12 October 2001

Dockets Management Branch
Department of Health and Human Services 8162 '01 OCT 15 A9:51
Food and Drug Administration; Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

CITIZEN PETITION:

The undersigned submit this petition under Section 360bbb-2 of the Federal Food, Drug and Cosmetic Act, section 553(e) of the Administrative Procedures Act, and Title 21 Subsection 10.30 of the Code of Federal Regulations to request the Commissioner of Food and Drugs to take the administrative actions listed below regarding anthrax vaccine adsorbed.

A. Action requested

(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 13 December 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 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.

OIP-0471 CP1

B. Statement of grounds

(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 13 December 1985.

The regulations of biologics was effectively transferred from the Assistant Secretary for Health and Scientific Affairs under the Secretary of Health, Education, and Welfare to the Commissioner of Food and Drugs and the Director, National Institutes of Health on 18 February 1972. On 14 August 1972, Food and Drug Commissioner Charles Edwards proposed procedures for the review of all biologic products. This review would encompass the overall safety and effectiveness of every biologic product. These procedures were finalized on 8 February 1973 and a total of six review categories evolved from this mandated review procedure. On 28 February 1973 a request for a safety, effectiveness and labeling review of Anthrax Vaccine, adsorbed was published in the Federal Register.

Anthrax Vaccine, adsorbed (now referred to as anthrax vaccine adsorbed or AVA) was placed in the review group of "Bacterial Vaccines and Toxoids with Standards of Potency, Single or in Combination". On 16 January 1981 the Food and Drug Administration (FDA) published a proposed rule to revise the reclassification procedures for the biologic products under review. In this proposed rule, FDA indicated that the final report for the products in the above review group had been received and would issue proposed orders (rules) based on this report prior to the issuance of any final rule for reclassification of certain products as Category III. FDA published this Proposed Rule in the Federal Register on 13 December 1985. In this Proposed Rule, the review committee (the Panel) spent a great deal of time explaining its evaluation criteria, methodology, etc. and used the products under its review in examples.[1]

[1] It is interesting to note that every product reviewed by the Panel was mentioned in this introduction, except anthrax vaccine adsorbed.

The Panel recommended that "*this product* [AVA] *be placed in Category I and the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.*" [2]

This recommendation clearly conflicts with the guidelines established by the Commissioner and with the evaluation criteria used by the Panel.[3] The Panel was aware that no clinical trials had taken place writing:

> *"The vaccine manufactured by the Michigan Department of Public Health has not been employed in a controlled field trial."*

---

[2] The Panel's report and recommendations can be found beginning at 50 FR 51002. The generic product review and specific product review of anthrax vaccine, adsorbed begin at 51058.

[3] The Commissioner indicated in the Federal Register Notice outlining the review procedure (38 FR 4319) that proof of effectiveness shall consist of controlled clinical investigations as defined in 21 C.F.R. § 130.12 (a)(50(ii) [This section can now be found at 21 C.F.R. § 601.25(d)(2)]. The Commissioner had proposed an amendment to § 130.12 in 1970 (35 FR 3073). After the comment period, the Commissioner concluded: "*The scientific principles set forth in the regulations, as amended by this order, constitute the essentials of an adequate and well-controlled clinical investigation. To make the criteria guidelines only would be contrary to the legal obligation that all claims of effectiveness for drugs marketed through the new drug and antibiotic procedure s must be supported by 'substantial evidence', derived from adequate and well-controlled clinical investigations.*" The Commissioner wrote: "*Well documented clinical experience in an uncontrolled or partially controlled situation may be of value in contributing information as to the drug's safety, side effects, contraindications, warnings and precautionary needs. It can as well be considered as corroborative evidence, along with data derived from adequate and well-controlled clinical investigations, to support claims of effectiveness. But it cannot alone rise to the level of adequate and well-controlled clinical investigations, even when done by an experienced investigator or reported by a number of investigators who have conducted inadequately controlled clinical trials.*" The amendment to Title 21 provides the opportunity for any person to seek exemption from some or all of the above criteria. The Michigan Department of Public Health (MDPH) did not seek exemption from these regulations during their licensing process.
The Panel used this rigorous standard as a basis of evaluation of effectiveness writing: "*it has become generally understood that a successful and acceptable vaccine must be: (1) Safe and (2) effective.*" "*It is the clinical trial, however, which must provide the final critical assessment of the efficacy and safety of the new vaccine.*"

The panel briefly mentions the data gathered in support of the license.[4] The Panel's use of data for a similar, but different, vaccine to support its recommendation that the anthrax vaccine be considered a Category I biologic is contrary to the 21 C.F.R. § 130.12 *et seq.* The Supreme Court has affirmed these provisions.[5] The Panel should have placed AVA as either a Category II or IIIB biologic product.

A Category II designation is for those biological products determined to be unsafe, ineffective, or misbranded. Based on a strict interpretation of the requirements, placing AVA in Category II would have been impossible, as the Panel did not have any evidence from the actual vaccine with which to make a determination of safety or efficacy. However, the absence of data cannot be construed to imply safety or efficacy. In fact, the Panel should have viewed this lack of data in terms of the FDA's mission to *"protect the public health as it may be impaired by drugs"* by ensuring that these drugs are safe and effective. The gravity of FDA's mission is stated in the

---

[4] Safety data for the product license application was gathered under DBS IND 180. Based on a review of the Progress Reports for DBS IND 180, this study was strictly for the purpose of establishing the safety of the vaccine. Vaccination was a condition of employment at the various mills; therefore one hundred percent participated. There were no "control groups". The Panel erroneously refers to these data in the specific product review in '4. Critique' as adequately establishing significant protection against cutaneous anthrax in fully immunized subjects. It is important to note that the license approval was based on the caveat that MDPH would provide efficacy data to the Division of Biologic Standards. In pre-licensure correspondence, Dr. Margaret Pittman wrote: *"Michigan has filed with the Division all required information and material for license except the results of an adequately controlled clinical investigation that establishes efficacy." "Therefore, it is recommended that license be granted and the NCDC (IND –180) be requested to obtain data with a view to determine human efficacy of the product."* [Exhibit 2] In fact, two additional Progress Reports were submitted by MDPH after license recommendation. As with the pre-licensure reports, these Progress Reports provide no data on the effectiveness of the vaccine. To date, the manufacturer has not complied with the AD Hoc Committee request to provide human efficacy data.

[5] In Weinberger, CW. v Hynson, Westcott and Dunning, Inc. (No. 72-394 and 72-414) FDA defended and the Court affirmed their revocation of the licenses of unproven drugs and vaccines. The Court determined that the FDA was within its regulatory authority to revoke the licenses of those drugs that relied on clinical data from other drugs as evidence of efficacy. Thus, the Supreme Court affirmed that efficacy data submitted for a drug license must come from clinical investigations performed with the drug itself, not from similar drugs or from bridging studies. The Panel, in relying on the clinical data of a different vaccine (a Merck, Sharp & Dohme product used in the "Brachman Study"), ignored the licensing requirements established by Congress and Supreme Court precedent.

announcement of procedures for review of safety, effectiveness, and labeling published on 18 August 1972 (37 FR 16679): "*The importance to the American Public of safe and effective vaccines...cannot be understated.*"

Dr. M. Pittman, the Ad Hoc Committee Chair, addressed the lack of data from DBS IND 180 in three separate 1969 memorandums:

> *"The lack of cases of anthrax in an uncontrolled population of approximately 600 persons in the Talladega mill can hardly be accepted as scientific evidence for efficacy of the vaccine." "It was also noted that clinical data establishing efficacy of the product had not been submitted..." "The fact that the vaccine has been used in a number of textile mills and that there has been no case of anthrax was substantive but not conclusive evidence of efficacy." [Exhibits 1, 2, 3]*

Even the Panel criticized studies such as that used in the licensure of AVA.[6] Yet the Panel determined that AVA should be placed in Category I. This placement in Category I was not without reservations or limitations as spelled out in the generic and specific product reviews. For example:

> *"It is recommended for individuals in industrial settings who come in contact with imported animal hides, furs, wool, hair (especially goat hair), bristles, and bone meal, as well as laboratory workers involved in ongoing studies on the organism."*

---

[6] In their Generic Statement on Requirements for a Well-Controlled Field Trial, the Panel, in describing the determination of safety and efficacy, writes: "*The final and most important step is the field trial, when a large number of presumably nonimmune humans is inoculated, and the incidence of the disease among vaccines and control subjects is compared.*" They discounted historical controls as no longer acceptable science. The decline in disease frequency after vaccination could not be interpreted as resulting from vaccination, because the changes may be due to natural disease cycles or changing socioeconomic conditions, or other conditions where the disease occurred. Likewise, the Panel considered the comparisons of the frequency of disease in those who do and do not volunteer for the study as unacceptable. Based on a review of the Progress Reports for DBS IND 180, this study was strictly for the purpose of establishing the safety of the vaccine. Vaccination was a condition of employment at the various mills; therefore one hundred percent participated. There were no "control groups". A review of the Brachman Study reveals that a large percentage of the employees at the various mills were non-volunteers, yet their numbers were considered in the effectiveness calculations. Additionally, the Brachman Study 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*. Neither DBS IND 180 nor the Brachman Study met the definition of a well-controlled field trial.

> *"In general, safety of this product is not a major concern, especially considering its very limited distribution and the benefit-to-risk aspects of occupational exposure in those individuals for whom it is indicated."*
>
> *"The Panel believes that there is sufficient evidence to conclude that anthrax vaccine is safe and effective under the limited circumstances for which this vaccine is employed."*
>
> *"This vaccine is recommended for a limited high-risk of exposure population along with other industrial safety measures designed to minimize contact with potentially contaminated material. The benefit-to-risk assessment is satisfactory under the prevailing circumstances for use."*

The Panel clearly intended to limit the use of this vaccine to those employed in industrial and laboratory settings. It weighed the absence of valid data with the intended population, i.e. industrial and laboratory workers, and concluded that the benefit outweighed the risk for this specific group of people. Nevertheless, the fact remains that the Panel ignored the C.F.R. as well as the Commissioners requirements in placing AVA in Category I.

Additionally, the specific product review revealed that AVA was improperly labeled.

> *"The labeling seems generally adequate. There is a conflict, however, with additional standards for anthrax vaccine. Section 620.24(a) defines a total primary immunizing dose as 3 single doses of 0.5 mL. The labeling defines primary immunization as 6 doses..."*

A review of late-1960's Annual Progress Reports on the licensing study indicates that the primary dosing schedule was three doses.[7] FDA recognized the discrepancy and recommended that the labeling be changed. The additional standards, published in the Code of Federal Regulations, were the standard approved by FDA. FDA noted that the labeling indicated six doses where the additional standards indicated three doses. The Panel concluded: "*Labeling revisions in accordance with this Report are recommended.*" The labeling has never been changed, and the FDA has not commented on or corrected this glaring discrepancy. Although the validity of the safety and efficacy evidence is circumspect, the mislabeled status of AVA is clear and warrants a Category II designation.

---

[7] NCDC Annual Progress Report to the Director, Division of Biologic Standards, 1 October 1968.

A Category III designation is given to those biological products determined by the Panel not to fall within either Category I or II on the basis of the Panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. Those biological products in Category III for which suspension of the product licenses pending submission of additional data are recommended are designated as Category IIIB. The recommendation for Category IIIB is based on the assessment of the present evidence of safety and effectiveness of the product.

It is possible that the Panel considered the extremely limited use of the vaccine between licensure in 1970 and 1981, when the Panel submitted its final report. If this were the case, then a small amount of evidence of safety may have been available to the Panel in addition to the safety data from DBS IND 180. However, no efficacy data was ever presented pre-licensure and none was gathered post licensure. Upon a cursory review of the data, Category IIIB would seem to be the logical placement of AVA by the Panel. The available data suggest that the vaccine is safe when weighed against the risk of exposure in an industrial or laboratory setting, yet there is no data on the effectiveness. The 1985 Specific Product Review reaffirmed this fact:

> *"Anthrax vaccine poses no serious special problems other than the fact that its efficacy against inhalation anthrax is not well documented."*

Despite the failure of the manufacturer to meet the regulatory standard for licensure of proven efficacy in humans required by the 1962 Harris-Kefauver amendment, the FDA categorized the anthrax vaccine as a Category I biologic. This meant that they found the vaccine to be "safe, effective, and not misbranded."

The safety and efficacy standards used by the Panel were referenced in the review's introduction:

> *"It has become generally understood that a successful and acceptable vaccine must be: (1) Safe and (2) effective. Safety means that the preparation used must not cause the disease against which it is directed and that the occurrence of reactions, both local and general, must be within acceptable limits. Efficacy implies a useful degree of clinical protection...It is the clinical trial, however, which must provide the final critical assessment of the efficacy and safety of the new vaccine."*

The foregoing discussion shows these standards were not attained. The 1985 review recommending that anthrax vaccine be considered as a Category I biologic clearly did not anticipate the use of the vaccine for a mass immunization program for two million U.S. military Servicemembers by the Department of Defense or an even larger number of the general population.

When the FDA was asked why a final rule has not been published Mr. Mark Elengold, the Deputy Director of the FDA Center for Biologic Evaluation and Research, responded in writing:

> *"FDA has not issued a final order regarding the findings of the panel regarding the anthrax vaccine. The priority has been to issue documents, such as license revocations, for products not placed in Category I. Since the panel did not propose further action with regard to the anthrax vaccine, based on the panel review the vaccine's current status would not change."* [8]

However, a Final Order is required for the placement of AVA as a Category I, II, or III biologic product. As first published in the Federal Register:

> *"After reviewing the comments, the Commissioner of Food and Drugs shall publish in the Federal Register a final order on the matters covered in the proposed order. The final order shall become effective as specified in the order."*

The Panel submitted its report and review of AVA twenty years ago. The Proposed Rule was published 16 years ago. To date, no action has been taken by FDA to promulgate a final order. In the mean time the manufacturer has not produced any human efficacy data as requested by the Chair of the license review committee, the vaccine remains mislabeled, the intended population of at risk workers has virtually disappeared, and the manufacturer has sold millions of doses to an agency that is using the product in an unapproved manner for an unapproved use.

Placing the AVA in Category II is warranted because: 1) there is no evidence of efficacy of this particular vaccine, 2) the safety data was gathered in a manner inconsistent with the requirements of a well-controlled field trial, and 3) the product is mislabeled. Placing the AVA in Category IIIb could be warranted as well, recommending license revocation on the basis of a panel's

---

[8] Mark Elengold, FDA Deputy Director of the Center for Biologic Evaluation and Research, April 6, 2001, email correspondence.

assessment of the potential risks and benefits. Like other biologic products under MDPH license #99, i.e., Diphtheria and Tetanus Toxoids Adsorbed, AVA must be reviewed and categorized properly. Ultimately, the license for AVA should be recommended for revocation due to lack of proper safety and efficacy data submissions, similar to the notice published on 29 May 2001 in the Federal Register for these other MDPH products.

Therefore, we respectfully request that you take the following action. Finalize the proposed rule with the following specific changes in the language detailed in Federal Register, Vol. 50, No. 240, Friday, December 13, 1985, page 51059, Specific Product Review:

Item 3. Analysis – a. Efficacy – (2) Human. Delete the entire paragraph.

Replace with:

> *"This product does not meet Federal requirements. The vaccine manufactured by the Michigan Department of Public Health has not been employed in a controlled filed trial. A similar vaccine prepared by Merck, Sharp & Dohme and employed in a placebo-controlled field trial is corroborative evidence of efficacy against cutaneous anthrax, but does not meet the Federal Food, Drug and Cosmetic Act requirement of substantial evidence. A review of the Center for Disease Control data pertinent to this product for the period 1962 to 1974 in at risk industrial workers indicates that no cases have occurred in fully immunized workers. This decline in disease is substantive but not conclusive evidence of efficacy and not within the meaning of a well-controlled field trial (see Generic Statement on Requirements for a Well-Controlled Field Trial). No meaningful assessment of its value against cutaneous or inhalation anthrax is possible."*

Item 4. Critique. Delete the entire paragraph.

Replace with:

> *"This product has not met the Federal Food, Drug and Cosmetic Act requirement of demonstrating substantial evidence of efficacy. The safety requirements appear to have been met. The product is currently mislabeled.*

Item 5. Recommendations. Delete the entire paragraph.

Replace with:

"The panel recommends that this product be placed in Category II and that the appropriate license(s) be revoked."

Or in the alternative, replace with:

"The panel recommends that this product be placed in Category IIIB and that the appropriate license(s) be suspended while the manufacturer completes the studies necessary to properly demonstrate efficacy of the product."

A proper recategorization of anthrax vaccine adsorbed as Category II, and the revocation of BioPort's license in accordance with 21 C.F.R. § 130.12 and the Food, Drug and Cosmetics Act is the decisive regulatory action that will *"protect the public health."*

INFORMATION KNOWN WHICH IS UNFAVORABLE TO THE PETITION:

To our knowledge, no exceptions to the safety, efficacy and labeling requirements of the Federal Food, Drug and Cosmetic Act are allowed.

(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.

"Enforcement of current good manufacturing practices (cGMPs), as pursued by the Food and Drug Administration (FDA) over the past nearly forty years, originated with the 1962 amendment to the Federal Food, Drug and Cosmetic Act (FD&C Act). Under these amendments, a drug was deemed to be adulterated if 'the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice' to assure that the drug is safe and has the identity and strength and meets the quality and purity characteristics which it is represented to possess (see 21 U.S.C. § 351(a)(2)(B)). Judicial opinions interpreting the cGMP provision of the FD&C Act have supported the FDA's view that the 1962 amendments significantly expanded the agency's authority by eliminating the requirement that the agency must demonstrate, through sampling and testing, that drugs actually are contaminated or deficient in some way. As the court in *United States v. Bel-Mar Laboratories Inc.* 284 F. Supp. 875 (E.D.N.Y. 1968), put it:

> *The 1962 amendments were intended to strengthen and broaden the [FD&C] Act...The purpose of [21 U.S.C.] § 351(a)(2)(B) was to attack commerce in unsafe and unreliable drugs in its incipiency by giving the Food and Drug Administration...additional authority to require that sound methods, facilities and controls be used in all phases of drug manufacturing and distribution. Thus, under the subject section, a drug is deemed to adulterated...regardless of whether the drug actually is deficient in some respect.*

The courts also have upheld the drug cGMP regulations against challenges that they were not specific and could not be enforced evenhandedly. For example, the *Bel-Mar* court said that the regulations apply to "an industry where manufacturing practices are in a state of constant change" and where there are "thousands of widely differing and complex products which are processed in a myriad of establishments under infinitely different circumstances." Nevertheless, the courts have found that the regulations provide a sufficiently well-defined standard against which a company's conduct can be measured. In fact, the court in *Bel-Mar* viewed the regulations as "intended to set minimum requirements."[9]

---

[9] Arthur Levine. FDA Enforcement Manual. Tab 1600. Pg 7. Thompson Publishing Group

a) All anthrax vaccine adsorbed (AVA) produced since 1991 is adulterated by virtue of its' having been produced using unapproved procedures in unapproved equipment.

MDPH[10] produced AVA sporadically throughout the 1970's and 1980's using the same equipment and the same manufacturing process that had produced AVA for DBS IND 180. The Division of Biologic Standards approved this equipment and the manufacturing process by awarding the AVA license in 1970.[11] MDPH's need for large-scale production of AVA came as the result of a 1988 contract with the U.S. Army.[12] Until the 1988 contract with DOD, production of AVA was infrequent, a batch being produced every three to four years, the largest being 7500 doses. The approved equipment consisted of one production line that MDPH alternately used for other vaccine products. The 1988 contract with DOD required MDPH to drastically increase production capacity.

MDPH originally had one fermentation train built around a 100-liter glass-lined fermentor. This fermentation train had a maximum capacity of 20,000 doses per production run and required many weeks to complete a batch and ready the equipment for the next production run. In order to meet the production requirements of the 1988 contract, two stainless steel fermentation trains were added in 1990.

The new fermentation trains used equipment different than that approved for the original facility. MDPH was aware of the need to gain FDA approval for this new equipment and applied for an amendment to their Establishment License Application (ELA) in December 1990, after the first two fermentation trains had been installed. The FDA approved this amendment to the ELA in

---

[10] BioPort Corporation is the current manufacturer and license holder for anthrax vaccine adsorbed (AVA). The original license holder was the Michigan Department of Public Health (MDPH). MDPH was partially privatized in 1996 with the sale of its biologics division to the Michigan Biologic Product Institute (MBPI). For the purposes of this petition BioPort, MDPH and MBPI are the same entity.

[11] The equipment and the manufacturing process are well described in U.S. Patent # 3,208,909. (Puziss, M. Wright, GG. Anaerobic Process for Production of a Gel-adsorbed Anthrax Immunization Antigen. United States Patent Office Record. September 28, 1965. page 1471).

[12] MDPH agreed to produce 300,000 doses for the Department of Defense (DOD) in 1988. The DOD entered into three additional AVA contracts with the manufacturer through 1998. These four DOD contracts with MDPH totaled several million doses.

1993.[13] The vaccine that came off each fermentation train was considered a sublot. Sublots from the fermentors were mixed together to form the final anthrax vaccine or FAV. Anthrax vaccine distributed with a designation Lot FAV--- prior to the 1993 ELA amendment approval is adulterated. Two additional stainless steel fermentation trains were subsequently added in early 1993, replacing the original glass-lined fermentation equipment. These four stainless steel fermentation trains produced AVA until the facility ceased operation in January 1998. No ELA amendment or these two additional fermentation trains was ever sought or made.[14] The vaccine made and distributed from these fermentation trains is likewise adulterated.

---

[13] In a 9 July 1990 telephone conversation FDA employee Rebecca Devine informed Dr. Myers, Responsible Head for MDPH, that FDA considered the additional fermentation trains a "major" change. An amendment to the establishment license was required. [Exhibit 4] Ms. Devine was referring to 21 U.S.C. § 356a *et seq* and 21 C.F.R. § 601.12(b)(1) wherein a supplement shall be submitted for any change in the equipment that has a substantial potential to have an adverse affect on the identity, strength, quality, purity or potency of the product as it may relate to the safety and effectiveness of the product. § 601.12 (b) requires approval prior to distribution of any product affected by such change. This ELA amendment application did not inform FDA that the entire production process was changed, from the seed fermentors to the bulk fermentors, to the filtration and sterilization process, to the "downstream" processes and equipment, i.e. centrifuge, bottling and filling. It merely stated that they would be adding two additional stainless steel fermentation trains to the facility.
The filters were changed from glass sintered to low-protein-binding nylon membranes. The sterilization process changed because the original method of flash heating the medium in an autoclave to 120° C did not ensure complete inactivation of the media. The new method of sterilization used a nylon membrane to filter the media. We are unaware of any attempt by MDPH to inform FDA of these changes or to gain approval of them through ELA amendments.
The equipment changes and process changes are discussed in detail in a civil suit brought by three former MDPH employees against the state of Michigan. Please reference American Arbitration Association Case No. 54 390 01376 98 Compensation for Inventions Developed During Employment. An additional report of these equipment and process changes are described in "Efficacy of a standard human anthrax vaccine against *Bacillus anthracis* spore challenge in guinea-pigs" by Bruce E. Ivins, et al in Vaccine, vol. 12, no. 10. pp 872-874, 1994.
Additionally, MDPH did not seek to amend their Product License Amendment (PLA) for any of these changes.

[14] Mr. A. Luttrell (BioPort Vice President for Quality Assurance/Quality Control) wrote Mr. J. Eltermann from the Center for Biologics Evaluation and Research on 14 January 1999 following up on a conference call between Ms. F. Kaltovich, Mr. Eltermann and himself. This letter confirms that FDA had not approved the two fermentation trains installed in 1993. [Exhibit 5]

b) The manufacturer of AVA has been found to be in violation of current Good Manufacturing Practice during every FDA inspection since 1988.

The Drug Industry Act of 1962 refined the concept of adulteration by amending section 501(a)(2) of the Federal Food, Drug and Cosmetic Act (the Act). A drug would be deemed "adulterated" and therefore subject to multiple seizures if it was made, processed, packaged, or held under methods, facilities, or controls that did not conform to current good manufacturing practice (CGMP). The Secretary would be authorized to issue interpretative regulations as to what constitutes CGMP, and these regulations would be prima facie evidence in any proceeding under this section of the Act.

FDA has regularly inspected the vaccine production facility. These inspections document a pattern of non-compliance with CGMP. Every inspection resulted in discrepancies ranging from unsanitary conditions and unapproved procedures to contaminated products, and changing equipment and products without approval. The following observations relating to anthrax vaccine production were made during inspections conducted in the following years:

1988.

> *"There is no written procedure for assessing stability characteristics of final biological products."*
>
> *"No direct physical accountability for packaged undated anthrax vaccine which was stored alongside of packaged and dated vaccine with the same lot number. Nine hundred and six vials of unfinished vaccine were distributed freely in 3 cardboard boxes with unknown number of vials in each carton. Removal of vials as needed was not indicated."*

1990.

> *"Anthrax prod. fac. was observed to be in a state of general disrepair in that there was: (A)Paint peeling from the walls (B)Exposed light fixtures (C)Cracked ceiling (D)Exposed raceways (E)Dirt & filth & dust on overhead pipes (F)Cluttered work space."*
>
> *"Anthrax prod. records are inconsistent in that procedures used to formulate Lot #21 are different from those used to formulate Lots #25, 26 & 27 in that media is autoclaved for sterilization for Lot #21 and filtered for sterilization for Lots #25, 26 & 27."*

1992.

"Changes in the manufacturing methods for...were not submitted as amendments to the product license application prior to releasing the material for distribution..."

"No SOP [standard operating procedure] exists to describe procedures for handling potentially infectious material..."

1993.

"There are insufficient personnel to assure compliance with current GMP regulations, e.g., failure to report changes in manufacturing, failure to maintain calibration records adequately, failure to adequately validate equipment used in the formulation or testing of product."

1994.

"There are insufficient personnel to assure compliance with current GMP regulations, e.g., failure to maintain calibration records adequately, failure to maintain environmental controls adequately in that production area temperatures were above 80°F, and failure to submit changes to CBER."

"There is no annual review of production batch records [anthrax]."

"Raw material [anthrax vaccine materials] stored in an unapproved warehouse, building (redacted) i.e., no ELA [establishment license application] supplement has been submitted for this area."

1995.[15]

"the company did not inform FDA of the procedural and equipment change during the production of..."

"facilities and equipment were not adequate."

"SOP's did not exist for many procedures."

---

[15] These observations were made on other portions of the MDPH facility. They are illustrative of the overall inability of MDPH to manufacture regulated biologic products in compliance with CGMP. The FDA did not inspect the anthrax production facility in 1995 or 1996 because it "came under military inspection." [Exhibit 6]

"SOP's were incomplete or incorrect."

"SOP's were not adhered to."

"Frequent contamination during vaccine manufacturing was documented but not investigated."

1996.[16]

"The firm had not completed cleaning validation studies for routine cleaning procedures on multi-use equipment."

"Validation studies to demonstrate microbial retention and compatibility have not been conducted for sterilizing filters..."

"There was condensate dripping onto open (redacted) tanks..."

"There was no procedure for clean-up of live rabies virus spills..."

1997.

CBER issues a "Notice of Intent to Revoke" citation to Michigan Biologic Products Institute on 11 March 1997. The Army responds by sending in a team to assist the manufacturer develop a "strategic compliance plan."

1998.

"The manufacturing process for Anthrax Vaccine is not validated."

"There are no written procedures , including specifications, for the examination, rejection, and disposition of Anthrax and Rabies."

"Prior to August 1997, the (redacted) filters used for harvest of Anthrax vaccine were neither validated nor integrity tested. This filter is the only sterile filtration step in the Anthrax manufacturing process."

"There is no written justification for redating lots of Anthrax vaccine that have expired."

"The firm does not trend multiple contaminations with microorganisms in sublots."

---

[16] Ibid.

In addition to these observations, FDA issued a Warning Letter to MDPH on 31 August 1995. A compliance follow-up inspection was conducted in 1996. This inspection resulted in a letter to MDPH of Notice of Intent to Revoke their license (11 March 1997). The 1998 inspection was also a compliance follow-up inspection as a result of the violative 1996 inspection. As a result of the 1998 inspection, MBPI "voluntarily" quarantined 11 lots of AVA. The failure of FDA to recall the quarantined vaccine resulted in some of it being shipped to the Canadian military and being used on their Servicemembers.[17] The conditions under which AVA has been manufactured as evidenced by continued violative inspections render that AVA adulterated and therefore a prohibited act.[18]

---

[17] Ann Rees, "Their Dangerous Dose", The Province [Vancouver, Canada], 25 Jun 2000

[18] As stated previously, failure to comply with CGMP renders the drug product adulterated. 21 U.S.C. § 331 states: *"The following acts and the causing thereof are prohibited: (b) The adulteration or misbranding of any food, drug, device or cosmetic in interstate commerce."*

c) AVA has been redated without an FDA approved procedure and has been labeled improperly.

The large quantities generated by the DOD contracts required stockpiling of vaccine. The manufacturer developed a program to extend the shelf life of AVA through redating.[19] Numerous Lots were redated without FDA approval.[20] Some of this AVA was labeled with the original Lot number. The Lot extension approval letters from FDA to the manufacturer indicated the new Lot number to be used with the particular Lots. The manufacturer failed to correctly indicate the approved Lot number on the final product containers (vials) or the package.[21] The AVA labeled under these conditions is considered misbranded, and therefore adulterated.

---

[19] Drug products that have an expiration date are required to have an approved stability testing program (21 C.F.R. § 211.137 and 211.166). This requirement was introduced in revisions to the Current Good Manufacturing Practices for Finished Pharmaceuticals in 1979. According to the compliance follow-up inspection conducted in 1998, MDPH did not have stability program until 1997. This program received several observations. (see observation #5, page 4 of Form FDA 483 dated 4-20 1998).

[20] MDPH did one of two things. For Lots FAV 008 through FAV016 MPDH removed the labels from the final containers by soaking the vials in alcohol and scrapping the labels off with razors. There was little to no attempt to reconcile the vials with the original Lot. This procedure was unapproved. Other Lots were redated by extending the shelf life without justification and in the absence of an approved procedure. Some of these Lots had exceeded their shelf life prior to being redated. (See observation 4. on page 4 of Form FDA 483 dated 4-20 February 1998.) This redated vaccine was subsequently distributed to MDPH customers.

[21] CGMP defines "Lot number" as "*any distinctive combination of letter, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.*" (21 C.F.R. § 210.3 (11)). 21 C.F.R. § 201.18 requires that the lot number on the label must be capable of yielding the complete manufacturing history of the package. An incorrect lot number may be regarded as causing the article to be misbranded. The Federal Food, Drug and Cosmetic Act (the Act) provides a definition of a misbranded drug: "*A drug or device shall be deemed to be misbranded – (a) False or misleading label. If its labeling is false or misleading in any particular.*" The Act further states: "*The following acts and the causing thereof are prohibited: (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.*"
Additionally, 21 C.F.R. § 601.12 states in part that: "*an applicant shall inform Food and Drug Administration (FDA) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling, established in the approved license.*"
Interestingly, after this mislabeling was brought to the attention of DOD and FDA officials in 1999, subsequent Lots have been correctly labeled.

d) The equipment used to manufacture AVA has not been used exclusively for the production of AVA.

21 C.F.R. § 600.11(3) *Work with spore-forming organisms* spells out one requirement to the manufacturer for assuring the safety and purity of biologic products. This section states in part:

> *"All vessels, apparatus and equipment used for spore-bearing microorganisms shall be permanently identified and reserved exclusively for use with those organisms.*

The manufacturer has at times used the equipment approved by the FDA for the manufacture of AVA to manufacture other biologic products.[22] When other quality assurance provisions in vaccine production are lacking, as has been repeatedly documented with AVA, a true safety hazard exists. The CGMP provisions of 21 C.F.R. apply equally to section 600. As it may be impossible to determine when and to what extent this permanently identified and reserved equipment was used in the production of other biologic products, all AVA must be considered adulterated.

It is clear that the AVA produced since the 1990 time frame is adulterated within the statutory provisions of the Federal Food, Drug and Cosmetic Act. The Agency has promulgated substantive rules based on the Act, with which to enforce the spirit and the intent of the Act. The many reasons rendering AVA adulterated likewise meet the regulatory threshold of adulteration. Enforcement of the current good manufacturing practices is the Food and Drug Administrations most important regulatory program for marketed products. 21 C.F.R. § 210.1(b) states:

> *"The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of*

---

[22] A Trip Report to the commander of USAMRIID (U.S. Army Research Institute for Infectious Disease) indicates that the "dedicated" anthrax fermentor has been used for botulinum toxoid for animal use between anthrax runs. This report further indicates that the new equipment (see footnote 13) will alternately produce botulinum toxoid and tetanus toxoid. The second indication that the dedicated anthrax equipment was being used for other products is found in correspondence between MDPH and the U.S. Army Contracting Officer (and others) regarding the unapproved use of government equipment (fermentation trains) for products not under contract. In this instance the equipment was being used to produce botulinum toxoid for animal use. Included in this second set of correspondence is a request by the manufacturer to be allowed to continue to use this equipment for alternative purposes in the future. [Exhibit 7, 8]

a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action."

We therefore respectfully request you declare all stockpiles of anthrax vaccine adsorbed in the possession of BioPort Corporation, and all doses in private, public, U.S. or foreign government possession, "adulterated" in accordance with the above C.F.R. and 21 U.S.C. 501(a)(2)(B).

INFORMATION KNOWN WHICH IS UNFAVORABLE TO THE PETITION:

We are unaware of any provisions in the Federal Food, Drug and Cosmetic Act that allow such a product to continue in interstate commerce or be placed in interstate commerce, nor of any acts of discretion taken that waive the provisions of the Act regarding adulterated products.

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

Compliance Policy Guides explain the Food and Drug Administration (FDA) policy on regulatory issues related to FDA laws or regulations. They advise compliance staffs as to the Agency's standards and procedures to be applied when determining industry compliance. Recently, FDA has assumed the additional role of assuring drug quality involving good manufacturing practice (CGMP) for the Government-Wide Quality Assurance Programs for drug purchase contract by the Department of Defense. Decisions regarding compliance are based upon inspection of the facilities, and the compliance history of the firm. FDA Compliance Policy Guides Manual, Sec. 400.200 Consistent Application of CGMP Determinations (CPG 7132.12) states:

> *"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."*

The FDA issued a Warning Letter to the anthrax vaccine manufacturer on August 31, 1995 for an inspection conducted from 24 April to5 May 1995. Another violative inspection took place 18 through 27 November 1996 resulting in a Notice of Intent to Revoke letter issued on March 11, 1997.[23] An FDA follow-up inspection conducted between 4 through 20 February 1998 found the previous deficiencies had not been corrected. All three inspections document CGMP violations.

On September 3, 1998, the FDA informed the new owner of the anthrax vaccine manufacturing facility, BioPort Corporation, that *"the Notice of Intent to Revoke issued to MBPI on March 11, 1997 will effectively transfer with the issuance of the license to BioPort and will remain in effect until all compliance issues have been satisfactorily resolved."* These regulatory actions, until corrected, made the manufacturer subject to the Compliance Policy Guide restrictions found in CPG 7132.12.

---

23 http://www.fda.gov/cber/infosheets/mich-inf.htm

The deficiencies in the Warning Letter, inspections, and the Notice of Intent to Revoke have never been corrected, as evidenced by the failure of the manufacturer to pass FDA's repeated inspections after it ceased production in January 1998.[24] Therefore, FDA was required by this long-standing (1981) policy to:

1. Advise the Department of Defense, the Department of Health and Human Services, and any other appropriate government agency that all government contracts "must" be disapproved for the manufacture, storage, bottling, or shipment across State lines of the anthrax vaccine adsorbed until the manufacturing deficiencies are corrected.

2. Reject the investigational new drug (IND) application submitted by the anthrax vaccine manufacturer, and prepared by the U.S. Army, on September 20, 1996 (IND 6847).[25,26]

---

[24] Violative inspections occurred in October 1998, November 1999 and October 2000.

[25] FDA accepted an investigational new drug (IND) application to use the anthrax vaccine for the specific indication of "inhalation anthrax" (IND 6847) dated September 20th, 1996. Following the departure of FDA Commissioner David Kessler, the Assistant Secretary of Defense for Health Affairs, Dr. Stephen Joseph, wrote to Acting Lead Deputy Commissioner Dr. Michael Friedman. Dr. Joseph asserted that DOD had "long interpreted" that the vaccine was effective for inhalation anthrax. His assertion ignored the IND application prepared by the Army for the anthrax vaccine manufacturer just six months earlier. Lead Deputy Commissioner Dr. Friedman's response, on March 13, 1997, abandoned the FDA's mandate to enforce the Food, Drug, and Cosmetic Act's statutory requirements of proven safety and efficacy in humans for specific applied uses. On 13 Mar 1997 FDA Lead Commissioner Michael Friedman wrote to ASD/Health Affairs Stephen Joseph – the language specifically said the DOD's use for the vaccine, *"was not inconsistent"* with the product's license. As the GAO noted in House Congressional Hearing on 11 October 2000, this also did not maintain that the use was "consistent" with the AVA label or license. Dr. Friedman acknowledged the lack of legally required human efficacy data to support such a decision: *"...while there is a paucity of data regarding the effectiveness of Anthrax Vaccine for prevention of inhalation anthrax, the current package insert does not preclude this use."* No human efficacy data, required by law, has ever subsequently been submitted to support Dr. Friedman's decision. 21 C.F.R. § 10.85 (k) states: *"A statement made or advice provided by an FDA employee constitutes an advisory opinion only if it is issued in writing under this section. A statement or advice given by an FDA employee orally, or given in writing but not under this section or Sec. 10.90, is an informal communication that represents the best judgment of that employee at that time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed."*
Dr. Friedman's memo of 13 March 1997 does not comply with the requirements of 21 C.F.R. § 10.85, and therefore is an informal communication versus an advisory opinion by the FDA.

Anthrax vaccine adsorbed produced under deficient CGMP conditions is well documented.[27] We respectfully request that you order all current and/or pending government contracts and drug applications for anthrax vaccine adsorbed be disapproved and the appropriate government agencies informed in accordance with Sec. 400.200 Consistent Application of CGMP Determinations (CPG 7132.12).

INFORMATION KNOWN WHICH IS UNFAVORABLE TO THE PETITION:

There is no evidence through FDA Freedom of Information Act discovery that documents any regulatory waivers or acts of discretion concerning this government policy.

---

[26] IND 6847 should also be terminated in accordance with 21 C.F.R. § 312.44 *et seq* whereby an IND can be terminated if *"the methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of [CGMP] as needed for subject safety. (see Action Request #2)*

[27] Any assertion that previous inspections do not apply to the anthrax vaccine manufacturing facility is obviated by BioPort's Dr. Robert Myers acknowledgement that: *"the intent to revoke our license would have been our total establishment license. It's a single establishment for all products."* (U.S. Army transcript of meeting held at Ft. Detrick, MD, May 25, 1999)

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

The Congress, through the Secretary of Health and Human Services and the Federal Food, Drug and Cosmetic Act, has given the Commissioner of Food and Drugs broad regulatory authority to ensure that the drugs the public receives are safe, effective and not misbranded. It is incumbent upon the Commissioner to enforce the regulations such that the public health is the primary consideration in any action. The Federal Food, Drug and Cosmetic Act (the Act) addresses the need to suspend, withdraw and revoke the licenses of those drugs whose safety, efficacy or labeling is in doubt.

a) The anthrax vaccine license was improperly issued.

In 1906 Congress passed the Federal Food and Drugs Act to regulate drugs generally. In 1938, Congress enacted the Federal Food, Drug and Cosmetic Act (the Act) to require, inter alia, that all drugs marketed after 1938 be "safe". Any drug marketed after 1938 must have a license known as an approved New Drug Application or be generally recognized as safe.

The Drug Industry Act of 1962 (often referred to as the Harris-Kefauver Amendment to the Act) established a legal requirement for a demonstration of efficacy in licensed drugs. To support a finding of efficacy, the law required "investigations" that resulted in "substantial evidence" of efficacy obtained through "adequate and well controlled investigations." A claim of substantial evidence could be rejected if it were found that the investigations were not adequate, were not well controlled, or had not been conducted by experts qualified to evaluate the drug. The various holders of the AVA license have yet to conduct a single adequate and well-controlled investigation that demonstrates efficacy in humans. There is no substantial evidence of efficacy with this vaccine. The Act's requirement to demonstrate efficacy was never met.

In May 1965, the U.S. Army contracted with the Department of Health, Education, and Welfare's Public Health Service Communicable Disease Center for:

> *"Development of a contract to obtain a ready supply of anthrax vaccine for use in industries where immunization is important and to stimulate a pharmaceutical company to prepare a protocol and a batch of vaccine for licensing by the PHS Division of Biologic Standards."* [Exhibit 9]

A patent for a process to manufacture an anthrax vaccine was filed on May 19, 1965 and awarded on September 28, 1965. An Investigational New Drug (IND) application was approved in January 1966 (DBS IND-180). The Michigan Department of Public Health (MDPH) submitted a Product License application in July 1967 (Ref. # 67-70). The investigational study was conducted in goat hair processing mills in Talladega. Correspondence between the investigators conducting the study and the National Institutes of Health indicate problems with the study. As an example, in January 1968 the study's Acting Chief, Dr. Philip Coleman, wrote

> *"As to the efficacy of the vaccine, we have no real method of determining the protection afforded."* [Exhibit 10]

A Feb 6 February 1969 memorandum from the licensing oversight committee to Dr. Margaret Pittman, of Department of Health, Education, and Welfare, critiques the study efforts by stating:

> *"The lack of cases of anthrax in an uncontrolled population of approximately 600 persons in the Talladega mill can hardly be accepted as scientific evidence for efficacy of the vaccine."* [Exhibit 1]

On January 22, 1969 Dr. U. Pentti Kokko, Director, Laboratory Division, National Communicable Disease Center wrote Dr. Roderick Murray, Director, Division of Biologics Standards, National Institute of Health. Dr. Kokko stating:

> *"There have been no controlled evaluation studies with the Michigan anthrax product as was done by Dr. Phillip Brachman using the Merck, Sharp and Dohme product."* [Exhibit 11]

On February 10, 1969, ad hoc committee head Dr. Margaret Pittman confirmed the inadequacy of the Talladega efficacy study of the licensed vaccine in a memorandum to Dr. Sam Gibson, Director of Licenses and Inspections, concerning the anthrax license application:

> *"On June 21, 1968 the Ad Hoc Committee recommended that license be granted following publication of Additional Standards: Anthrax Vaccine. It was noted also that clinical data establishing efficacy of the product had not been submitted and that data be requested from NCDC ... it is recommended that license be granted and that NCDC (IND-180) be requested to obtain data with a view to determine human efficacy of the product."*

Regardless, Dr. Pittman recommended licensure of the vaccine but wrote:

"It was noted also that clinical data establishing efficacy of the product had not been submitted and that data be requested from NCDC [National Communicable Disease Center]."

Dr. Pittman supported licensure of the vaccine despite her acknowledgement that the legal requirement of a valid human efficacy study had not been met. Instead, she based her decision on guinea pig tests, which were, and still are, irrelevant to the standards required for product licensure. Dr. Pittman affirmed this in another memorandum to Dr. Gibson on September 30, 1969:

"The recent information submitted by NCDC and Ft. Detrick for DBS IND-180 was discussed. It was emphasized that the epidemiological study did not provide control data, whereby the effectiveness of the vaccine could be evaluated. The fact that the vaccine has been used in a number of textile mills and that there has been not cases of Anthrax was substantive but not conclusive evidence of efficacy."

At some point data from an earlier study was submitted and accepted. The study, conducted by Dr. Philip Brachman and others, was used a different vaccine. The "Brachman Study" was published in 1962.[28] On 2 November 1970 license approval was recommended by the Department of Health, Education, and Welfare without any efficacy data. The License was granted on 10 November 1970.

During Congressional hearings on the AVA in 1999 the General Accounting Office (GAO) noted:

"MDPH was granted a license for a similar vaccine that differed from the original vaccine in three ways. First, the manufacturing process changed when MDPH took over. Second, the strain of anthrax that Merck used to grow the original vaccine was changed, and another strain was used to grow the MDPH vaccine. Finally, to increase the yield of the protective antigen (which is believed to be an important part of the vaccine's protective effects), the ingredients used to make vaccine were changed from the original vaccine." [29]

---

[28] P.S. Brachman et al., Field evaluation of a human anthrax vaccine, American Journal of Public Health, vol. 52 (1962), pp. 632-645.

[29] Medical Readiness: Safety and Efficacy of the Anthrax Vaccine (04/29/1999), T-NSIAD-99-148, 29 Apr 1999.

AVA is a biologic product as defined in 42 U.S.C. § 262(i), and is subject to the provisions of the Food, Drug, and Cosmetics Act (21 U.S.C. § 301 et seq.), which applies to biological products. On August 18, 1972 nine days after assuming responsibility for the regulation of biologics, the Food and Drug Administration published a proposal in the Federal Register establishing procedures for review of safety, efficacy, and labeling of biological products. This notice reiterates that the applicability of the Act and the Harris-Kefauver amendment to the Act:

"Because all biological products are drugs...."

The record reflects, however, that the license was granted without the legal standard having ever been met. Despite requests to the manufacturer by the National Institute for Health and Public Health Service for evidence of efficacy, there is no record of any scientifically valid human efficacy data having ever been submitted in support of this specific anthrax vaccine.

b) Even with a newly renovated production facility, BioPort is incapable of complying with CGMP or of producing an AVA of consistent safety, purity, potency and quality.

BioPort Corporation is now solely focused on the production of anthrax vaccine adsorbed and the approval of its renovated facility. BioPort continues to be unable to meet current good manufacturing practice standards as illustrated by the following Form FDA 483 observations:

October 1998:

> *"Stability testing has not always been performed in accordance with stability protocols, for example..."*
>
> *"CBER has not been notified in accordance with Error and Accident reporting of the following..."*
>
> *"On 6/30/98, the firm installed a new reaction tank mixer on Tank (redacted). There is no data documenting that the new mixer is equivalent to the old mixer, including mixing profiles. In addition, CBER has not been notified of this change."*

November 1999:[30]

> *"The manufacturing process for Anthrax Vaccine Adsorbed is not validated."*

October 2000:

> *"The design and construction...do not assure sterility of products filled..."*
>
> *"The following product lots failed initial sterility testing for release or for stability testing...Investigations into these initial sterility failures are incomplete..."*

---

[30] Thirty observations were noted. The inspection report ends with this comment: "*The observations noted in this FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the GMP regulation.*"

"Investigations are incomplete, inaccurate, or not conducted."

"There is no assurance equipment is operating as designed."

Biologic products can be marketed only with a license issued under the Public Health Service Act. The Food and Drug Administration Modernization Act of 1997 amended the Public Health Service Act to state specifically that biological products are subject to the drug provisions of the Federal Food, Drug and Cosmetic Act. The Center for Biologics Evaluation and Research (CBER) licensing powers dominate its law enforcement approach toward these products.

CBER need not rely on postmarketing enforcement actions such as seizure and injunction because FDA regulations authorize immediate suspension of a biological product's license. The FDA may summarily suspend the AVA license if the Agency believes that grounds for license revocation exist that create a danger to health (21 C.F.R. § 601.6). FDA enforcement policies define two broad reasons for suspension and withdrawal of a license application: *"scientific (inadequate proof of safety, effectiveness or suitability for intended use) and regulatory (inadequate manufacturing controls, failure to report required information, or submission of false information)"* AVA has met the threshold for suspension for multiple reasons in both categories.

The scientific threshold is affirmed in *Weinberger v Hynson* 412 U.S. 609 622 (1973). Studies conducted, and data presented, for the licensure of AVA have not met the most cursory standards of scientific validity and the license must therefore be immediately suspended for the public health.

The regulatory threshold for immediate suspension has also been met. *John D. Copanos & Sons, Inc. v FDA* 854 F.2d 510 (D.C. Cir. 1988) and *American Public Health Association v Veneman* 394 F. Supp 1311 (1972) affirm the Agency's authority to immediately withdraw a license. In *Veneman* the court states:

> *"Thus it could not be clearer that the Secretary must begin the procedures to withdraw a drug when he concludes that there is no substantial evidence of efficacy."*

> *"It* [the FDA argued, unsuccessfully] *has discretion in the selection of cases to notice for hearing. This argument is unpersuasive in view of the clear language of the statute and regulations and the Congressional intent to rid the marketplace of ineffective drugs."*

The Agency may immediately suspend a product or establishment license for failing to: 1) report a change in manufacturing procedures and: 2) for changing manufacturing methods to the extent that the company needs to show its new methods meet applicable standards.

BioPort may argue that Notice is required prior to suspension of the license. FDA enforcement policies anticipate this contingency:

> *"Normally the FDA will not withdraw an approved product application without providing the opportunity for a hearing. However, in practice, the agency has granted few hearing requests. Most often, the agency concludes that ... no genuine issue of material fact warranting a hearing and, consequently, denies the request ..."*

In the case of BioPort though, prior notice has been given in the form of multiple Form FDA 483 List of Observations (discussions of objectionable conditions by FDA investigators), as well as Warnings and a Notice of Intent to Revoke (NOIR) their license. Regardless, the FDA has the authority to *"suspend biological product approvals without giving companies the opportunity to request a hearing"*.

If the FDA Commissioner believes the product is an *"imminent hazard"* the Secretary of the Department of Health and Human Services may also act (Tab 701). 21 C.F.R. § 2.5 defines the Commissioner's authority to exercise judgment in the event of an *"imminent hazard"* as well. The regulation refers to a *"chain of events"* and *"occurrences"* which may ultimately result in a *"harm to the public health."* Such a chain of events is extensively documented in this petition. The improper licensure and adulterated nature of anthrax vaccine adsorbed represents an *"imminent hazard"* and warrants an immediate license suspension.

The importance of expeditious enforcement once a problem has been identified was recently articulated by the FDA's top enforcement officer, Associate Commissioner for Regulatory Affairs Dennis Baker:

> *"I believe in a strong enforcement program that is tied to education and outreach [efforts]. I also believe in a strong enforcement program once a problem is identified. Certainly, I believe in notifying the firm of the problems and giving it time to correct them, but if the violations are not corrected, I believe in proceeding with enforcement straight away. Too often we tend to talk these things to death and we need to move things along."*

The problems have been identified. The manufacturer has had 30 years to gather valid efficacy data and it has not. The manufacturer has had ample opportunity to notify FDA of equipment and process changes and it has not. The manufacturer has endangered the public health by producing other biologic products in the equipment dedicated for the manufacture of AVA. The manufacturer has had at least 13 years to rectify current good manufacturing practice deficiencies and it has not. It is time to stop talking about these problems and *"move things along."*

We therefore respectfully request you immediately suspend the AVA license (License #1260), and move expeditiously to withdraw and revoke this license in accordance with the Federal Food, Drug and Cosmetic Act. The Commissioner's prompt action and prioritization of FDA resources on this Citizen's petition is in the best interest of the public health.

INFORMATION KNOWN WHICH IS UNFAVORABLE TO THE PETITION:

We are unaware of any provisions in the Federal Food, Drug and Cosmetic Act that allow such a product to continue in interstate commerce or be placed in interstate commerce.

Prepared by:

Russell E. Dingle
71 Shaughnessy Drive
East Hartford, CT 06118
860-568-8767

And

Thomas L. Rempfer
3811 Phelps Road
West Suffield, CT 06093
860-668-1513

Supported by:

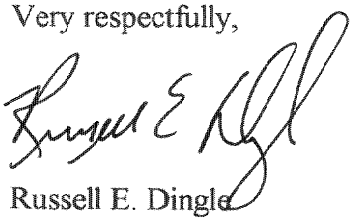
John Michels, Jr.
McLean, VA

John Richardson
Pittsboro, NC

James Turner
Washington, D.C.

Sammie Young
Silver Spring, MD

Very respectfully,



Russell E. Dingle

Thomas L. Rempfer

Note: Please use Russell E. Dingle for any and all contact regarding this Citizen Petition.

Exhibit 1

UNITED STATES GOVERNME.. DEPARTMENT OF HEA..H, EDUCATION, AND WELF
PUBLIC HEALTH SERVICE

Memorandum

To Filt

TO : Dr. Margaret Pittman, Chief, LBP M. P

DATE: February 6, 1969

Ref. No. 67-70

FROM : Ad Hoc Committee

SUBJECT: Michigan Department of Health Anthrax Vaccine, Evaluation of Clinical Data submitted under IND-180 on January 22, 1969

As requested, we have reviewed the clinical data contained in Dr. Kokko's letter of January 22, 1969 and its attached report. Our comments are as follows:

1. The lack of cases of anthrax in an uncontrolled population of approximately 600 persons in the Talladega mill can hardly be accepted as scientific evidence for efficacy of the vaccine. There is no indication of the frequency or the detail with which the bacteriological studies on goat hair were conducted during this period. We do not question that there might be up to 10 cases of expected anthrax per 600 workers, but without evidence of actual exposure in this mill during this time, and the apparently unpredictable incidence and distribution of anthrax in various mills (see Fig. 1, Brachman et al, Am. J. Pub. Hlth 52:632, 1962),

2. It was noted that site of inoculation reaction rates were higher, presumably due to closer follow-up. The nature and degree of reactions is not well defined.

3. The results from the ——————————— technique are not clear. We cannot evaluate the data without details for performing and interpreting the test.

4. It would be helpful if any stored human sera from the earlier study with the Merck Sharp & Dohme product could be compared by the —— echnique with sera from persons receiving the Michigan product. Since no simultaneous animal potency comparison of the MSD and Michigan products has been possible, this would provide at least some evidence of a comparable response in man.

John C. Feeley, Ph. D.

Charles R. Manclark, Ph. D.

Joseph P. O'Malley, M. D.

Robert W. Kolb

HELP ELIMINATE WASTE HEW COST REDUCTION PROGRAM

Exhibit 2

UNITED STATES GOVERNMENT

Memorandum

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

Concur KJG 2-10-69

TO : Dr. Sam T. Gibson, Assistant Director, L & I

DATE: February 10, 1969

Ref no 67-7

FROM : Chief, LBP and
Chairman, Ad Hoc Committee

SUBJECT: Michigan Department of Health: Application for license for Anthrax Vaccine

On June 21, 1968 the Ad Hoc Committee recommended that license be granted following publication of Additional Standards: Anthrax Vaccine. It was noted also that clinical data establishing efficacy of the product had not been submitted and that data be requested from NCDC.

No comments were received on the Proposed Notice of Rule Making published December 14, 1968, and it is understood that these standards have been forwarded with request for publication in the Federal Register.

C

ıned.

Safety data appear to be satisfactory.

Michigan has filed with the Division all required information and material for license except the results of an adequately controlled clinical investigation that establishes efficacy. No cases of anthrax have occurred among vaccinees. Laboratory data have been submitted that show that the product does have specific ability to protect guinea pigs. Therefore, it is recommended that license be granted and that NCDC (IND-180) be requested to obtain data with a view to determine human efficacy of the product.

Margaret Pittman

Margaret Pittman, Ph. D.

HELP ELIMINATE WASTE HEW COST REDUCTION PROGRAM

00000

Exhibit 3

UNITED STATES GOVERNM. T

DEPARTMENT OF HE TH, EDUCATION, AND WEL.
PUBLIC HEALTH SERVICE

Memorandum

10-1-69

TO : Dr. Sam T. Gibson, Assistant Director, L & I

DATE: September 30, 1969

Ref. No. 67-70

FROM : Margaret Pittman, Ph. D., Chief, LBP M.P.
Chairman, Ad Hoc Committee

SUBJECT: Michigan Department of Public Health, visit by Dr. George R. Anderson and Dr. J. R. Mitchell

Anthrax Vaccine
(DBS personnel: Drs. J. C. Feeley and M. Pittman)

The recent information submitted by NCDC and Ft. Detrick for DBS-IND-180 was discussed. It was emphasized that the epidemiological study did not provide control data, whereby the effectiveness of the vaccine could be evaluated. The fact that the vaccine has been used in a number of textile mills and that there has been no case of Anthrax was substantive but not conclusive evidence of efficacy.

It was also noted that Michigan Lot 3 was more reactive than one lot prepared by Ft. Detrick and one lot prepared by Merck, Sharp & Dohme. With gel diffusion tests it was demonstrated that the first two lots induced antibodies that were lower in titer and of shorter duration than did the MSD product. However, the first two lots were fractionated antigen and a true comparison could not be made.

Michigan Lot 2 now in current use was less reactive than Lot 3. Lot 7 will be put into use by the end of this year.

Dr. Anderson was informed that all requirements for filing the application for Anthrax Vaccine had been fulfilled but that license could not be issued until the Additional Standards: Anthrax Vaccine had been published. A nontechnical block was delaying their publication. Dr. Anderson was appreciative of the information.

Exhibit 4

CONVERSATION RECORD

DATE	TIME	CHECK ONE	CIRCULATION
7/9/90	3:15 AM (PM)	☒ INCOMING ☐ OUTGOING ☐ MEETING	Dr. Habig FYI Product Correspondace Anthrax Va

CENTER REPRESENTATIVE: Rebecca Devine

ORGANIZATION REPRESENTATIVE: Dr. Bob Meyers

TELEPHONE NO.:

ORGANIZATION: Mich. Dep. of Public Health

SUBJECT: June 14, 1990 letter regarding Anthrax Vaccine Fermentor.

TEXT	ACTION REQUIRED
I told Dr. Meyers that we had received a June 14, 1990 letter informing us of a new fermentor in the Anthrax Vaccine Production area plus the addition of a [illegible] seed fermentor. I informed him that this is considered a major change and should be submitted in the form of an Establishment Licens Amendments which should include validation data.	none until receipt of amendment

FORM FDA 2574 (6/88) OVERPRINT NO. 1

BioPort

3500 North Martin Luther King Jr. Blvd., Building One, 3rd Floor, Lansing, Michigan 48906
Tel: (517) 335-9934 Fax: (517) 335-9118

January 14, 1999

Mr. Jay Eltermann
Division Director
Division of Manufacturing and Product Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, HFM-99
Rockville, MD 20852

Attn: HFM-205

Dear Mr. Eltermann:

In our recent telephone conversation on January 14, 1999, Ms. Florence Kaltovich, SAIC, and I informed you that Fermentation Trains 3 and 4 for the manufacture of Anthrax Vaccine Adsorbed (AVA) were never submitted for approval to FDA/CBER. The trains were installed in 1993 in the AVA facility on the second floor of Building 12. As we discussed, we have written an Information Paper that briefly discusses what issues we have reviewed to ascertain the safety of the affected AVA lots including lot numbers FAV023 and higher. As you requested, we will prepare a "Category II" supplement that describes Fermentation Trains 3 and 4 including retrospective validation information and data.

If you have any questions, or require more information, please do not hesitate to contact me at 517-335-8096.

Sincerely,

Anthony M. Luttrell
Vice President, Quality Assurance/Quality Control

Exhibit 6

3

Memorandum

To: Telecon File

From: Florence Kaltovich

Date: 01/30/98 10:33 AM

Dr. Jackie Little from FDA/CBER/OC called me on January 29, 1998. We finally spoke on January 30, 1998. She questioned me about the inspection I had conducted In November 1996 at Michigan Biologic Products Institute. The specific question she asked concerned the lack of an inspection of the Anthrax vaccine manufacturing facility. I responded by telling her that indeed there was a plan to inspect the facility, but the person with product expertise could not join the inspection team for the dates identified. Therefore, I was told by the Office of Compliance not to inspect the anthrax vaccine facility nor any of the product related records.

Approximately 10 minutes later, Mr. James Simmons, Director, Office of Compliance, FDA/CBER, and Dr. Little called back. Mr. Simmons asked me about the two inspections I had conducted at MBPI in May/April 1995 and November 1996. The specific question concerned two sentences in the Establishment Inspection Reports about why the Anthrax vaccine manufacturing facility was not inspected. The sentences were: "Anthrax vaccine was not covered due to military inspection." I explained that in 1995, it was not my position to lead the inspection and therefore that sentence was written by Dr. Lyn Olson. In 1996, I reiterated the same information that I had told Dr. Little in the previous conversation. Mr. Simmons asked me who specifically in the Office of Compliance told me not to inspect the facility. I told him I believed it was Dr. Little. Dr. Little did not recall making this statement. Mr. Simmons asked me what I knew about the DoD audits of the MBPI facility. I responded that I knew a lot more now than I had at the time. I explained that my client was DoD and that I was not at liberty to discuss the specific issues without their permission. He asked me if I was performing inspections of manufacturing facilities for DoD and I responded, "yes". Mr. Simmons thanked me and the conversation ended.

I called Mike Gilbreath and Bob Myers to request that we discuss the audits conducted by DoD with Mr. Simmons. Dr. Myers agreed to the telecon. I called Mr. Simmons and discussed the audit issue. Mr. Simmons asked me if I had ever

audited the Anthrax vaccine facility. I told him that I had been in the facility two times. He asked me if the inspections had been conducted as per cGMP requirements. I answered "yes". He took my name and number and said if he needed to have this conversation, he would call me.

DEPARTMENT OF HEALTH & HUMAN SERVICES

ATTACHMENT V
Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Date: May 19, 1995

From: Lyn D. Olson, Ph.D., DEL, HFM-208
Florence A. Kaltovich, MS, MHS, DEL, HFM-207
Kelley L. Clark, Investigator, Grand Rapids RP, DetDO
Scott D. Barlow, Investigator, Grand Rapids RP, DetDO

Subject: Annual Biologics Inspection of Michigan Department of Public Health, License #099
April 24 - May 5, 1995

To: Inspection Task Force, Office of Compliance, HFM-605

THROUGH: Margaret A. Tart, Acting Director, DEL, HFM-205
Bascom Anthony, M.D., Director, DBP, HFM-425
Dennis Trent, Ph.D., Director, DV, HFM-460
Joseph Fratantoni, M.D., Director, DH, HFM-330

I. SUMMARY OF FINDINGS

The annual, unannounced biologics inspection of Michigan Department of Public Health (MDPH) was performed April 24-May 5, 1995. The inspection included all licensed biologic products, although was not reviewed during the course of the inspection

The last inspection was conducted in 1994 for bacterial vaccines, at which time 15 observations were noted.

During the inspectional period (April 24-May 5, 1995), we observed the following activities: checking in of plasma; rabies production (virus inoculation; change of media; BPL inactivation; alum absorption; collection of precipitate); charging of the diphtheria fermenter with media; pertussis harvest; labeling. Facilities were inspected. We reviewed the following documents: human albumin production records; immunoglobulin production records; rabies sublots and final lot batch records; diphtheria batch records; tetanus batch records; pertussis batch records; DTP production records; media fills; SOPs; stability protocols; investigational reports; complaint files; adverse event records; training program and records; WFI P&IDs; WFI test data; calibration and validation programs and records; maintenance logs.

Fifty observations were made during the 1995 inspection. The observations included failure to notify FDA of procedural and equipment changes as well as new master cell banks for rabies production (#1,2,); lack of control over all divisions involved in manufacturing (#3); lack of experience and authority on the part of the QA group (#4,5); no environmental monitoring during

JAN 14 1997

Michigan Biologic Products Institute
3500 N. Martin Luther King Jr. Blvd.
Lansing, MI 48909

11/18-27/96/FAK/LPN/PR/WDT
FOI/MI/73886Y96.N27

SUMMARY OF FINDINGS

This was a compliance followup inspection of a biologics manufacturer, according to a 10/31/96 CBER Office of Compliance memo and DET-DO workplans (WATS #103826). The firm is licensed by CBER to manufacture blood derivative products, including albumin and immune globulin, as well as toxoids and vaccines.

The previous inspection, in April and May 1995 was classified OAI due to GMP and other deficiencies. At that time Michigan Biologic Products Institute (MBPI) was the Michigan Department of Public Health, Biologic Products Division, license #0099. The firm submitted a 6/9/95 written response to the FDA 483. They also held a meeting with CBER on 6/15/95 to discuss planned renovations to the vaccine production building 16.

CBER issued an 8/31/95 Warning Letter to the firm, who in turn submitted a 9/30/95 response (with a copy dated 12/16/95 sent to DET-DO). Subsequent correspondence occurred between CBER and the firm, to clarify specific issues. The latest was a 5/2/96 CBER response to a 3/22/96 MBPI letter.

Currently we covered the manufacture of blood derivatives and rabies vaccine, and corrections to previous deficiencies. The firm is renovating facilities for manufacture and testing of diphtheria, tetanus and pertussis vaccines. In addition, anthrax vaccine was not covered, since it comes under military inspection.

The firm has corrected many of their previous deficiencies, and has an active validation program in place. However, they lack an adequate quality assurance program for oversight of activities, and there are still significant GMP deficiencies.

An FDA 483 was issued for deficiencies in validation, environmental monitoring, preventive maintenance, water systems, cleaning, product protection, record review, employee practices, stability, facilities, equipment, and other areas. In addition, some of the 1995 FDA 483 items remain uncorrected or corrections have not been completed. The management promised corrections and a written response to DET-DO and CBER.

Complaint CIN-6881, for rabies vaccine was also covered. The firm did not have any significant complaints for blood derivatives or other products, which would indicate a sterility or container/closure integrity problem.

3/19/96

Exhibit 7

DISPOSITION FORM

For use of this form, see AR 340-15; the proponent agency is TAGO.

REFERENCE OR OFFICE SYMBOL	SUBJECT
SGRD-UIZ-S(70-1z)	Trip Report

TO: THRU: Dep Cdr for Admin
Dep Cdr for Development
Dep Cdr for Research

FROM Safety Officer, USAMRIID

DATE 26 September 1988

CMT 1 Mr. Kuehne/bjm/733

TO: Commander, USAMRIID

1. Activity visited: Michigan State Department of Public Health, Lansing, MI. Date of visit: 22 Sept 1988. Travel order #MRI 9-27.

2. Purpose of trip: To visit and inspect the anthrax vaccine production and animal testing facilities of the Michigan Department of Public Health to assess adequacy to fulfil requirements of MRDC contract as specified in the CDC/NIH Biosafety Guidelines.

3. Persons contacted: Dr. John Mitchell, Chief, Division of Biological Products, Dr. Harvey Burgoyne, Chief, Vaccine Production, Ms. Judy Boice, and Mr. Richard Hoort, all from Michigan State Department of Public Health.

4. Findings:

a. Background

This facility has been making anthrax vaccine for the US Army since 1970. The vaccine has been used, in addition, by various textile manufactures for employee immunizations, but demand has been low. Production runs have been made every 3-4 years and the largest run has been 7,500 doses. The vaccine is licensed by the FDA for human use. The vaccine is produced in a 100 liter batch fermentor in a very small area consisting of a small room housing the fermentor and holding tank, and an average sized adjoining laboratory in part of the second floor of a building which is used for other purposes (Bldg 12). The building was constructed in 1939. The fermentor is used between anthrax runs to produce botulinum toxoid which is licensed by the USDA for animal use only. For anthrax vaccine production, the V-770-NPI-R non-encapsulated strain of Bacillus anthracis is used which was originally supplied by Dr. George Wright of Fort Detrick. This strain produces an extracellular soluble protective antigen. During the fermentation, exhaust effluent gas passes through a heater-incinerator, then through a filter and then ducted to the outside. At the end of the run, the liquid passes through sequential filters to remove the cells and enters a holding tank. The fermentor is then self-steam-sterilized. Filters in stainless steel housings are autoclaved in toto. All filling and packaging operations are done in an adjacent building.

The proposed contract with the US Army is for 300,000 doses of anthrax vaccine to be produced in approximately 2-3/4 years. A new fermentor has been ordered but will not be operational until six months from now, by which time about 10,000 or more doses will have been produced with the current fermentor. (A new production facility is planned, but groundbreaking will not occur until perhaps 1991, so is not apropos to this initial contract. The new facility will sequentially produce anthrax vaccine, botulinum toxoid, and tetanus toxoid).

Exhibit 8

DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY
FORT DETRICK, FREDERICK, MD 21702-5014

REPLY TO
ATTENTION OF

19 October 1995

Special Projects Branch

Michigan Department of Public Health
ATTN: Dr. Robert C. Myers
3500 North Martin Luther King Blvd.
Lansing, Michigan 48909

SUBJECT: Facilities Contract No. DAMD17-92-E-2001

Dear Dr. Myers:

It has come to my attention that the facilities for the above subject contract were used for purposes not authorized in accordance with Section C.1 of the contract.

Please provide me the details of the use of the unauthorized use of the facilities (what was produced, period of usage, disposition of product, etc.). After I review this information, I will make a determination as to what needs to be done to compensate the Government for the use of the facilities and what actions should be taken, so that this will not happen in the future.

If you have any questions, please feel free to contact Mr. B.C. Baker III at (301) 619-2035.

Sincerely,

Michael A. Younkins
Contracting Officer

cc: Dr. Anna Johnson-Winegar
COR

8 Feb 96

Anna,
I got this from B.C. today. He said he thought you had a copy. I hadn't seen this response, so I put it on the list of pending actions I gave B.C. last month.
Any further action required?
Marie

I think we need a decision. Either we tell them it was o/c (no charge) — or we get tough and charge them plus slap their wrists for mw. I guess the first option will go with the first option. Do you have a recommendation?

FAX TRAN

MICHIGAN DEPARTMENT
3500 NORTH MARTIN L
LANSING, MICHIG
517-335-
FAX: 517-33

To: B.C. Baker III **Da**

Fax #: 301 619 2505 **Pa**

From: Robert C. Myers

Subject: Your 10-19-95 letter

COMMENTS:

This transmittal responds to Mr. Younkins letter of
located on the second floor of Building 12 at the Mi
other than those specified to be in accordance with

The facility is not only used for defense vaccines pu
manufacture of the USDA licensed product Clostrid
efforts of the MDPH with respect to these facilities
for defense vaccines since the Persian Gulf conflict began. Because of this focus, inventories of the veterinary product were exhausted. Since it was time to requalify the facilities in any event, the opportunity that this production break afforded was directed toward the establishment of new inventories of the veterinary product.

The specific usage of these facilities over the period of time in question is summarized in the table on the following page.

During and immediately after the conflict, MDPH was informed that the Army would assist MDPH in meeting other commitments not met during that time period because of the almost complete diversion of resources to the defense vaccine support effort. We would have asked the Army to purchase this vaccine from someone else to maintain a supply for use in horses in the United States, but there is no other manufacturer of the vaccine. We did enter into discussions in this regard for the use of Type B toxoid generated by the Salk Institute. In the end, such use was not feasible for the veterinary product. We are at this time requesting that you approve our use of these facilities for the stated purpose without charge as such use was the direct result of our efforts to serve your needs over the last five years.

If further information is needed please let me know.

Use of Building 12 Facilities for Manufacture of Type B Toxoid for Veterinary Use

Type of Use	Time Period
Decontamination and minor repair	July 1995
Manufacture veterinary Bot	August and September 1995
Decontaminate and requalify facility	October, November and December 1995
Resume manufacture of Anthrax vaccine	January 1996

FAX TRANSMISSION

MICHIGAN DEPARTMENT OF PUBLIC HEALTH
3500 NORTH MARTIN LUTHER KING BLVD
LANSING, MICHIGAN 48909
517-335-8120
FAX: 517-335-9486

To: 7 Mar BC will talk to Mike Y. about this and let me know.

Fax #:

From:

Subject:

Date: December 14, 1995

Pages: 1, including this cover sheet.

COMMENTS:

This transmittal responds to Mr. Younkins letter of October 19,1995 on the use of the facilities located on the second floor of Building 12 at the Michigan Department of Public Health for uses other than those specified to be in accordance with Section C.1 of contract DAMD17-92-E-2001.

The facility is not only used for defense vaccines purposes, but also is utilized for the manufacture of the USDA licensed product Clostridium Botulinum Type B Toxoid. The entire efforts of the MDPH with respect to these facilities has been to serve the needs of the U.S. Army for defense vaccines since the Persian Gulf conflict began. Because of this focus, inventories of the veterinary product were exhausted. Since it was time to requalify the facilities in any event, the opportunity that this production break afforded was directed toward the establishment of new inventories of the veterinary product.

The specific usage of these facilities over the period of time in question is summarized in the table on the following page.

During and immediately after the conflict, MDPH was informed that the Army would assist MDPH in meeting other commitments not met during that time period because of the almost complete diversion of resources to the defense vaccine support effort. We would have asked the Army to purchase this vaccine from someone else to maintain a supply for use in horses in the United States, but there is no other manufacturer of the vaccine. We did enter into discussions in this regard for the use of Type B toxoid generated by the Salk Institute. In the end, such use was not feasible for the veterinary product. We are at this time requesting that you approve our use of these facilities for the stated purpose without charge as such use was the direct result of our efforts to serve your needs over the last five years.

If further information is needed please let me know.

MCMR-PLD (70) 2 April 1996

MEMORANDUM FOR Commander, U.S. Army Medical Research Acquisition Activity,
ATTN: Mr. B.C. Baker, Fort Detrick, MD 21702-5014

SUBJECT: Contract DAMD17-92-E-2001

1. This is in reference to the enclosed contractor's letter dated 14 December 1995 regarding unauthorized use of the facilities.

2. It is my understanding that no costs have been charged by the contractor to this contract. Some, or all, of the equipment listed in the contract would require normal maintenance since it is being used to produce the anthrax vaccine required under Contract DAMD17-91-C-1139.

3. It is also my understanding that administration of this contract was assigned to DCMAO. Please contact the DCMAO property administrator and explain the situation regarding the unauthorized use of equipment and find out if it is within their authority to evaluate the situation and recommend appropriate action. Also ask them if they can find out if the contractor has incurred any costs for maintenance, etc., for this equipment and whether the costs have been charged to C-1139 or to any other Government contract.

4. Please call me on extension 7439 if there are any questions.

/s/

Encl

ANNA JOHNSON-WINEGAR, Ph.D.
Contract Officer Representative

SGRD-PLD 15 December 1993

MEMORANDUM FOR Commander, U.S. Army Medical Materiel Development Activity, ATTN: SGRD-UMB (LTC Balady), Fort Detrick, Frederick, MD 21702-5009

SUBJECT: Contract DAMD17-92-E-2001

1. Enclosed is my technical contract file for the subject contract. The equipment identified under Section B was purchased under contract DAMD17-88-C-8242 and is currently being used for production of anthrax vaccine. No costs for maintenance have yet been submitted by the contractor, nor has a formal maintenance plan been prepared since the equipment remains in use on Government contracts.

2. I would be happy to arrange an inventory inspection should you deem it necessary. I would suggest a meeting at the Michigan Department of Public Health sometime in the near future to discuss current status of this and related contracts for anthrax vaccine production and efforts related to botulinum toxoid.

3. If you have any further questions regarding this contract, please do not hesitate to call me.

ANNA JOHNSON-WINEGAR, Ph.D.
DIRECTOR, MEDICAL BIOLOGICAL
DEFENSE RESEARCH PROGRAM
ANNA JOHNSON-WINEGAR, Ph.D.
Contracting Officer's
Representative

CF:
SGRD-RMA-RD (Ms. Shirley Wade)
SGRD-UMS (Mr. Ferguson)

MCMR-PLD 19 September 1995

MEMORANDUM FOR Director, U.S. Army Medical Research Acquisition Activity, ATTN: MCMR-AAA-V (Mr. B.C. Baker), Fort Detrick, Frederick, MD 21702-5014

SUBJECT: Facilities Contract No. DAMD17-92-E-2001 with the Michigan Department of Public Health

1. It has come to my attention that the contractor has used facilities covered by this contract for purposes not authorized and in violation of Section C.1 of the contract which states:

> "Use of Government property for other than U.S. Army Medical Research and Development Command (USAMRDC) contracts requires the written authorization of the Contracting Officer."

2. It is requested that you write to the contractor as soon as possible stating that we are aware of this violation and ask for details of the use of the facilities (what was produced, period of usage, disposition of the product, etc.). It is recommended that you inform the contractor that the Government will consider charging the Michigan Department of Public Health for the use of the facilities, restoration of the property to the condition before unauthorized use, and any other actions appropriate in the circumstances, after we have reviewed their response.

3. The point of contact on this action is Ms. Maxine Losee, extension 7066.

/S/

ANNA JOHNSON-WINEGAR, Ph.D.
Contracting Officer's
Representative

Exhibit 9

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service
Communicable Disease Center
Atlanta, Georgia 30333

THIS MEMORANDUM SETS FORTH THE TERMS OF AGREEMENT FOR SERVICES, SUPPLIES, MATERIALS, OR EQUIPMENT TO BE FURNISHED TO THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, COMMUNICABLE DISEASE CENTER BY:

U.S. ARMY, BIOLOGICAL LABORATORIES, FORT DETRICK, MARYLAND

I. DESCRIPTION OF SERVICES: Development of a contract to obtain a ready supply of cholera vaccine for use in industries where immunization is important and to stimulate a pharmaceutical company to prepare a protocol and a batch of vaccine for licensing by the PHS Division of Biologics Standards.

II. DURATION OF AGREEMENT:

Remainder of Fiscal Year 1965

III. ESTIMATED TOTAL COST:

$35,000

IV: PAYMENT TO BE MADE TO/BIOLOGICAL LABORATORIES/BY:

U. S. ARMY FORT DETRICK, MARYLAND

REIMBURSEMENT BY STANDARD FORM 1081. CREDIT BILLING TO:

Communicable Disease Center
Atlanta, Georgia 30333

Appropriation to be charged: 7550343

This agreement is made under the authority of the Economy Act, approved June 30, 1932, as amended, (31USC 686).

U.S. Army

By: _____

Date: 30 April 1965 Title: Chief, Current Year Section, Prod. Div.
Technical Service Division, OTLG

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
COMMUNICABLE DISEASE CENTER

By: _____

Title: Chief, Communicable Disease Center Date: MAY 10 1965

Exhibit 10

#40

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NATIONAL
COMMUNICABLE DISEASE CENTER
ATLANTA, GEORGIA 30333
TELEPHONE: (404) 633-3311

January 25, 1968

Ref. no. 67-70

Dr. Roderick Murray, Director
Division of Biologics Standards
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Murray:

Dr. B. H. Olson, Chief, Division of Antibiotics and Fermentation, Bureau of Laboratories, Michigan Department of Public Health, has requested that we submit information to you regarding the package insert and clinical data obtained with the use of Michigan produced Anthrax Vaccine, Adsorbed. It is my understanding that this information is to be used in connection with Michigan's license application for the vaccine.

Our information on these two points was included in Progress Report #1: DBS-IND 180 submitted October 20, 1967. A copy of the "package insert" ("Instructions for the Use of Anthrax Protective Antigen, Aluminum Hydroxid Adsorbed") that we provide with the vaccine is enclosed. I have also enclosed a copy of our clinical results following the use of the vaccine through June 1967. Since June, we have distributed an additional ——— of the vaccine and, although many of the clinical response forms have not been returned, we have not had any unexpected reactions reported.

As to the efficacy of the vaccine, we have no real method of determining the protection afforded. Perhaps some importance may be attached to the fact that in this country only two cases of anthrax were reported to the NCDC last year and both cases were in unvaccinated individuals. One case was in a goat hair processing plant in Massachusetts and the second case was a veterinarian in Mississippi.

We have not conducted any in vitro serological tests to determine the "antibody" levels obtained with the vaccine.

Sincerely yours,

Philip H Coleman

Philip H. Coleman, D.V.M., Ph.D.
Acting Chief
Investigational Vaccines Activity

Enclosures (2)

cc: Dr. B. H. Olson

0000

Exhibit 11

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NATIONAL
COMMUNICABLE DISEASE CENTER
ATLANTA, GEORGIA 30333
TELEPHONE: (404) 633-3311

January 22, 1969

Dr. Roderick Murray, Director
Division of Biologics Standards
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Murray:

Following your review of the 1968 progress report for Anthrax Protective Antigen, Aluminum Hydroxide Adsorbed (DBS-IND 180), you asked for clarification of several points in your letter dated January 14, 1969.

Only those clinical reactions from the use of Lot 3 were included in the Progress Report #2. Lot 2 was introduced in July 1968, and the next progress report will include the surveillance of both Lots 2 and 3.

The Lot 2 label does not include the manufacturer. To comply with your request, the following information will be placed on each bottle:

Prepared by Bureau of Laboratories
MICHIGAN DEPARTMENT OF PUBLIC HEALTH
Lansing, Michigan 48914
U. S. License No. 99

The antibody assays employing the agar-gel precipitin inhibition technique were forwarded to this office on October 24, 1968. The enclosed figures and descriptions of the agar-gel test results were removed from the appropriate sections of the Second Annual Report to the Army Investigational Drug Review Board (AIDRB) submitted by Paul J. Kadull, M.D., Chief, Medical Investigational Division, Fort Detrick, Maryland.

There have been no controlled evaluation studies with the Michigan anthrax product as was done by Dr. Philip Brachman using the Merck, Sharp and Dohme product. Indirect evidence of the protection afforded by the Michigan product can be inferred from our experience with immunized populations in several goat hair processing plants. The textile mill in Talladega, Alabama employs approximately 600 people, and the goat hair is known to be contaminated by laboratory examinations. From past experience, Dr. Brachman stated that in an unimmunized population of 600, up to 10 cases of anthrax a year could be expected. There have been no reported cases of anthrax from the Talladega processing plant during the period in which the Michigan Anthrax Protective Antigen has been used.

If additional information is needed, please let me know.

Sincerely yours,

U. Pentti Kokko, M.D.
Director, Laboratory Division

Enclosures