REDACTED

DEPARTMENT OF HEALTH & HUMAN SERVICES MF 6/5/97 Public Health Service

MAR 1 1 1997

Food and Drug Administration
Center for Biologics Evaluation and Resear
1401 Rockville Pike
Rockville MD 20852-1448

CERTIFIED - RETURN RECEIPT REQUESTED

Robert Myers, D.V.M.
Responsible Head
Michigan Biologic Products Institute
3500 North Martin Luther King, Jr., Blvd.
P.O. Box 30035
Lansing, Michigan 48909

Dear Dr. Myers:

The Food and Drug Administration (hereinafter "FDA" or "the agency") conducted an inspection of Michigan Biologic Products Institute, Lansing, Michigan, between November 18 and 27, 1996. During the inspection, FDA investigators documented numerous significant deviations from the applicable standards and requirements of Subchapter C, Parts 210 and 211, and Subchapter F, Parts 600-680, Title 21, Code of Federal Regulations, and the applicable standards in your license. The deviations noted on the Form FDA 483, Inspectional Observations, issued at the conclusion of the inspection include, but are not limited to the following:

1. Failure of the quality control unit to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products [21 CFR 211.22(a)] in that the filters and plastic bags used during production and storage of blood derivatives and the pre-sterilized foil/plastic bags used as buffer bags in production did not undergo release by the quality control unit.

2. Failure of the quality control unit to approve or reject all procedures or specifications impacting on the identity, strength, quality, and purity of drug products [21 CFR 211.22(c)]. For example:

   a. Validation of loading patterns for the performed in June 1995, was not reviewed/approved by Quality Assurance ("QA").
   b. Temperature mapping of the Incubator Room performed on April 19, 1996 was not reviewed by QA.
   c. Analytical method validation for vas not reviewed/approved by QA.
   d. Eight deviations of the air handling system in the aseptic fill area identified during the May 1, 1996, requalification of the building were not reviewed/approved by QA.

3. Failure to establish and/or follow written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess and to assure that such procedures, including any changes, are drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by quality control [21 CFR 211.100]. For example:

   a. The standard operating procedure ("SOP") entitled was not followed in that there was no qualification for operation of the dryer indicating it can operate as designed and intended.

   b. The SOP entitled was not followed in that investigations had not been initiated of continuously exceeded environmental action limits for nonviable particulates in the filling suite.

   c. SOP entitled was not followed in that temperature deviations noted on temperature recording charts for walk-in cold rooms and freezers in building had not been investigated and notification of departure was not issued. Additionally, there is no written procedure for the review of temperature recorder charts.

   d. SOP entitled does not specify the operating temperature ranges for each refrigerator and freezer in the Blood Derivatives section.

   e. SOP entitled does not describe the preparation of the sterile storage bottle.

   f. SOPs for operation of the autoclave, used for sterilization of for Albumin (Human), Immune Globulin (Human), and other equipment, do not include load pattern diagrams or descriptions.

   g. SOP entitled " did not have the correct load patterns for trays filled with . ials.

4. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization processes [21 CFR 211.113(b)] in that:

   a. Validation studies to demonstrate microbial retention and compatibility have not been conducted for sterilizing filters used for Albumin (Human) and Immune Globulin (Human).

   b. The Water For Injection ("WFI") tubing in building used for final rinse of ., contained pooled water after use. The tubing was not stored so that the WFI would drain.

c. There is no written procedure to prevent the flow of personnel between room (rabies viral lab) and the cell culture laboratory.

5. Failure to establish and follow control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [21 CFR 211.110(a)] in that:

a. There was no qualification for operation of the used to produce the Albumin and Immune Globulin powders as described in SOP
b. All load patterns have not been validated for the autoclave in room used for sterilization.

6. Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)] in that specifications have not been established for pressure differential readings taken from magnehelic gauges in the capper, filling, and gowning rooms.

7. Failure to establish and/or follow written testing programs designed to assess the stability characteristics of drug products [21 CFR 211.166(a)] in that there is no documentation available to support acceptable storage temperature excursion time frames for samples of Immune Globulin (Human) and Rabies Vaccine.

8. Failure to follow the stability program for the rabies vaccine [21 CFR 211.166(a)(2)] to assure valid estimate of stability in that there is limited control over storage conditions of samples prior to time zero which can be as long as three months.

9. Failure to establish separate or defined areas or other control systems for manufacturing and processing operations to prevent contamination or mixups [21 CFR 211.42(c) and 600.11(a)] in that:

a. The door to the powder harvest room which is a controlled Class area, was propped open to room which is an uncontrolled area, during powder harvest.
b. There is no separate airlock for degowning after working with live rabies virus.
c. There is no segregation of quality control raw material testing for and research activities in room
d. The gowning room was open to the and open to the simultaneously.

10. Failure to clean, maintain, and sanitize equipment and utensils at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a)] in that:

    a. Cleaning validation studies have not been completed for routine cleaning procedures on multi-use equipment.
    b. Rust was observed on the freezer used to store intermediate products.

11. Failure to maintain or follow written procedures for cleaning and maintenance of equipment including utensils, used in the manufacture, processing , packing, or holding of a drug product [21 CFR 211.67(b)] in that the SOP entitled ' does not list the parts to be washed and does not describe the procedure used to clean the parts.

12. Failure to routinely calibrate, inspect, or check automatic, mechanical, or electronic equipment used in the manufacture, processing, packaging, and holding of a drug product according to a written program designed to assure performance [21 CFR 211.68(a)] in that the temperature control system of the manifold loading area of the has not been calibrated. The is used to produce the Albumin and Immune Globulin powders.

13. Failure to store and handle components and drug product containers and closures in a manner to prevent contamination [21 CFR 211.80(b)] in that chemicals tested and released as in compliance with good manufacturing practices were not segregated from chemicals not tested and released.

14. Failure to identify and control rejected components, drug product containers, and closures under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable [21 CFR 211.89] in that materials rejected by quality control are not clearly labeled "rejected."

15. Failure to calibrate instruments, apparatus, gauges, and recording devices at suitable intervals [21 CFR 211.160(b)(4)] in accordance with an established written program, in that:

    a. The conductivity meter for distillate in the WFI system in building was past due for calibration and had not been calibrated.
    b. The chart recorder on the used to store at - or colder, was past due for calibration on November 14, 1996, and was reading Review of the chart recorder records indicated that the temperature of the freezer was out of specification ( since April 1996.
    c. All chart recorders and temperature probes which monitor the product temperature in the reaction tanks and the jacket temperatures were past due for calibration.

16. Failure to maintain buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition [21 CFR 211.56(a) and 600.11(a)] in that:

a. There is no spill clean-up or periodic floor cleaning when plasma spills onto the floor during the several hour plasma pool/thaw process.
b. Dead insects were present in room
c. A live insect was observed in capping room

17. Failure to establish written procedures describing the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities [21 CFR 211.56(b)] in that:

a. There is no SOP for the clean-up of live rabies virus spills in room
b. The floors, walls, and ceilings of the production area were not cleaned at the prescribed frequency as required by SOP entitled '

18. Failure to maintain buildings used in the manufacture, processing, packing, or holding of a drug product in a good state of repair [21 CFR 211.58] in that:

a. Condensate was observed dripping from tank piping onto open tanks filled with
b. Standing water was observed underneath the pasteurizer in room and underneath the
c. Rust and chipped paint were observed on the banister and around the centrifuges in room and on the transfer cage in the capping room.
d. Chipped paint was observed on the walls of room
e. A leak was observed in the ceiling of room
f. In cold room the lights were inoperable, stains and flaking paint were observed on the walls, and the thermostat was iced over.

19. Failure to provide adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination [21 CFR 211.42(b)] in that:

a. Plastic bags, used to cover the ; after product freezing, were stored without protection on top of the freezer in the wash room.
b. Boxes of packaged gowning supplies were on the floor in the hallway outside of the second floor gowning room for the post virus inactivation area.
c. A tipped box containing an opened plastic bag with pre-sterilized foil/plastic bags was on the floor in the hallway outside of
d. In Rooms and here was no segregation and labeling of clean and dirty glassware.

20. Failure to assure that the equipment used in the manufacture, processing, packing, or holding of a drug product is of appropriate design and of adequate size for its intended use and for its cleaning and maintenance [21 CFR 211.63] in that an indoor/outdoor thermometer, which can not be calibrated, monitors the temperature in freezer used to store retention samples of pastes and powders.

21. Failure to concurrently record the performance of each step in the manufacture and distribution of products [21 CFR 600.12(a)] in that the temperature recorder chart times did not agree with manually recorded log book times for sterilization.

22. Failure to assure that equipment with surfaces that contact components, in-process materials, or drug products is not reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of a drug product [21 CFR 211.65 and 600.11(b)] in that a cutting board constructed of plywood, which is not a sanitary or easily cleaned surface, is used in room for

23. Failure to properly identify storage containers and their contents as well as major equipment used during the production of a batch of a drug product [21 CFR 211.105(a)]. For example, the label on the cartridge filter housing stored inside indicating the status and contents was not readable.

While these deviations were documented in the most recent inspection, we note that significant deviations have been documented during previous FDA inspections of May 4 through May 7, 1993; May 31 through June 3, 1994; and April 24 through May 5, 1995. The seriousness of these deficiencies was emphasized to you in a letter dated December 22, 1993, and a Warning Letter dated August 31, 1995.

Based on the nature and number of the deficiencies identified during the recent inspection, it is the agency's judgment that management of the Michigan Biologic Products Institute has not fulfilled its responsibilities to exercise control in all matters relating to compliance with federal regulations and the applicable standards of your establishment and product licenses, or to assure that personnel are adequately trained and supervised and have a thorough understanding of the procedures that they perform, as required by 21 CFR 600.10(a) and (b), and 21 CFR 211.25(a) and (b).

The above identified deviations are not intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility as Responsible Head to assure compliance with all requirements of the federal regulations and the standards in your license.

We have reviewed your letter dated January 16, 1997, regarding the corrective actions which you proposed to the observations of the most recent inspection. We note that your firm has

repeatedly promised corrective actions in the past, but follow-up inspections continue to show that adequate, effective, and long term corrective action has not been taken. Accordingly, we have no assurance that the corrective actions will be properly implemented to correct the deficiencies noted during the most recent inspection.

Pursuant to 21 CFR 601.5(b), this letter is to provide you with notice that, unless you demonstrate or achieve compliance with the applicable standards and regulations, it is the intent of the FDA to institute proceedings to revoke U.S. license 0099-001, issued to Michigan Biologic Products Institute, 3500 North Martin Luther King, Jr., Blvd., Lansing, Michigan, for the manufacture of Diphtheria Toxoid Adsorbed, Tetanus Toxoid Adsorbed, Rabies Vaccine Adsorbed, Antihemophilic Factor (Human), Immune Globulin (Human), Albumin (Human), Anthrax Vaccine Adsorbed, Pertussis Vaccine Adsorbed, Diphtheria & Tetanus Toxoids Adsorbed, and Diphtheria & Tetanus Toxoids & Pertussis Vaccine Adsorbed, and to issue a notice of opportunity for hearing on the proposed revocation pursuant to 21 CFR 12.21(b). The agency will proceed with the revocation of U.S. license 0099-001 unless you do the following:

1. Within ten (10) days of receipt of this letter, advise FDA in writing of your commitment to correct the noted deficiencies, explaining the approach by which compliance will be achieved in an expeditious manner.

2. Within thirty (30) days of receipt of this letter, submit a comprehensive report and detailed approach supplementing your January 16, 1997, response addressing the methods which will be used to bring your facility into compliance, including a proposed completion date for correction of the noted deficiencies. Your plan should include corrective actions regarding all noted deficiencies, and should specifically emphasize your firm's plan for:

   a. ensuring that the QA Section functions in an adequate, effective, and timely manner, including addressing all QA oversight deficiencies;

   b. conducting a thorough review of all standard operating procedures to achieve compliance with good manufacturing practices as specified in 21 CFR 210 and 211;

   c. establishing a system of training and evaluation to ensure that personnel have capabilities commensurate with their assigned functions and a thorough understanding of the manufacturing operations which they perform;

   d. conducting a review of all observations listed on the Form FDA 483 issued November 27, 1996, to determine whether or not product quality has been affected, including addressing the need for possible recall of product if deemed necessary.

These submissions should be sent to Mr. James C. Simmons, Director, Office of Compliance, HFM-600, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, Rockville, Maryland, 20852-1448. Mr. Simmons may be reached at (301) 594-2066. Additionally, a copy of all submissions should be sent to the FDA's Detroit district office, 1560 E. Jefferson Avenue, Detroit, Michigan, 48207-3179, to the attention of Ms. Brenda Holman. In addition, we request a meeting with you at your earliest convenience to discuss the compliance status of your firm. We suggest that you also invite representatives from the State of Michigan and the Department of Defense to attend the meeting. Please telephone Mr. Simmons to discuss an appropriate date and time for the meeting.

If we do not receive an adequate response within the prescribed time, or if subsequent inspection of your firm finds your corrective actions to be inadequate, we shall proceed pursuant to the regulations governing formal evidentiary public hearings, as found in 21 CFR 12.21(b), and publish in the Federal Register a notice of opportunity for hearing on a proposal to revoke U.S. license 0099-001 and your product licenses for the manufacture and sale of Diphtheria Toxoid Adsorbed, Tetanus Toxoid Adsorbed, Rabies Vaccine Adsorbed, Antihemophilic Factor (Human), Immune Globulin (Human), Albumin (Human), Anthrax Vaccine Adsorbed, Pertussis Vaccine Adsorbed, Diphtheria & Tetanus Toxoids Adsorbed, and Diphtheria & Tetanus Toxoids & Pertussis Vaccine Adsorbed.

If you choose not to bring your establishment into compliance and wish to waive the opportunity for a hearing, you must contact Mr. Simmons within ten (10) days of receipt of this letter. The waiver must be confirmed in writing and may be accomplished by your voluntary request that U.S. license 0099-001 be revoked.

Copies of this letter have been sent to members of the Michigan Biologic Products Commission. In addition, the appropriate state officials will be notified of this administrative action.

Sincerely yours,

Mark A. Elgin

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

cc: The Honorable John R. Engler
Governor, State of Michigan
P.O. Box 30013
Lansing, Michigan 48909

Dennis L. Schornack
Chairman, Michigan Biologic Products Commission
3500 North Martin Luther King, Jr., Blvd.
P.O. Box 30035
Lansing, Michigan 48909

James Haveman
Commission Member, Michigan Biologic Product Commission
3500 North Martin Luther King, Jr., Blvd.
P.O. Box 30035
Lansing, Michigan 48909

Mary Lannoye
Commission Member, Michigan Biologic Product Commission
3500 North Martin Luther King, Jr., Blvd.
P.O. Box 30035
Lansing, Michigan 48909