an average year involve changes which fall under § 601.12 *Changes to be reported* (21 CFR 601.12).

Under this regulation, important proposed changes in location, equipment, management and responsible personnel, or in manufacturing methods and labeling, are required to be reported to CBER not less than 30 days in advance of the time such changes are intended to be made (§ 601.12(a)). Proposed changes in manufacturing methods and labeling may not become effective until notification or acceptance is received from the Director, CBER (§ 601.12(b)).

This document is not intended to affect the reporting requirements in § 601.12, but to provide clarifying descriptions of those requirements. This guidance does not apply to manufacturers of Whole Blood, blood components, Source Leukocytes, and Source Plasma. Guidance on reporting requirements in those areas is currently under evaluation within CBER. In addition, this document does not address labeling changes. For guidance on the submission of advertising and promotional material, see the Office of Establishment Licensing and Product Surveillance Advertising and Promotional Labeling Staff (APLS) Procedural Guidance Document (August 1994).

To facilitate the approval process, CBER performed a review of the types of changes being reported and assessed the relative impact of each change on product purity, potency, and safety. Results of this analysis have provided CBER the rationale for describing three categories of changes based on potential effect on product safety, purity, and potency, with each category associated with a different notification mechanism. In general, the types of changes for which CBER recommends less stringent reporting represent changes which, for the most part, have not been associated with demonstrable effects on product purity, potency, or safety, and/or which are readily amenable to on-site scrutiny during inspection of the production facility. In many instances, manufacturers will need to evaluate changes addressed in the three categories using validated standard operating procedures (SOP's) or specifications.

Regardless of whether a supplement is required to be filed, the manufacturer in making such changes must conform to the current good manufacturing practice (CGMP) requirements of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) and the regulations in 21 CFR parts 210 and 211. Changes affecting the method of manufacture require validation under the CGMP regulations. In addition, manufacturers must comply with the recordkeeping requirements under the CGMP regulations and ensure that relevant records are readily available for FDA inspection.

This document identifies and categorizes the types of changes in manufacturing processes and establishments which may be implemented with and without prior approval by CBER.

This guidance document is not binding on either FDA or licensed manufacturers of biological products and does not create or confer any rights, privileges, or benefits for or on any person. It does, however, describe CBER's current interpretation of § 601.12. Where this document reiterates a requirement imposed by statute or regulation, the force and effect as law of the requirement is not changed in any way by virtue of its inclusion in this document.

Section A of this document contains general definitions of each category of change as it pertains to notification or reporting requirements outlined in § 601.12(a) and (b). This section also defines a Periodic Report for Category I changes. Section B of this document provides instruction on sending submissions to CBER. Section C of this document augments these definitions with selected examples of modifications appropriately falling under each category. Section D of this document contains guidance on categorizing proposed changes which may not be listed in section C. Section E of this document discusses the kind of information the agency is asking manufacturers to submit in a Periodic Report.

II. Guidance and Rationale

A. Definitions

General definitions of each category of reporting changes are as follows:

1. Category I—Change(s) for Which No Supplement Submission is Required and Which May be Described in a Periodic Report

This category includes modifications to procedures, process parameters, components, manufacturing methods, reagents, equipment and facilities which do not rise to the level of the "important" changes required to be reported under § 601.12. These are changes that are designed to tighten control on the production process, or have not been associated with adverse impact on product safety, purity or potency. Manufacturers should qualify and, as necessary, validate such changes before implementing them. These changes should be shown not to affect the integrity of the product. For this category, the manufacturer generates and retains all relevant data defining (and, as necessary, validating) changes which are implemented. In order to expedite the agency's review of changes, such data should be readily accessible for FDA-establishment inspections. The agency recommends that the firm notify CBER in a Periodic Report (see description below) of the changes and dates of implementation.

2. Category II—Change(s) Requiring a Supplement Submission and Which May be Implemented Prior to CBER Approval

This category includes modifications to location, equipment, management, and personnel that do not change manufacturing methods, but have the potential to adversely affect product safety, purity, and potency. For these changes, the manufacturer should submit a standard supplement, accompanied by all relevant supporting data, with a request to implement not less than 30 days following the supplement's receipt by CBER's Document Control Center. Such supplements should be clearly marked "Category II Supplement, Changes to be Implemented" at the top of the cover letter. CBER will confirm the submission and its receipt date in the reference number assignment letter. CBER intends to follow relevant application review policies in assigning supplement review.

CBER will process Category II changes as establishment or product license application supplements and will take official action on such supplements on, before, or after this 30-day period. If CBER officials do not contact the sponsor via telephone or written correspondence within 30 days following the documented receipt date to question or reject the "Category II" status, the manufacturer may implement the change. CBER may communicate with the firm during this 30 day period for clarification or to advise that the change is considered to be a Category III supplement (see description below).

Manufacturers should be aware that Category II changes are implemented subject to agency approval. The agency may refuse to approve a supplement for a change that has already been implemented. In assessing a manufacturer's plans to correct a problem, the agency intends to consider the manufacturer's reasons for making the change and the alternatives available to the manufacturer, among other things. If the circumstances warrant, the agency may require the change to be immediately discontinued. When circumstances permit, it is FDA's intent to allow manufacturers to correct a problem with minimal expense and without unnecessary waste.

3. Category III—Change(s) Which Require CBER Approval Prior to Implementation

This category includes changes in manufacturing methods and requires manufactures to submit all relevant supporting documentation and await CBER's approval prior to implementation. As with Category II submissions, CBER intends to follow relevant application review policies in assigning supplement review.

4. Periodic Reports

A Periodic Report is a voluntary written report submitted every 6 months listing and briefly describing Category I changes and providing the date of implementation of such changes. Reports should include separate descriptions of EACH change affecting a licensed product and should identify for each change the specific establishment location involved. (See section E of this document for requested information.)

B. Where to Submit Supplements and Periodic Reports

Three copies of all supplements and periodic reports should be submitted to the Center for Biologics Evaluation and Research (HFM-99), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448.

C. Selected Examples

1. Category I

CBER currently considers the following examples to be changes that will not ordinarily rise to the level of the "important" changes required to be reported under § 601.12. These changes need not be submitted to CBER prior to implementation and may be submitted in a periodic report as "Category I changes." This listing provides representative samples of Category I changes and is not all inclusive.

i. Change in purchasing source of approved final fill components (stoppers, vials, seals) that meet established specifications. This does not include change(s) in composition of such components or suppliers of ancillary chemicals and drug products such as diluents.

ii. Change in harvesting and/or pooling procedures which does not affect method of manufacture, recovery, storage conditions, sensitivity of detection of adventitious agents, or production scale; e.g., collection in smaller quantities to improve process efficiency.

iii. Changes in cell inoculum; e.g. mode of expansion (attached versus suspension; bioreactor versus spinner), cell density, staging of culture. This excludes viral products; e.g., vaccines and in vitro diagnostic kits.

iv. Change in storage conditions of reference standard or panel based on stability data generated with an FDA-approved protocol.

v. Extension of dating period for in-house reference standards, based on real-time data, according to an FDA-approved protocol.

vi. Replacement of inhouse reference standard or reference panel (or panel member) according to FDA-approved standard operating procedures (SOP's) and specifications.

vii. Tightening of specifications for reference standard or lot release analyses.

viii. Establishment of new Working Cell Bank derived from previously approved Master Cell Bank according to an FDA-approved SOP.

ix. Narrowing (tightening) of specifications for intermediates and endproducts to provide greater assurance of product purity and potency.

x. Use of alternative storage containers for intermediates, with no change in sterility, depyrogenation status, or composition of container.

xi. Change in storage conditions of inprocess intermediates based on data from an FDA-approved stability protocol (labeling not affected).

xii. Change in bulk pool size for formulation without process scale-up.

xiii. Batch size changes for ancillary components (specimen diluents, positive and/or negative controls, substrate buffers, etc.) where all equipment contact surfaces remain chemically identical to approved equipment.

xiv. Change in the number of vials per fill with no scale-up or impact on parameters defined in the environmental assessment.

xv Change in shipping conditions (e.g., temperature, packaging, custody) based upon data derived from studies following an FDA-approved protocol.

xvi. Rework of biologic product which has failed final release testing using FDA-approved rework protocol. Note: Any lot of product subject to rework should be so noted on the product release protocol.

xvii. Change in stability test protocol to include more stringent parameters; e.g., additional assays, tightened specifications, etc.

xviii. Replacement of equipment with that of identical design and operating principle involving no change in process parameters.

xix. The following modifications of areas not used for production or storage of intermediate or finished product (such as testing laboratories, materials storage, warehouse, employee break areas, etc.):

(a) Addition of outside areas that do not adversely affect the product manufacturing area or utility systems;

(b) Expansion or reorganization of off-site support space that does not affect the product manufacturing areas;

(c) Modification to or relocation of support space within a product manufacturing facility that does not affect plant utility systems and flow patterns, or adversely affect product purity or environmental conditions (e.g., addition of half partitions or benches).

xx. The relocation of equipment within appropriate areas of approved facilities, not increasing risk to product purity or integrity of testing (e.g., relocation of fermentor in fermentation suite).

xxi. Upgrade in air quality, material, or personnel flow where product specifications remain unchanged. Involves no change in equipment or physical structure of production area.

xxii. Changes in personnel other than the Responsible Head (21 CFR 600.10) or individuals serving in a capacity of alternative or temporary Responsible Head.

2. Category II

CBER currently considers the following examples to be "important" proposed changes in location, equipment, management and responsible personnel. These changes must be reported pursuant to § 601.12(a) and meet the definition of a "Category II Supplement." This listing provides representative samples of Category II changes and is not all inclusive.

i. Addition of back-up systems for manufacturing processes which are identical to the primary system and serve as an alternate resource (not expansion of capacity) within an approved production area.

ii. Upgrade to production air handling or water systems using like equipment and not affecting established specifications; e.g., removal of dead legs in water for injection (WFI) system. (Does not include replacement of parts or routine repair and maintenance (Category I).)

iii. Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology.

iv. Expansion of existing manufacturing support systems (WFI, heating, ventilation, and air-conditioning (HVAC)); e.g., adding an additional WFI loop.

v. Relocation of operations within the same production area of an approved facility with no change in equipment or room classification.

vi. Modification of an approved manufacturing area which does not adversely affect safety, purity or potency of product; e.g., adding new interior partitions or walls to increase control over the environment and replacing or adding new surfaces to enhance cleaning.

vii. Change in Responsible Head (21 CFR 600.10) or individuals serving in a capacity of alternative or temporary Responsible Head.

3. Category III.

CBER currently considers the following examples to be "important" proposed changes in manufacturing methods. These changes require CBER approval before they may be implemented under § 601.12(b), and meet the definition of a "Category III Supplement." This listing provides representative samples of Category III changes and is not all inclusive.

i. Establishment of new Master Cell Bank.

ii. Change in inhouse reference standard or reference panel (panel member) resulting in modification of reference specifications.

iii. Establishment of alternate test method for reference standards, release panels, product intermediates, or endproduct.

iv. Replacement of existing test method with new procedure or method; e.g., change from radioimmunoassay (RIA) to enzyme-linked immunosorbent assay (ELISA).

v. Change in process parameters; e.g., growth cycle, chromatographic medium, process time and/or temperature, filtration process.

vi. Change in sequence of processing steps, including addition of processing step; e.g., viral removal or inactivation.

vii. Change in production scale (up or down) involving changes in equipment, process parameters, or process methodology.

viii. Change in chemistry or formulation of solutions used during processing.

ix. Changes in conjugation chemistry or process.

x. Change in composition of the biological product or ancillary components.

xi. Change in dosage form.

xii. Any change which results in detectable relaxing of product specifications and modification in potency, sensitivity, or specificity.

xiii. Change in fill volume (per vial) from an approved production batch size and/or scale.

xiv. Reprocessing of product without a previously approved reprocessing protocol.

xv. Change in stability testing program; e.g., substitution of analytical methods or potency assay, broadening of acceptance criteria, change in storage temperature, change in test algorithm.

xvi. Extension of dating period for intermediate or endproduct.

xvii. Change in storage conditions for licensed final product or intermediate based on real-time data from FDA-approved stability protocol (labeling affected).

xviii. The following changes in manufacturing location that affect process

conditions and thereby have the potential to affect product safety, purity, or potency:

(a) Use of a previously unapproved manufacturing area or facility;

(b) Change in air quality, water quality, material, or personnel flow for licensed product manufacturing areas.

(c) Change from single product manufacturing to multiple product manufacturing using same equipment and/or personnel.

(d) Renovation to physical structure that alters product, material, and/or personnel flow.

xix. Addition to or replacement of an FDA-approved manufacturing step performed under contract to a second facility.

D. Categorization of Proposed Changes

Before implementing a change which is not identified above or does not clearly fit into one of the defined categories, manufacturers should discuss the proposed change with CBER. If guidance is not sought, the change should be reported in the form of a Category III supplement, subject to CBER approval prior to implementation.

Requests for information regarding categorization of proposed changes not included in the above categories may be addressed to the Director of the appropriate applications Division within the Office with assigned product, or establishment, responsibility at the Center for Biologics Evaluation and Research (HFM–99), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448.

E. Information Requested for Category I Periodic Reports

FDA requests that manufacturers submit the following information for each Category I change in the order shown: (1) Name of the manufacturer; (2) the establishment license number; (3) the report dates (time period covered by the report); (4) the product(s) affected (list each one); (5) the change implemented, including: (a) A brief description and reason for the change and/or modification, (b) the establishment location involved, (c) the date the change was implemented, and (d) a cross-reference to the Approved Validation Protocol or Standard Operating Procedure, if applicable; and (6) the signature of the Responsible Head and the date signed.

Dated: March 31, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95–8382 Filed 4–5–95; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 93F–0201]

Asahi Denka Kogyo K. K.; Withdrawal of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the withdrawal, without prejudice to a future filing, of a food additive petition (FAP 3B4378) proposing that the food additive regulations be amended to provide for the safe use of sodium 2,2′-methylenebis(4,6-di-*tert*-butylphenyl) phosphate as a clarifying agent in polypropylene articles intended for contact with food to include the use at temperatures up to and including retort conditions.

FOR FURTHER INFORMATION CONTACT: Helen R. Thorsheim, Center for Food Safety and Applied Nutrition (HFS–216), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3092.

SUPPLEMENTARY INFORMATION: In a notice published in the Federal Register of July 29, 1993 (58 FR 40656), FDA announced that a food additive petition (FAP 3B4378) had been filed by Asahi Denka Kogyo K. K., c/o Japan Technical Information Center, Inc., 1002 Pennsylvania Ave. SE., Washington, DC 20003. The petition proposed to amend the food additive regulations in § 178.3295 *Clarifying agents for polymers* (21 CFR 178.3295) to provide for the safe use of sodium 2,2′-methylenebis(4,6-di-*tert*-butylphenyl) phosphate as a clarifying agent in polypropylene articles intended for contact with food to include the use at temperatures up to and including retort conditions. Asahi Denka Kogyo K. K. has now withdrawn the petition without prejudice to a future filing (21 CFR 171.7)

Dated: March 22, 1995.

Eugene C. Coleman,

Acting Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 95–8515 Filed 4–5–95; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 94F–0121]

BASF Corp.; Withdrawal of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the withdrawal, without prejudice to a future filing, of a food additive petition (FAP 3B4384) proposing that the food additive regulations be amended to provide for the safe use of hydroxypropyl acrylate and butanediol diacrylate as monomers in the production of acrylic polymers intended for use in food packaging adhesives.

FOR FURTHER INFORMATION CONTACT: Diane E. Robertson, Center for Food Safety and Applied Nutrition (HFS–216), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3089.

SUPPLEMENTARY INFORMATION: In a notice published in the Federal Register of April 25, 1994 (59 FR 19730), FDA announced that a food additive petition (FAP 3B4384) had been filed by BASF Corp., 9401 Arrow Point Blvd., suite 200, Charlotte, NC 28273. The petition proposed to amend the food additive regulations in § 175.105 *Adhesives* (21 CFR 175.105) to provide for the safe use of hydroxypropyl acrylate and butanediol diacrylate as monomers in the production of acrylic polymers intended for use in food packaging adhesives. BASF Corp. has now withdrawn the petition without prejudice to a future filing (21 CFR 171.7).

Dated: March 22, 1995.

Eugene C. Coleman,

Acting Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 95–8516 Filed 4–5–95; 8:45 am]

BILLING CODE 4160–01–F

Health Care Financing Administration

[BPO–130–N]

Medicare and Medicaid Programs; Quarterly Listing of Program Issuances and Coverage Decisions—Fourth Quarter 1994

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Notice.

SUMMARY: This notice lists HCFA manual instructions, substantive and interpretive regulations and other Federal Register notices, and statements of policy that were published during October, November, and December of 1994 that relate to the Medicare and Medicaid programs. Section 1871(c) of the Social Security Act requires that we publish a list of Medicare issuances in the Federal Register at least every 3 months. Although we are not mandated to do so by statute, for the sake of completeness of the listing, we are including all Medicaid issuances and Medicare and Medicaid substantive and interpretive regulations (proposed and final) published during this timeframe. We are also providing the content of revisions to the Medicare Coverage Issues Manual published between October 1 and December 31, 1994. On August 21, 1989, we published the content of the Manual (54 FR 34555) and indicated that we will publish

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

Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)

APRIL 1996

April 1996

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

I. Introduction

FDA is issuing this guidance document as part of its on-going initiatives to provide manufacturers with increased flexibility to bring important and improved human biological products to market more efficiently and expeditiously. This document addresses the concept of product comparability and describes current FDA practice concerning product comparability of human biological products regulated by the Center for Biologics Evaluation and Research (CBER), including therapeutic biotechnology-derived products, regulated by CBER, and therapeutic biotechnology-derived products regulated by the Center for Drug Evaluation and Research (CDER). It describes those steps that manufacturers may perform and which FDA may evaluate to allow manufacturers to make manufacturing changes without performing additional clinical studies to demonstrate safety and efficacy.

As with other guidance documents FDA does not intend this document to be all inclusive. It is intended to provide information and does not set forth requirements. Manufacturers may follow the procedures outlined in this document or may choose to use alternative procedures that are not provided in this document. Prior to using alternative procedures a manufacturer may wish to discuss the matter with FDA to prevent expenditure of resources generating data that FDA may later determine to be unacceptable.

Although this guidance document does not create or confer any rights for or on any person and does not operate to bind FDA or the public, it does represent the agency's current thinking on demonstration of product comparability. Where this document reiterates a requirement imposed by statute or regulation, the force and effect as law of the requirement is not changed in any way by virtue of its inclusion in this document.

II. Background

Historically, biological products have been complex mixtures of molecular species that were difficult to characterize as individual entities. In some cases, the specific active moiety could not be identified, or the active moiety existed in a milieu of other components that

had the potential to affect many of its characteristics. In other cases, the source materials had the potential for transmitting infectious agents. Because of the limited ability to characterize the identity and structure and measure the activity of the clinically-active component(s), a biological product was often defined by its manufacturing process. The manufacturing process for a biological product encompassed manufacturing methods, equipment, and facilities, and was a reason for the current establishment license application (ELA) requirement for biologics. FDA recognized that changes in the manufacturing process, equipment or facilities could result in changes in the biological product itself and sometimes required additional clinical studies to demonstrate the product's safety, identity, purity and potency.

Improvements in production methods, process and control test methods, and test methods for product characterization have led to the evolution of the regulation of biological products. For example, when a biologics manufacturer institutes a change in its manufacturing process, before FDA approval of its product but after completion of a pivotal clinical study, it may not be necessary for the manufacturer to perform additional clinical studies to demonstrate that the resulting product is still safe, pure, and potent. A sponsor may be able to demonstrate product comparability between a biological product made after a manufacturing change and a product made before implementation of the change through different types of analytical and functional testing, with or without preclinical animal testing, described in this document. FDA may determine that two products are comparable if the results of the comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity, or potency.

FDA recognizes that a manufacturer may seek to make changes in the manufacturing process used to make a particular product for a variety of reasons, including improvement of product quality, yield, and manufacturing efficiency. FDA has examined proposed manufacturing changes on a case-by-case basis to determine the type of data, including clinical data, that were necessary to determine product comparability. FDA's evaluations were based, in part, upon the type of manufacturing change and the type of biological product involved. In 1990, in the "Cytokine and Growth Factor Pre-Pivotal Trial Information Package," FDA stated that "significant changes in the manufacturing process...between the time of pivotal clinical studies and submission of the PLA may result in the need to conduct additional validation, animal and in vitro studies, and/or clinical studies". In the 1994 " Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use," FDA included a section entitled "Issues Related to Manufacturing Changes (Demonstration of Product Equivalence)." In discussing manufacturing changes during clinical development in this document, FDA acknowledged that such changes were frequent. FDA stated that "depending on the type of in vitro assays and animal studies and quality of the data, extensive clinical data

demonstrating equivalence may not be necessary." Manufacturers were expected to document all manufacturing changes made during development so that the procedures and manufacturing changes used in the pivotal clinical trials could be validated and the relationship to the marketed product used in earlier trials could be determined.

In the past, FDA has approved manufacturing changes made during or after completion of clinical studies in situations where comparability data have provided assurance that the product would continue to be safe, pure, and potent (effective). Such manufacturing process changes, implemented before or after product approval, have included changes implemented during the expansion from pilot scale to full scale production, the move of production facilities from one legal entity to another legal entity, and the implementation of changes in different stages of the
manufacturing process such as fermentation, purification, and formulation. In each case, FDA reviewers have used their collective scientific and regulatory experience to provide the best evaluation consistent with the applicable regulatory scheme and current knowledge.

For manufacturing changes prior to product approval, FDA interprets the phrase, "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency," in 21 CFR 601.2(a) to include clinical data generated from a precursor product, made prior to a manufacturing change, so that the manufacturer can demonstrate that the precursor product is comparable to the manufactured product. Therefore, a manufacturer may demonstrate comparability between a product made before a manufacturing change and a product made after a manufacturing change. If a manufacturer is able, in FDA's judgement, to demonstrate comparability, FDA may permit the manufacturer to implement the changes without conducting an additional clinical trial(s) to demonstrate efficacy.

FDA recognizes that improvements in production methods, process and control test methods, and test methods for product characterization have allowed manufacturers of biological products to readily identify and assess the impact of changes made to production processes and production facilities. For example, techniques for isolation of macromolecules, product and process related, have improved greatly in recent years. The manufacturer's ability to establish sensitive and validated assays for characterizing the product and biological activity and to evaluate the significance of differences noted in such assays can provide the basis for FDA to assess product comparability without the necessity of repeating clinical efficacy studies.

FDA has reviewed its existing guidance documents in order to clarify inconsistency or ambiguity that could potentially arise from this document and existing guidance. FDA has not found past guidance that it considers inconsistent with the guidance set forth here. However, to

the extent that there is any prior guidance from FDA that is interpreted by manufacturers or others as inconsistent with this document, such guidance is superseded. To the extent that a manufacturer may have found or interpreted previous guidance to be ambiguous concerning the issue of manufacturing changes, FDA now clarifies that the comparability guidance described in this document and currently employed by FDA is FDA's operative policy for these products. See, e.g., 1983 Interferon Test Procedures: Points to Consider in the Production and Testing of Interferon Intended for Investigational Use in Humans; 1990 Cytokine Pre-Pivotal Trial Information Package (including reference that a product used in a pivotal clinical trial should be manufactured in a manner which is essentially identical to the manufacturing process that the manufacturer intends to use after approval); and 1995 FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products (including reference that certain aspects of pilot production should be identical to those applied to a full commercial scale).

III. Product Comparability Testing

This document addresses comparability testing for manufacturing changes made prior to product approval and after product approval. For manufacturing changes prior to product approval, under currently applicable laws and regulations, the manufacturer must fully describe the change in any license application or investigational new drug application (IND). FDA urges manufacturers to consult with FDA prior to implementing changes that may result in comparability testing, in order to avoid delay in the review of applications.

Manufacturing changes may result in no observed alteration in a product. Alternatively, a minor alteration in one or more product characteristics, with no previously documented effect, can have either no effect or a substantial effect on the pharmacology of the product. Likewise, a major alteration in one or more product characteristics with no documented effects on the pharmacology of the product, can have either no effect or a substantial effect on the pharmacology of the product. The most important factor to FDA as it assesses product comparability is whether it is anticipated that any of any of these manufacturing changes will translate into significant changes in clinical safety or efficacy.

Manufacturers should carefully assess manufacturing changes and evaluate the product resulting from these changes for comparability to the pre-existing product. Determinations of product comparability may be based on chemical, physical, and biological assays and, in some cases, other non-clinical data. If a sponsor can demonstrate comparability, additional clinical safety and/or efficacy trials with the new product will generally not be needed. FDA will determine if comparability data are sufficient to demonstrate that an additional clinical study(ies) is unnecessary.

Knowledge of the process involved in the manufacture of the product is an integral component in determining the design of an appropriate comparability assessment program. In determining the types of tests needed, FDA may consider the extent of the manufacturing change(s) and the stage of manufacturing at which the change(s) occurs. Comparability testing programs may include a combination of analytical testing, biological assays (in vitro or in vivo), assessment of pharmacokinetics and/or pharmacodynamics and toxicity in animals, and clinical testing (clinical pharmacology, safety, efficacy), with the usual progression of complexity from analytical to animal studies to human pharmacokinetics and/or pharmacodynamics to clinical safety and efficacy studies. However, comparability testing is not simply a hierarchical system in which a particular test result necessitates the next level of testing. In fact sometimes many of the tests performed are complementary. For example, analysis of the pharmacokinetics profile often suggests biological events not reflected in other types of analyses, e.g., in vitro assays.

Manufacturers should provide to FDA extensive chemical, physical and bioactivity comparisons with side-by-side analyses of the "old" product and qualification lots of the "new" product. When available, fully characterized reference standards for drug substance and final container material should also be used. Tests should include those routinely used for release of the bulk drug substance and final drug product in addition to tests specifically directed at fully evaluating the impact of the change on the product. Additional testing usually includes in-process assays at the manufacturing step(s) which are most likely affected by the manufacturing change(s).

□

Manufacturers may use the following categories of tests:

A. Analytical Testing

Analytical testing includes both chemical and physical assays. Tests should be selected which are sensitive to the full range of differences which might result from the process change. The sensitivity and breadth of analytical testing is an important determinant of the nature and extent of additional testing which should be done. These tests should include tests routinely done on all production lots, those initially used to fully characterize product structure and identity and establish product consistency from one production lot to another, and new tests if applicable.

B. Bioassays

Bioassays are functional tests which sponsors should use to assess the activity/potency of the product. These tests may also serve as measurements of the biological integrity (e.g., correct conformation) of the product and thus complement other analytical measurements. Sponsors should validate these assays and have a specific range of

acceptable values for defining product activity. They may include appropriate in vitro tests (e.g. cell growth, enzymatic activity, anti-viral assays, infectivity assays) or in vivo tests in relevant animal models. If the in vivo mechanism of action of the product is known, the bioassay (when possible) should reflect this activity. Consideration should be given to in vivo and/or in vitro models as predictors of the biological effects in humans. For example, with vaccines, sponsors should evaluate the degree of correlation of the test(s) performed (e.g., assessment of immunogenicity) with clinical protection and submit such information to FDA so that it may be determined if a clinical study should be conducted following manufacturing changes. In cases where a product has multiple activities which are not completely correlated or the mechanism of action for clinical usage is unknown, manufacturers may need to consider performing more than one functional assay. When a drug substance has more than one form and a manufacturing change shifts the distribution of forms, determination of the bioactivity of the various forms may be of value in assessing the impact of the change.

The combined precision of the analytical and functional tests and their ability to assess significant aspects of the product are important. Both sponsors and FDA should evaluate data from both types of testing modalities to determine the extent of additional tests needed.

C. Preclinical Animal Studies

In addition to the various in vitro studies, in vivo studies in animals may be used in comparability evaluations to determine pharmacokinetics parameters, pharmacodynamic activity, or toxicity endpoints. Animal pharmacokinetics data may be needed to assess comparability even in the absence of demonstrated differences in the analytical testing or the functional assays for the product. This is because analytical testing may be insensitive to changes affecting pharmacokinetics, and in vitro functional tests may not reflect the time-dependent aspects of distribution. Differences in in vivo exposure originating from differences in pharmacokinetics may lead to differences in therapeutic activity. Therefore, assessment of pharmacokinetics is often considered complementary to the functional assay. For hormones however, in vivo potency assays often take into account potential pharmacodynamics and pharmacokinetics profiles in animals. For these hormone products, when bioavailability is in question, clinical pharmacology studies may be needed to demonstrate comparability.

Adequate pharmacokinetics measurements may include determination of Cmax, Tmax, AUC and t « in either parallel or cross-over study designs. In cases where complications may arise from immune responses to heterologous proteins, cross-over design may be inappropriate. In other cases, sponsors should consider complicating factors related to binding proteins and levels of endogenous protein. In cases where animal studies may

not be relevant, clinical pharmacology studies may be needed to show comparability.

Prior to product approval, manufacturers generally should not need to repeat all toxicology studies that were performed with the product manufactured by the previous manufacturing process in order to demonstrate product comparability. In some cases, additional animal studies may only be needed if immunogenicity is the major safety concern. The necessity and extent of additional toxicity studies may depend upon the safety profile of the pre-existing product and on the magnitude of the manufacturing process change and/or effect on the product. Situations in which additional studies may be needed include those where the product has a narrow therapeutic range or where specific safety concerns are present, e.g., when the manufacturing process change raises concerns about possible toxic impurities or adventitious agents which cannot be assessed by analytical testing.

D. Clinical Studies

Clinical studies include human pharmacology studies, immunogenicity, safety, and/or efficacy trials. Although comparability testing can include some form of clinical efficacy studies, usually one of the purposes of comparability testing, not including efficacy studies, is so FDA may determine on the basis of such comparability data that additional clinical efficacy studies, of a sufficiency to support initial licensure or approval, are unnecessary. Human pharmacology studies, generally, may be needed to evaluate changes which may affect product pharmacokinetics or pharmacodynamics, e.g., change in product formulation.

In cases where a manufacturing change(s) results in a product with structural and/or bioactivity differences, and/or differences in pharmacokinetics patterns, and those differences are meaningful with respect to potential impact on the product's safety, purity, or potency (efficacy), an additional clinical study(ies) usually may be needed to evaluate the product's safety and/or efficacy. Additionally, when the analytical and other preclinical testing is not sufficiently sensitive or broad enough to detect such meaningful differences, additional clinical study(ies) may be needed.

E. Additional considerations

In terms of comparability testing, manufacturers should generally perform extensive analytical testing complemented by functional testing if manufacturing changes occur in the process of producing the bulk drug substance. Examples of such changes include the following: a change in manufacturing site; modifications to cell or seed strains, including changes to the master cell bank; fermentation; and isolation or purification. In some cases, complementary pharmacology data or biologic response data (e.g., antibody titers for vaccines) may be needed.