



MAY - 4 1998

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448CERTIFIED - RETURN RECEIPT REQUESTED

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

Dear Dr. Myers:

As you know, the Food and Drug Administration (FDA) conducted an inspection of your facility between February 4 and February 20, 1998. At the conclusion of the inspection, the investigators presented you with a 19-page, 53-item Form FDA 483. The inspection was conducted, in part, to determine the implementation and effectiveness of the Strategic Plan for Compliance submitted to FDA that was in response to FDA's March 11, 1997, notice that unless your firm demonstrated or achieved compliance with the applicable regulations and standards, the FDA would institute proceedings to revoke U.S. license 0099-001, issued to Michigan Biologic Products Institute, Lansing, Michigan.

While we believe that the recent inspection indicates your firm has made progress in achieving compliance with the applicable regulations and standards in the areas of blood derivative product manufacture and operations, deficiencies in the areas of vaccine product manufacture and operations were documented.

The corrective actions outlined in your March 20, 1998, letter have been reviewed by the FDA's Office of Regional Operations and Center for Biologics Evaluation and Research (CBER). In earlier letters dated April 7 and 28, 1998, the FDA has communicated concerns about the time frame for changes and improvements to your vaccine manufacturing facility and the eleven lots of anthrax vaccine in quarantine. While our review has found your response to the Form FDA 483 to be generally acceptable, we have the following comments:

Form FDA 483 Item 1A

We acknowledge your plans to initiate validation studies in 2Q98, however, please be advised that your validation plans should include provisions that testing be performed at specific intervals to qualify the proposed maximum storage time, and a proposed maximum storage time between formulation and filling.

separate cover. However, it does not deal with "sampling" for the _____ Please be advised that there is no data indicating whether any of the three sampling methods will give results that are representative of the entire lot's _____ Please comment.

Form FDA 483 Item 5B & 6

We acknowledge the implementation of Quality Systems of Deviations, however, please address other stability failures besides potency, such as reductions in _____ below specifications and how they will be filed and investigated. In addition, please explain in detail how all potency tests conducted on the present stockpile will be "re-evaluated" for acceptability.

Form FDA 483 Item 7

Regarding lots FAV028, FAV031, FAV033, FAV035, and FAV038, please provide your plan for the disposition of these lots should the volume study show that the remainder of the lots' vials were not adequately filled and/or should the container/closure integrity studies be unsatisfactory.

Form FDA 483 Item 8

Please comment as to whether the data to date from the stability program indicated that the product is stable at room temperature for any given length of time. In addition, please be advised that a validation study needs to be initiated using short intervals of time between testing to confidently estimate the amount of time the finished product can be exposed to room temperature.

Form FDA 483 Item 17

Your response states that product bottles are taken to Building _____ or storage prior to filling. Please clarify whether product bottles will be immediately transferred to Building _____ or stored in Building _____ until they have passed Quality Control (QC) release testing.

Form FDA 483 Item 26B

In your response you define a "mock run" for media fill as a "batch production run" minus cells and virus. Please note that while it is correct to exclude virus from the media run, it is important to include cells and cell handling steps as part of the mock runs. The early steps in the rabies vaccine manufacturing process involving the direct handling and manipulation of cells and the cells themselves are a potential place where contaminants can be introduced in to the process. Therefore, media runs performed with cells are essential.

Form FDA 483 Item 26E

Please provide your rationale for testing rinsates for endotoxin, since endotoxin tends to adhere to glass surfaces, giving false negative results. Please note that spiking studies are most commonly used to assess the efficacy of the process for removing endotoxin.

Form FDA 483 Item 1C

We acknowledge your commitment to establish and implement an anthrax vaccine specific media validation SOP. Please submit this SOP when completed for review by appropriate CBER personnel. In addition, please note the validation studies should be performed prior to initiating production of anthrax vaccine following the renovations.

Form FDA 483 Item 1D

We acknowledge your commitment to perform formal disinfectant studies prior to reopening the anthrax production facility, however, please be advised that disinfectant studies need to be performed in the anthrax potency testing facility as soon as possible. Further, please note that since _____ are used to make subsequent dilutions for challenge potency testing, the disinfectant studies need to be conducted with higher concentrations of spores.

Form FDA 483 Item 1E

We acknowledge the development of stability studies (protocol) for holding times of anthrax sublots. Please describe the additional laboratory analyses proposed to be performed on the anthrax sublots.

Form FDA 483 Item 1H

We acknowledge the institution of an expiration date of _____ for the working seed spore stock suspensions. Please note that a validation study should be performed to insure that an expiration date of _____ the working seed spore stock suspensions is appropriate. In addition, please be advised of the need to evaluate and set expiration dates for the working challenge (virulent strain) spore stock used in potency testing.

Form FDA 483 Item 1L

You did not respond to this item; please provide your response.

Form FDA 483 Item 2A

Please describe how the sublots will be tested and at what intervals to determine an acceptable hold time.

Form FDA 483 Item 2B

We acknowledge the implementation of the "Quality Review Board" (QRB) to determine the disposition of quarantined materials, however, your response does not include any specifications as to why a subplot is quarantined or when disposal can occur. In addition, please provide time frames for the QRB's review of any given subplot and how often the QRB meets to review quarantined material.

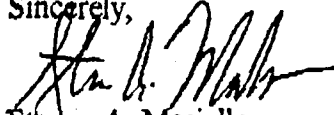
Form FDA 483 Item 3

We acknowledge the receipt of _____ dated March 16, 1998, dealing with _____, and the agency's review and assessment will be provided under

Please respond to the above items within 15 working days of receipt of this letter so that the agency may continue to assess your firm's overall compliance status. If you are unable to complete your response within this time frame, please notify us in writing as to when your response will be complete.

Your reply should be sent to the FDA, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions, please contact Diane Alexander at (301) 827-6201.

Sincerely,



Steven A. Masiello
Acting Director
Office of Compliance
Center for Biologics
Evaluation and Research

cc: Mr. Anthony M. Luttrell
Director, Quality Assurance/Quality Control
Michigan Biologic Products Institute
3500 North Martin Luther King, Jr., Blvd.
P.O. Box 30035
Lansing, Michigan 48909

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

DEC 22 1993

Dr. Robert Myers
Responsible Head
Michigan Department of Public Health
3500 North Logan
Lansing, MI 48909

Dear Dr. Myers:

An inspection of the blood products manufacturing facilities located at 3500 North Logan, Lansing, Michigan, conducted on May 4-7, 1993, revealed significant deviation from Title 21, Code of Federal Regulations, Parts 210-211 and 600-680. During the inspection of your firm, our inspectors observed the following:

1. Failure to have written procedures, maintain, or calibrate instruments or equipment used to manufacture albumin, immune globulin, or factor VIII.
2. Failure to have written procedures to recall a product.
3. Failure to maintain or conduct annual reviews of production batch records.
4. Failure of an adequate number of qualified personnel to comply with current Good Manufacturing Practices, e.g., failure to report changes in manufacturing, failure to adequately maintain calibration records, failure to adequately validate equipment used in the formulation or testing of products.

Please be advised that the above observations have been observed previously at your establishment. The above listed deviations are not intended to be an all inclusive list of the deficiencies which may exist at your facility. As Responsible Head, it is your responsibility to assure that your establishment is in compliance with all requirements of the federal regulations. You should take prompt action to correct these deviations.

Please notify this office in writing, of the specific steps you have taken to correct the noted deviations and to prevent their recurrence. If corrective action cannot be completed, state the reason for the delay and the time within which the corrections will be completed.

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Your response and any proposal for a meeting to discuss these issues should be sent to Mr. P. Michael Dubinsky at the address listed below.

Sincerely,

P. Michael Dubinsky
Acting Director
Office of Compliance
Center for Biologics
Evaluation and Research

cc: HFM-2, M. Beatrice
HFM-300, J. Epstein
HFM-205, S. Vargo
HFM-400, C. Hardegree
HFM-50, DCC, EIF